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Oxytocin in brain health and disease: How can it exert such pleiotropic neuromodulatory effects?

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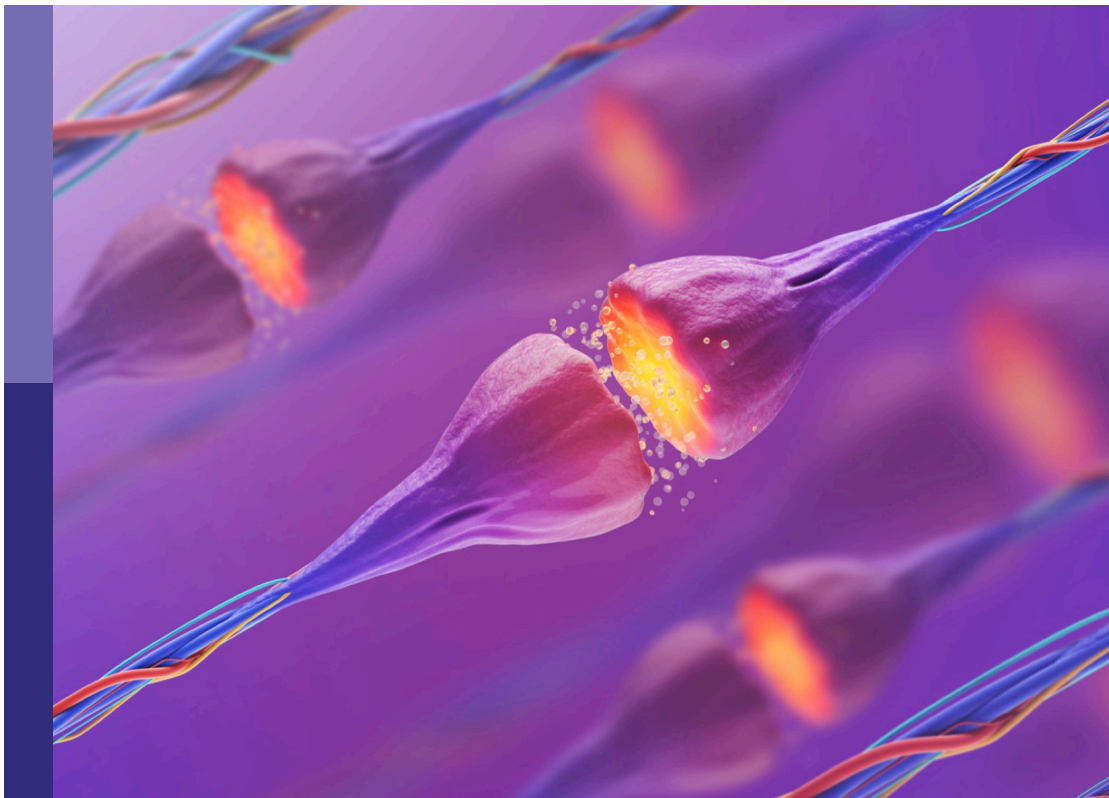

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Oxytocin in brain health and disease: How can it exert such pleiotropic neuromodulatory effects?

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Editorial: Oxytocin in brain health and disease: how can it exert such pleiotropic neuromodulatory effects?

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Editorial on the Research Topic
Oxytocin in brain health and disease: how can it exert such pleiotropic neuromodulatory effects?

Introduction

The pituitary hormone, oxytocin (Oxt), is gaining more and more interest from researchers in neuroscience over the years. Such attention is due to the multitude of heterogeneous effects on neural circuits and pro-social behavioral responses that Oxt elicits through its receptor, the Oxt receptor (OxtR). Imbalances in the oxytocinergic system are implicated in neuropsychiatric diseases associated with altered socio-emotional competence (i.e., autism spectrum disorder, depression), but also in some neurodegenerative diseases, such as Huntington's Disease and amyotrophic lateral sclerosis. Understanding the complex neurobiology of the oxytocinergic system in physiologic and pathologic conditions is a still open scientific challenge. The potentiality of Oxt to be used as a drug treatment further increases the need to extend, collect, and organize knowledge concerning this molecule.

In this special issue, we feature an assortment of contributions (8 reviews, 1 opinion, 2 original research articles) exploring through different approaches and from multiple angles the specific effects exerted by Oxt in the brain. This collection expands and collects current understanding in the neurobiology of Oxt and will provide direction and guidance for future studies in this field.

Reviews and opinion

Oxt is widely released in the brain, exerting specific neuromodulation of each cerebral region. Manjila et al. integrated brain wide connectivity of Oxt neurons with OxtR expression in mice. Accordingly, they provided insights for three functional circuit-based modules across the whole brain, modulated by the Oxt. These modules regulate respectively (i) the internal state (functional circuits for 1. Attention, 2. Threat, alert, and defense states, 3. Sleep/awake states), (ii) somatic/visceral responses (functional circuits

for 1. Pain, 2. Sensory/motor regulation, 3. Body physiology and metabolism), (iii) cognitive responses (functional circuits for 1. Learning and memory, 2. Reward and value assessment, 3. Reproduction). The specific effects of Oxt on the neurons of one of these circuit—the learning and memory circuit, involving the hippocampal formation—have been finely investigated in multiple studies, as review in Talpo et al. Variations in the oxytocinergic functional modulation of the different neurons in each hippocampal subregion appear to account for distinct information processing tasks exerted by each subregion, comprehensively summarized in this review.

An additional element of complexity in the neuromodulation operated by Oxt is due to the presence in many brain regions of higher order G-protein coupled heteroreceptor complexes of the OxtR. Borroto-Escuela et al. reviewed the existence of D2R-OxtR, OxtR-GHS-R1a, 5-HT2AR-OxtR, and 5-HT2CR-OxtR heterocomplexes. In line with this evidence crosstalk between Oxt and other neurotransmitters should be seriously considered.

Central neuromodulatory functions of Oxt are related especially to emotional and social behaviors. Triana-Del Rio et al., Coccia et al., Chen et al. and Muscatelli et al. described different aspects of these pro-social behavioral responses elicited by the Oxt. Triana-Del Rio et al. summarized how Oxt signaling in the limbic network modulates social and stress/threat-related behaviors, starting from the description of the underling cellular and molecular mechanisms. Authors describe how these responses are especially important in the interactions with conspecifics. Coccia et al. extended this concept by explaining the importance of empathy in social decision-making to survive in social environment. Indeed, Oxt modulates some of the major components of social decision-making (emotional discrimination, social recognition, emotional contagion, social dominance, and social memory) and is associated to empathy-like and pro-social behaviors in rodents. In the context of conspecific interactions, strong evidence of the role of Oxt is offered by the analysis of the parental caregiving behaviors of male mice, as discussed in the opinion paper by Chen et al. Referring to a recent paper by Kazunari Miyamichi's team (Inada et al., 2022), authors clarified that plasticity processes occur at hypothalamic oxytocinergic neurons when male mice become fathers, determining a behavioral switch from aggressivity to the conspecific young mice to caring for their pups. Muscatelli et al. also described differences in the dynamics of Oxt related to specific life stages, focusing especially on the role of Oxt in newborn mice. They reported that neonatal Oxt plays a key role in modulating/adapting sensory input and feeding behavior, thus establishing mother-infant bond and structuring all future social interactions.

Impairment of the oxytocinergic system have been reported in many pathological conditions, spanning from autism spectrum disorder to neurodegenerative diseases. Zayan et al. reviewed the modulatory effects elicited by Oxt on the thermosensory system—the sensory system that allows thermoregulation in mammals—that is strongly impaired in autism spectrum disorder. Based on the currently available literature, Bergh et al. described how Oxt could be implicated in Huntington's disease, amyotrophic lateral sclerosis, and frontotemporal dementia. Oxt seems indeed to play a pivotal role in determining altered social cognition and psychiatric features across these diseases. These pieces of evidence open the way for possible therapeutic strategies using Oxt.

Original research articles

Xu et al. by using medicated lollipops, a well-tolerated modality for an oro-mucosal administration of drug, demonstrated that Oxt blood concentration increased similarly as given by lingual and nasal routes. Accordingly, by taking advantage of an established anti-saccade paradigm, they proved that Oxt modulates top-down social attention by increasing anti-saccade error rates and response latencies for social stimuli and by reducing state anxiety similarly to what obtained following both intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) administration. It remains to be evaluated whether these functional effects are mediated in the brain by Oxt crossing the BBB or acting indirectly on the receptor expressed by vagal afferences.

Additionally, Ghafouri-Fard et al. showed that the expression of the oxytocin related genes (FOS, ITPR, RCAN1, and RGS2) was significantly downregulated in periodontitis tissues compared to control tissues, suggesting a potential role for oxytocin-related pathways in the development and progression of periodontitis. However, further research is needed to understand the underlying mechanisms and the correlation between the expression of these genes and the pathological stage of periodontitis.

Conclusions

The papers in this Research Topic provide insights into the neurobiology of Oxt in health and disease, spanning from the delineation of the pro-social role of Oxt, to the description of the effect of Oxt on specific brain networks, the clarification of crosstalk phenomena between Oxt and other neurotransmitters, the identification of the intracellular pathways activated by Oxt. Then, they provide an overview of the current body of knowledge about Oxt in the brain and highlight the many potentialities of research in this field. In this view, we hope that this Special Topic can stimulate further studies unraveling the missing pieces of knowledge in the mechanisms of oxytocinergic brain modulation, possibly accelerating the development of therapeutic strategies and drugs that use this molecule.

Author contributions

All authors contributed to this editorial and approved the submitted version.

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Conflict of interest

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Downregulation of oxytocin-related genes in periodontitis

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Periodontitis is a common oral disorder leading to tooth loss in both developed and developing regions of the world. This multifactorial condition is related to the abnormal activity of several molecular pathways, among them are oxytocin-related pathways. In this study, we enrolled 26 patients and 28 controls and assessed the expression of four oxytocin-related genes, namely, *FOS*, *ITPR*, *RCAN1*, and *RGS2*, in circulation and affected tissues of enrolled individuals using real-time PCR. Expression of *FOS* was downregulated in total periodontitis tissues compared with total control tissues [ratio of mean expression (RME) = 0.23, *P*-value = 0.03]. Expression of *FOS* was also lower in total blood samples of patients compared with total controls. Expression of *ITPR* was downregulated in total periodontitis tissues compared with total control tissues (RME = 0.16, *P*-value = 0.01). Moreover, the expression of *ITPR* was reduced in total blood samples of patients compared with controls (RME = 0.25, *P*-value = 0.03). Expression of *RCAN1* was downregulated in total periodontitis tissues compared with total control tissues (RME = 0.17, *P*-value = 0.01). However, the expression of *RCAN1* was not different in blood samples of affected vs. unaffected individuals. Finally, the expression of *RGS2* was lower in total periodontitis tissues compared with total control tissues (RME = 0.24, *P*-value = 0.01) and in total blood samples of affected individuals compared with controls (RME = 0.42, *P*-value = 0.05). This study provides data about the association between expressions of oxytocin-related genes and the presence of periodontitis. Future studies are needed to unravel the mechanistic links and find the correlation between expressions of these genes and the pathological stage of periodontitis.

KEYWORDS

periodontitis, oxytocin, *FOS*, *ITPR*, *RCAN1*, *RGS2*

Introduction

Periodontal diseases are common conditions in both developed and developing regions of the world with a global prevalence of 20–50% (Nazir, 2017). The chronic inflammatory disease of the periodontium is called periodontitis. This condition might result in the loss of periodontal ligament and damage to alveolar bone adjacent to the periodontium (de Pablo et al., 2009). As the principal cause of tooth loss, periodontitis is one of the major dangers to the health of the oral cavity (Benjamin, 2010). This condition is a multifactorial disorder with different etiologies related to host immune response, tissue destruction pathways, and bone resorption pathways (Qasim et al., 2020). Notably, transcriptomics analyses have shown a remarkable difference in the expression profiles of numerous genes between periodontitis and normal samples (Zhang et al., 2020). Oxytocin-related pathways have recently been found to be correlated with the pathogenesis of periodontitis. First, oxytocin has been shown to facilitate proliferation and enhance migratory potential and differentiation of periodontal stem cells into osteoblasts (Ge et al., 2019). Moreover, periodontal disorders have been considered possible risk factors for adverse pregnancy outcomes (Bansal et al., 2011). Prostaglandins, which are produced during the course of periodontitis (Bâge et al., 2011), have also been shown to increase the number of oxytocin receptors in the myometrium (Sánchez, 2008). In addition, periodontal diseases have been found to increase systemic inflammatory responses and expressions of prostaglandin E2 and proinflammatory cytokines in pregnant women (Latorre Uriza et al., 2018). Based on these observations, we have hypothesized that the expression of oxytocin-related genes might be different between patients with periodontitis and normal subjects. To test this hypothesis, we designed this study and measured the expression levels of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in the affected tissues and the circulation of patients with periodontitis vs. appropriate controls. These genes have been recently found to be correlated with oxytocin signaling through an *in silico* approach and have also been shown to be dysregulated in related disorders (Behtaji et al., 2021).

Materials and methods

Tissues and blood samples

Tissue samples were excised during surgical procedures from patients with chronic periodontitis (stages II–IV) according to the criteria previously described (Sayad et al., 2020a). Other criteria were age ≥18 years and the presence of a minimum of 16 teeth. Cases with a history of smoking, systemic disorders, intake of antibiotics or anti-inflammatory medicines, pregnancy, and breastfeeding were excluded. The presence of other inflammatory conditions was another exclusion criterion since we wanted to exclude the effects of inflammation in other sites on the expression of the mentioned genes. All cases were assessed by a university-affiliated periodontist. Control samples were obtained from bleeding on probing-free sites of individuals undergoing crown lengthening after careful examination by the periodontist. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences.

TABLE 1 Primer sequences.

Gene name	Sequence
B2M	F: AGATGAGTATGCCTGCCGTG R: GCGGCATCTTCAAACCTCCA
FOS	F: TACTACCACTCACCCGCAGA R: CGTGGGAATGAAGTTGGCAC
ITPR	F: GACGCAGTGCTACTCAACAAAC R: CAAATGCAGGAGCTGGATCAC
RCAN1	F: AGACTGAGTTTCTGGGAAAGGA R: CAGAAACTGCTTGTCTGGATTTG
RGS2	F: GGGAGAACGATAATGCAAAGTG R: AAGTAGCTCAAACGGGTCTTC

Expression assays

Total RNA was isolated from tissues and blood specimens using PicoPure RNA Isolation Kit (Thermo Fisher Scientific). All steps were performed using instructions provided in the kit manual. Then, the cDNA synthesis kit (Smobio, Taiwan) was used to produce cDNA from RNA. Relative expressions (RE) of *FOS*, *ITPR*, *RCAN1*, and *RGS2* were quantified in all specimens using the qRT-PCR kit (GeneDireX, Miaoli County, Taiwan). Reactions were conducted on the LightCycler 96 instrument in duplicate. The *B2M* gene was used as a normalizer. **Table 1** displays the sequences of primers used for the quantification of *FOS*, *ITPR*, *RCAN1*, and *RGS2* levels.

Statistical methods

The R software and ggplot2, ggfortify, and ggpubr packages were used for data analyses. Transcript amounts of *FOS*, *ITPR*, *RCAN1*, and *RGS2* were measured from Ct and efficiency parameters. Gene expression data were normalized to transcript the levels of *B2M*. As gene expression figures were extremely skewed on a linear scale, a logarithmic transformation was performed to obtain parametric and

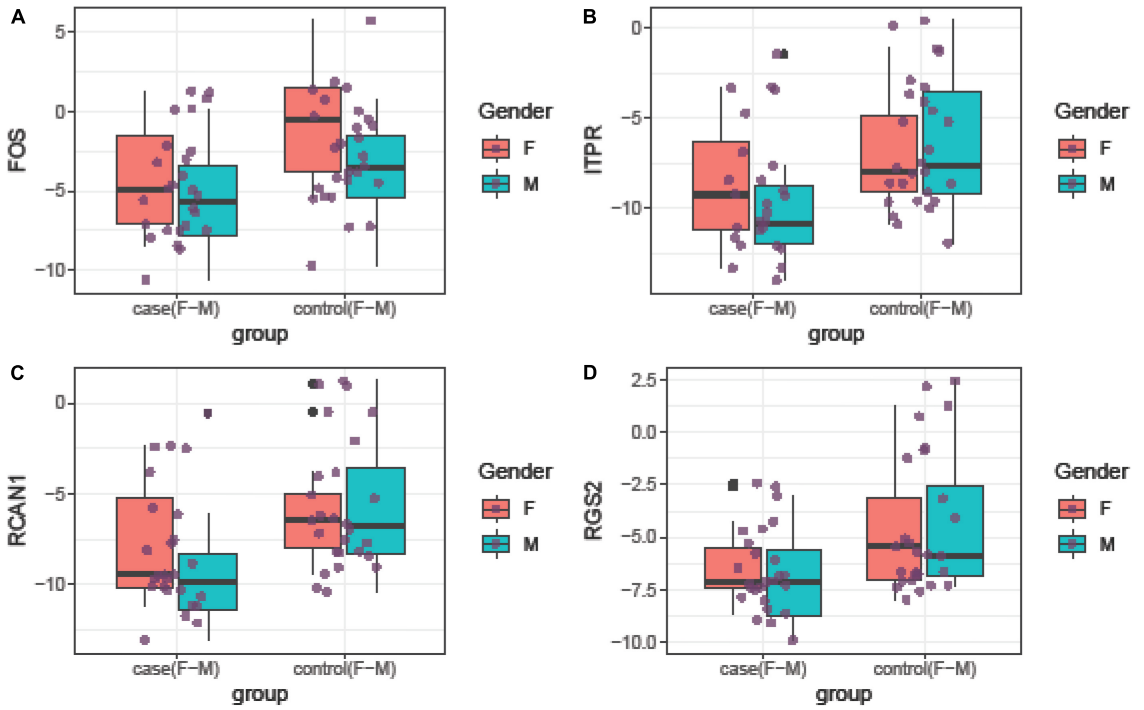

FIGURE 1
Relative expression amounts of *FOS* **(A)**, *ITPR* **(B)**, *RCAN1* **(C)**, and *RGS2* **(D)** genes in affected tissues compared with control tissues.

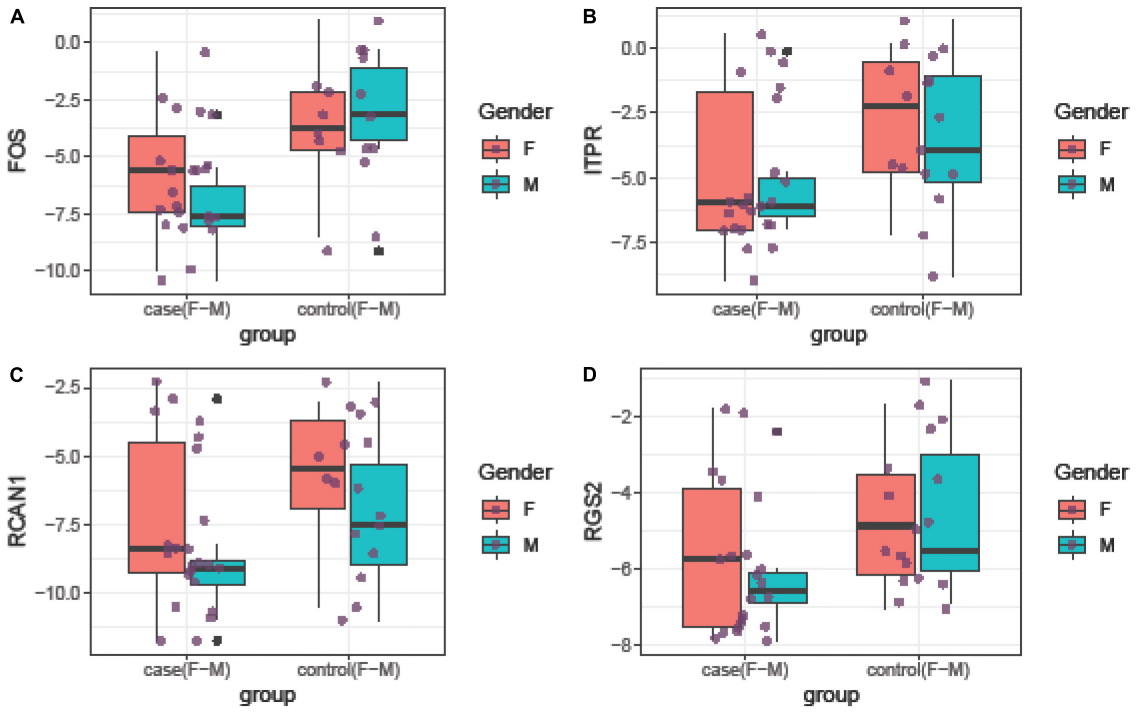

FIGURE 2
Relative expression amounts of *FOS* **(A)**, *ITPR* **(B)**, *RCAN1* **(C)**, and *RGS2* **(D)** genes in blood samples of patients with periodontitis compared with controls.

TABLE 2 General features of study participants.

Parameters	Periodontitis patients	Controls
Total number of tissue samples	26	28
Female	16	12
Male	10	16
Mean age ± SD	37.6 ± 2.5	37.5 ± 1.7
Total number of blood samples	23	17
Female	15	10
Male	8	7
Mean age ± SD	38.1 ± 2.9	37.9 ± 2.6

accurate data. The significance of the difference in mean values of expressions of genes was evaluated using the *t*-test. The correlations between expression levels of *FOS*, *ITPR*, *RCAN1*, and *RGS2* were valued using the Spearman correlation test. Receiver operating characteristic (ROC) curves were spotted to measure the diagnostic values of expression levels of genes using pROC and the caret package. Youden's J statistic was used to discover the optimum threshold. Area under curve (AUC) values were quantified.

Results

This study was conducted on samples obtained from 26 patients with periodontitis and 28 controls. Table 2 shows the demographic data of cases and controls.

Expression assays

Relative expressions of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in tissue and blood samples of patients and controls are depicted in Figures 1, 2, respectively.

Expression of *FOS* was downregulated in total periodontitis tissues compared with total control tissues (RME = 0.23, *P*-value = 0.03) and in affected tissues obtained from women compared with female control tissue (RME = 0.12, *P*-value = 0.03). Yet, this difference was not seen among men (*P*-value = 0.13). Expression of *FOS* was also lower in the total blood samples of patients compared with total controls (RME = 0.15, *P*-value < 0.001) and in blood samples of affected men compared with control men (RME = 0.07, *P*-value = 0.02). Among women, there was a trend toward downregulation of *FOS* in the blood samples of the affected individuals (RME = 0.23, *P*-value = 0.06). Expression of *ITPR* was down-regulated in total periodontitis tissues compared with total control tissues (RME = 0.16, *P*-value = 0.01) and in the affected tissues obtained from males compared with

TABLE 3 Statistical parameters of assessment of expression of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in the tissues and blood specimens obtained from patients compared with controls.

		FOS				*ITPR*				*RCAN1*				*RGS2*			
Number of samples		SE	Ratio of mean expressions	*P*-Value	95% CI		SE	Ratio of mean expressions	*P*-Value	95% CI		SE	Ratio of mean expressions	*P*-Value	95% CI		SE	Ratio of mean expressions	*P*-Value	95% CI	
Case/Control (Tissues)																					
Total	26/28	0.92	0.23	**0.03**	−3.95	−0.25	0.96	0.16	**0.01**	−4.59	−0.73	0.96	0.17	**0.01**	−4.45	−0.61	0.74	0.24	**0.01**	−3.54	−0.54
F	16/12	1.36	0.12	**0.03**	−5.88	−0.24	1.27	0.30	0.18	−4.38	0.86	1.31	0.26	0.16	−4.64	0.80	1.05	0.36	0.18	−3.72	0.76
M	10/16	1.25	0.25	0.13	−4.61	0.65	1.47	0.08	**0.02**	−6.76	−0.63	1.48	0.09	**0.03**	−6.52	−0.32	1.11	0.16	**0.02**	−4.98	−0.38
Case/Control (Blood)																					
Total	23/17	0.84	0.15	**0.00**	−4.41	−0.99	0.89	0.25	**0.03**	−3.81	−0.18	0.88	0.32	0.07	−3.45	0.12	0.62	0.42	**0.05**	−2.52	0.00
F	15/10	1.06	0.23	0.06	−4.34	0.11	1.13	0.23	0.07	−4.48	0.20	1.07	0.30	0.12	−3.98	0.48	0.80	0.50	0.22	−2.68	0.65
M	8/7	1.38	0.07	**0.02**	−6.83	−0.73	1.49	0.28	0.24	−5.16	1.46	1.46	0.30	0.25	−4.93	1.43	1.01	0.31	0.12	−3.93	0.52

Bold values indicate significant p-values (<0.05).

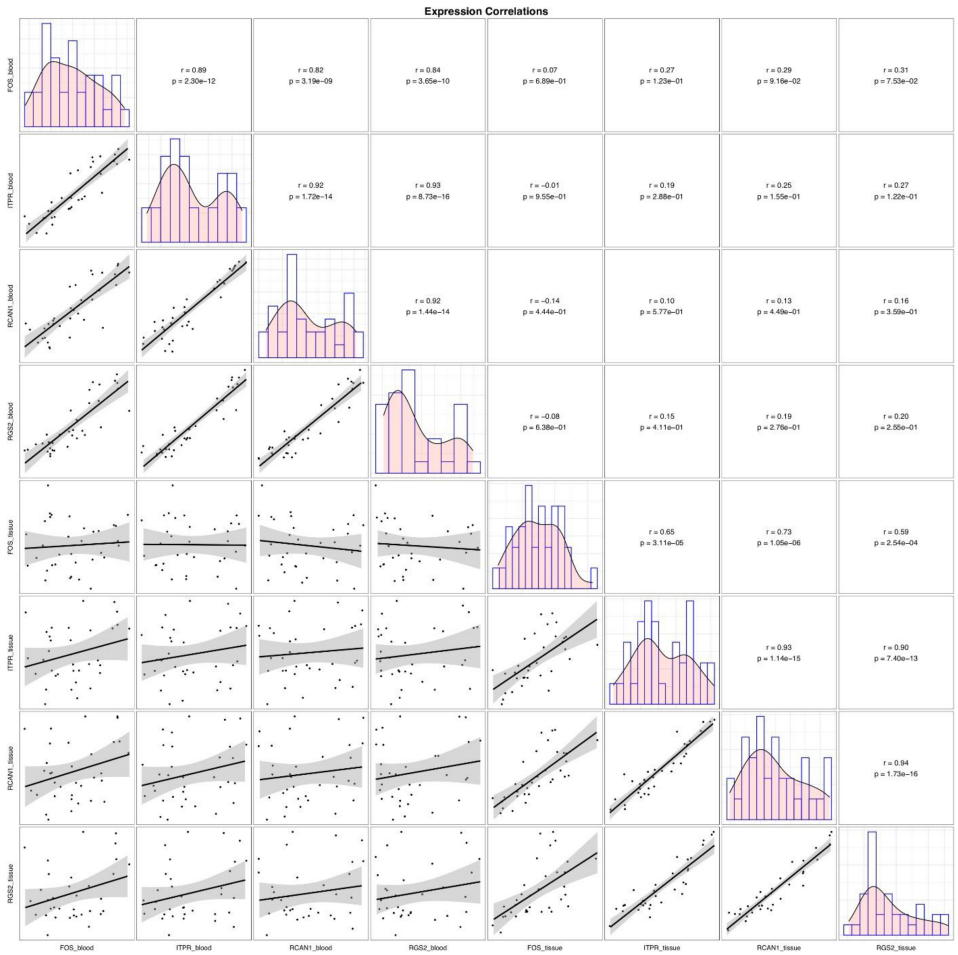

FIGURE 3
Correlations between tissue/blood levels of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes. The distributions of parameters are indicated on the diagonals. The bivariate scatter plots with fitted lines are shown in the inferior parts. Correlation coefficients and *P*-values are shown in the upper part of the diagonal.

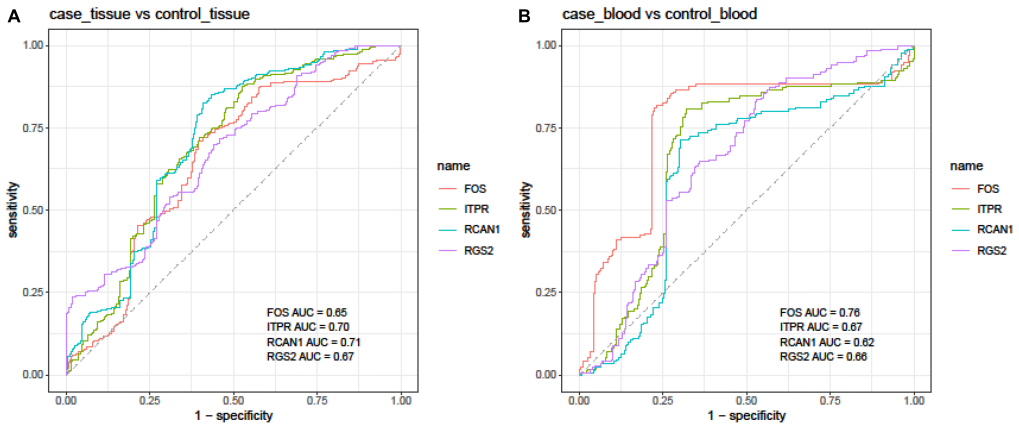

FIGURE 4
Receiver operating characteristic (ROC) curves depicted using the Bayesian generalized linear model.

male control tissue (RME = 0.08, *P*-value = 0.02). Yet, this difference was not seen among females (*P*-value = 0.18). Moreover, the expression of *ITPR* was reduced in total blood samples of patients compared with controls (RME = 0.25, *P*-value = 0.03). Expression of *RCAN1* was downregulated in total periodontitis tissues compared with total control tissues (RME = 0.17, *P*-value = 0.01) and in affected tissues obtained from men compared with male control tissue (RME = 0.09, *P*-value = 0.03). However, the expression of *RCAN1* was not different in blood samples of affected vs. unaffected individuals. Finally, the expression of *RGS2* was lower in total periodontitis tissues compared with total control tissues (RME = 0.24, *P*-value = 0.01), affected tissues obtained from men compared with male control tissue (RME = 0.16, *P*-value = 0.02), and total blood samples of affected individuals compared with controls (RME = 0.42, *P*-value = 0.05). Table 3 shows the detailed results of the assessment of expression of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in the tissue and blood specimens of periodontitis patients compared with controls.

Although expressions of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes were consistently correlated in each set of clinical samples (blood or tissue samples), their expressions in blood samples were not correlated with their expression in tissue samples (Figure 3).

Finally, we assessed the diagnostic power of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in different sets of blood and tissue samples using the Bayesian generalized linear model (Figure 4).

In tissue samples, the best diagnostic power was achieved using the expression levels of *RCAN1* (AUC = 0.71, sensitivity = 0.81, and specificity = 0.59), followed by *ITPR* (AUC = 0.70, sensitivity = 0.87, and specificity = 0.47). In blood samples, *FOS* had the best performance in the separation of affected individuals from controls (AUC = 0.76, sensitivity = 0.82, and specificity = 0.77). The combination of expression levels of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes did not improve the diagnostic power either in tissue or blood samples (Table 4).

TABLE 4 Statistical parameters of ROC curves in tissue and blood samples.

		FOS			*ITPR*			*RCAN1*			*RGS2*			All		
	Number of samples	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
Case/Control (Tissue)																
Total	26/28	0.65	0.71	0.60	0.70	0.87	0.47	0.71	0.83	0.59	0.67	0.72	0.54	0.65	0.82	0.44
Case/Control (Blood)																
Total	23/17	0.76	0.82	0.77	0.67	0.81	0.68	0.62	0.71	0.70	0.66	0.84	0.47	0.72	0.72	0.70

Discussion

Periodontitis is a complex disorder associated with the dysregulation of several genes (Sayad et al., 2020a,b). Most of the assessed genes and pathways have been those related to the regulation of immune responses (Sayad et al., 2020a). However, it is clear that dysregulation of these pathways does not completely explain the pathogenic events during the course of this disorder (Sayad et al., 2020a). Thus, the identification of other relevant pathways in periodontitis is expected to improve our understanding

of this disorder. Oxytocin has been shown to suppress inflammatory responses, induce antibiotic-like impacts, enhance wound healing and regenerative cascades, and inhibit stress-related immune diseases (Li et al., 2017). Moreover, several lines of evidence indicate an association between oxytocin-related pathways and periodontitis (Båge et al., 2011; Bansal et al., 2011; Ge et al., 2019). We have recently reported an association between a number of genes and oxytocin in the context of breast cancer (Behtaji et al., 2021). In this study, we assessed the expression of *FOS*, *ITPR*, *RCAN1*, and *RGS2* genes in the circulation and affected tissues of patients with periodontitis compared with normal controls.

Expression of *FOS* was downregulated in total periodontitis tissues compared with total control tissues and in affected tissues obtained from women compared with female control tissue. Yet, this difference was not seen among males. Expression of *FOS* was also lower in total blood samples of patients compared with total controls and in blood samples of affected men compared with male controls. Among women, there was a trend toward the downregulation of *FOS* in blood samples of affected individuals. FOS is a nuclear phosphoprotein that interacts with the JUN/AP-1 transcription factor. The complex formed between SMAD3, SMAD4, JUN, and FOS has a critical role in the regulation of TGF-β signaling (Zhang et al., 1998). Moreover, FOS participates in the regulation of the development of cells predestined to make and preserve the structure of the skeleton as well as immune system (Wagner and Eferl, 2005). Downregulation of this nuclear phosphoprotein in tissues and blood samples of patients with periodontitis might facilitate the development of this disorder through dysregulation of immune responses and interruption of the regenerative processes in the bone structures.

Expression of *ITPR* was downregulated in total periodontitis tissues compared with total control tissues and in affected tissues obtained from men compared with male control tissues. Yet, this difference was not observed among women. Moreover, the expression of *ITPR* was reduced in total blood samples of patients compared with controls. *ITPR1* has been shown to regulate autophagy and the sensitivity of cancer cells to chemotherapeutic drugs (Li et al., 2019). Notably, disruption in the regulatory mechanisms of autophagy has been demonstrated in periodontitis (Jiang et al., 2020). Meanwhile, numerous pharmaceutical and nutraceutical agents have been shown to modulate autophagy, thus serving as useful therapies for periodontitis (Lorenzo-Pouso et al., 2019).

Expression of *RCAN1* was downregulated in total periodontitis tissues compared with total control tissues and in affected tissues obtained from men compared with male control tissue. However, the expression of *RCAN1* was not different in blood samples of affected vs. unaffected individuals. RCAN1 has been shown to interact with calcineurin A and suppress calcineurin-related signaling pathways (Torac et al., 2014). Consistent with our results, expression of RCAN1 has been shown to be decreased in endothelial cells obtained from periodontal tissues affected by chronic inflammation (Peters et al., 2016).

Finally, the expression of *RGS2* was lower in total periodontitis tissues compared with total control tissues, affected tissues obtained from men compared with male control tissue, and total blood samples of affected individuals compared with controls. This gene has been shown to control signaling using G-protein coupled receptors (Nunn et al., 2010). This family of proteins has an important role in the development of bone diseases (Luo et al., 2019). Future studies are needed to appraise whether the contribution of RGS2 in the pathogenesis of periodontitis is exerted through the modulation of bone structure.

Moreover, we assessed the ability of these transcripts to separate affected tissues/blood samples from unaffected ones. In tissue samples, the best diagnostic power was achieved using the expression levels of *RCAN1* followed by the *ITPR*. In blood samples, *FOS* had the best performance in the separation of affected individuals from controls.

Conclusion

This study provides data about the association between the expression of oxytocin-related genes and the presence of periodontitis and warrants upcoming studies to unravel the mechanistic links. Furthermore, we suggest an assessment of the correlation between the expression of these genes and the pathological stage of periodontitis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.DRC.REC.1400.018). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SG-F wrote the manuscript and revised it. MH and AS designed and supervised the study. BH and LG collected the data and performed the experiment. NN analyzed the data. All authors read and approved the submitted manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer AS declared a past co-authorship with the authors SG-F and AS to the handling editor.

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Oxytocin in Huntington's disease and the spectrum of amyotrophic lateral sclerosis-frontotemporal dementia

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Neurodegenerative disorders (NDDs) such as Huntington's disease (HD) and the spectrum of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are characterized by progressive loss of selectively vulnerable populations of neurons. Although often associated with motor impairments, these NDDs share several commonalities in early symptoms and signs that extend beyond motor dysfunction. These include impairments in social cognition and psychiatric symptoms. Oxytocin (OXT) is a neuropeptide known to play a pivotal role in the regulation of social cognition as well as in emotional behaviors such as anxiety and depression. Here, we present an overview of key results implicating OXT in the pathology of HD, ALS and FTD and seek to identify commonalities across these NDDs. OXT is produced in the hypothalamus, a region in the brain that during the past decade has been shown to be affected in HD, ALS, and FTD. Several studies using human post-mortem neuropathological analyses, measurements of cerebrospinal fluid, experimental treatments with OXT as well as genetic animal models have collectively implicated an important role of central OXT in the development of altered social cognition and psychiatric features across these diseases. Understanding central OXT signaling may unveil the underlying mechanisms of early signs of the social cognitive impairment and the psychiatric features in NDDs. It is therefore possible that OXT might have potential therapeutic value for early disease intervention and better symptomatic treatment in NDDs.

KEYWORDS

oxytocin, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, neurodegenerative diseases, huntingtin, TDP-43

Introduction

Neurodegenerative disorders (NDDs) are a group of diseases caused by progressive and irreversible deterioration of neurons within the central nervous system (CNS). Current treatment is only symptomatic but does not modify disease progression or reverse the neuronal dysfunction. These disorders are characterized by selective cellular vulnerability to the pathogenic process that often involve the accumulation of disease-associated proteins. Important research questions are centered on understanding the underlying mechanisms of selective vulnerability as well as what changes occur early and could be targeted for therapeutic disease-modifying interventions. Recent work has indicated interesting similarities between Huntington's disease (HD) and the spectrum of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Vercruysse et al., 2018). The concept of an ALS and FTD disease spectrum continuum has emerged, largely from an overlap in pathological and genetic associations between the two conditions (Neumann et al., 2006; Renton et al., 2011; Strong et al., 2017). Although previous research has mainly focused on the well-known disturbances in motor function and accompanying neuropathology of movement-regulating neurons for HD and ALS, recent work show early manifestation of psychiatric symptoms and altered social cognition as well as selective vulnerability of hypothalamic neurons in both HD and the spectrum of ALS and FTD disorders (Vercruysse et al., 2018; Gabery et al., 2021). Understanding the underlying mechanisms of selective vulnerability of hypothalamic neurons and the link to early psychiatric symptoms in these disorders may open up for novel avenues for therapeutic interventions for these disorders.

Several genes have been identified in the familial forms of these NDDs. HD is caused by an expansion of the trinucleotide CAG within the *huntingtin* (*HTT*) gene (HDCRG, 1993), while there are several known genetic mutations in ALS such as *superoxide dismutase 1 (SOD1)*, *chromosome 9 open reading frame 72 (C9ORF72)* and, *trans-activation responsive RNA-binding protein (TARBP)*. The latter two genes are also affected in FTD as well as *progranulin (GRN)* and *microtubule associated protein tau (MAPT)* (Taylor et al., 2016; Greaves and Rohrer, 2019). Also, CAG expansions within the *ataxin-2* have also been shown to be associated with ALS (Elden et al., 2010).

Cognitive and social behavioral alterations are key early features that are present in HD, ALS, and FTD (Craufurd et al., 2001; Phukan et al., 2007; Paulsen et al., 2008; Steenland et al., 2010; Ahmed et al., 2014; Bott et al., 2014; McCarter et al., 2016; Herzog-Krzywoszanska and Krzywoszanski, 2019; Blasco et al., 2020; Boentert, 2020; Singh and Agrawal, 2021). In particular, social cognitive impairment (e.g., processing of facial expression of emotions, theory of mind, and empathy) in NDDs has the potential to disrupt interpersonal relationships, thereby eliminating the benefits that social interactions may bring for patients suffering from these debilitating conditions (Christidi et al., 2018). The underlying biological mechanisms mediating these features in NDDs are not well understood. However, given that both altered social cognition as well as psychiatric features constitute a common denominator in the early phases across all three diseases, it is likely that that there could also be common pathologies in HD, ALS, and FTD.

Hypothalamic alterations can be observed in all three NDDs, including loss of different hypothalamic neurons (Gabery et al., 2010, 2015, 2021; Vercruysse et al., 2018; Ahmed et al., 2021c). The neuropeptide oxytocin (OXT) has long been known to play a pivotal role in the regulation of complex social cognition and behaviors, including prosocial behavior and pair-bonding (Heinrichs et al., 2009; Galbally et al., 2011; Odent, 2013) as well as in emotional behavior including anxiety and depression (Neumann and Landgraf, 2012; Jurek and Neumann, 2018; Onaka and Takayanagi, 2019; Yoon and Kim, 2020). OXT is synthesized in the paraventricular nucleus (PVN) and supraoptic nucleus of the hypothalamus (Gimpl and Fahrenholz, 2001). OXT binds to OXT-receptors (OXTR) that are located throughout the brain most prominently within the limbic structures (Jurek and Neumann, 2018). Interestingly, in a recent study, distinct OXTR expression patterns have been shown in psychiatric disorders as well as in metabolic regulation processes across development in humans (Rokicki et al., 2022). Furthermore, genetic variation of OXTR has also been shown to be associated with social impairment in HD (Saiz-Rodríguez et al., 2022). When exogenously administered, OXT facilitates social encounters, improved social cognitive outcomes as well as emotion recognition in healthy and clinical groups characterized by social deficits, such as autism and social anxiety disorder (Heinrichs et al., 2009; Keech et al., 2018).

Other hypothalamic specific neuropeptides that have been studied in NDDs include hypocretin (orexin) which has been shown to be reduced in both HD and ALS (Gabery et al., 2010, 2021) as well as in Parkinson's disease (Fronczek et al., 2007). Like OXT, hypocretin is exclusively produced in the hypothalamus and is involved in the regulation of sleep, emotion, and metabolism (Tyree et al., 2018). Other hypothalamic specific neurons such as vasopressin has also been shown to be reduced in HD (Gabery et al., 2010), but not in ALS or FTD (Piguet et al., 2011; Gabery et al., 2021). Hypothalamic expression of neuropeptide Y (NPY), a neuropeptide involved mostly in appetite regulation has also been studied and is preserved in HD, ALS, and FTD (Gabery et al., 2010; Piguet et al., 2011).

Hence, several studies have indicated that the OXT system may be implicated across both HD and the spectrum of ALS/FTD and therefore constitute an interesting common denominator (Gabery et al., 2010, 2015, 2021; Jesso et al., 2011;

Finger et al., 2015). Given the role OXT has on social cognition and emotional regulation, there may be a link between the pathology in the OXT system identified in these disorders and some of the early social cognitive and psychiatric features. OXT system may provide a common therapeutic target for disease intervention. Understanding similarities and differences of these disorders including of how the OXT system is affected may provide important information in that direction. This review therefore focuses on the current state of knowledge regarding changes in the OXT system in these particular NDDs and highlights the major results obtained so far in this emerging field.

Clinical features and neuropathology of Huntington's disease

The clinical diagnosis of HD is based on a positive gene test in combination with the manifestation of overt motor disturbances including chorea (exaggerated involuntary movements), rigidity and gait imbalance (Novak and Tabrizi, 2010; Ross et al., 2014). The onset of motor disturbances usually occurs in midlife (30–55 years of age) followed by 20 years of disease progression. Individuals with HD also experience a range of non-motor symptoms and signs. These include cognitive changes, such as executive dysfunction and altered social cognition, as well as psychiatric symptoms such as anxiety, depression, irritability, and apathy (Duff et al., 2007; Paulsen et al., 2008). The disease-causing mutation is an expansion of a CAG trinucleotide repeat in the *HTT* gene which encodes an extended polyglutamine (Q) of the HTT protein (HDCRG, 1993; Ross et al., 2014). Individuals carrying more than 36Q will develop HD, but there is reduced penetrance if the patient is carrying between 36 and 39Q (Duyao et al., 1993). Despite a major hallmark of HD pathology being the formation of intraneuronal aggregates of the mutant HTT protein, the role of these aggregates in the pathogenesis is not well understood (DiFiglia et al., 1997; Ross and Shoulson, 2009; Cisbani and Cicchetti, 2012). In HD, the most pronounced neuropathology is observed in the striatum of the basal ganglia and the cerebral cortex which are regions associated with motor function (Vonsattel et al., 1985). The site of pathology for psychiatric signs and symptoms as well as altered social cognition is still not established but may in part be explained by dysfunctional neural circuities and neuronal cell death in the hypothalamus. Hypothalamic alterations have been observed decades before onset of motor disturbances (Politis et al., 2008; Soneson et al., 2010; Cheong et al., 2019). Recent studies have aimed to increase the understanding of the non-motor features of HD and in particular the role of OXT in this paradigm. A summary of the main results for the role of OXT in HD pathology can be found in **Table 1**.

Changes in the oxytocin system in Huntington's disease

The first clinical study to investigate OXT pathology in clinical HD was conducted by Gabery et al. (2010). Immunohistochemically processed post-mortem brain tissue from HD patients of different Vonsattel grades (grades 2–4) revealed a selective 45% OXT neuronal loss as well as a reduced cell size of the remaining OXT neurons. The Vonsattel grading system is a five-step grading system (0–4) for neurodegeneration in HD focusing on the striatum, the most affected brain region (Vonsattel et al., 1985). Furthermore, a case report based on one HD patient with Vonsattel grade 0 showed the same low number of OXT-expressing neurons as late-stage HD patients with Vonsattel grade 2–4 (Gabery et al., 2015). The same patient had deceased before the onset of any motor signs and symptoms, however, had developed anxiety and sleep disturbances (Gabery et al., 2015). These results suggest that early changes in hypothalamic neuronal populations expressing emotion-regulating neuropeptides could contribute to the early behavioral phenotype of HD. However, one study reported no changes in number of OXT neurons within the PVN (van Wamelen et al., 2012). This discrepancy in results may stem from different quantification approaches used. In the study from Gabery et al. stereological quantification with the physical dissector principle was applied while this was not the case in the study by van Wamelen et al. (2012).

In several studies, OXT has been measured in both blood and cerebrospinal fluid (CSF) samples from individuals with HD. A recent study showed a significant 38% reduction in OXT CSF levels in individuals carrying the mutant *HTT* gene (Hellem et al., 2022). No changes in OXT plasma levels in HD patients have been found, highlighting that changes in OXT levels occur centrally and not in the periphery (Unti et al., 2018; Fisher et al., 2021; Hellem et al., 2022).

There are a number of different transgenic mouse models for HD (Pouladi et al., 2013). A decrease in OXT mRNA levels in the CNS of both the R6/2 mouse expressing a short fragment of mutant *HTT* as well as HD190QG expressing a longer fragment of mutant *HTT* gene was observed (Kotliarova et al., 2005). A decrease of OXT mRNA levels has also been reported in a viral vector model with overexpression of mutant HTT selectively in the hypothalamus (Hult et al., 2011). Furthermore, R6/2 mice displayed loss of OXT-expressing neurons, which was not found in two other HD animal models; the BACHD and the HD190Q transgenic HD mice (Kotliarova et al., 2005; Soylu-Kucharz et al., 2016; Henningsen et al., 2021). In the PVN of HD190QG mice, lower levels of OXT mRNA were associated with a high frequency of mutant HTT aggregates (Kotliarova et al., 2005). Furthermore, pretreatment with OXT before intracerebroventricular (icv) injection 3-nitropropionic acid (3-NP)-induced HD mouse model prevented the development

TABLE 1 Summary of oxytocin (OXT) results in Huntington's disease (HD).

Tissue	HD stage	Analysis	Treatment		Results	References
Clinical HD		IHC, stereology		↓	Number of OXT neurons	Gabery et al., 2010; Gabery et al., 2015
		IHC		=	Number of OXT neurons	van Wamelen et al., 2012
		IHC, stereology		↑	Atrophic OXT neurons	Gabery et al., 2010
	Premanifest and manifest	EIA, ELISA, RIA		=	OXT plasma level	Unti et al., 2018; Fisher et al., 2021; Hellem et al., 2022
	Premanifest	ELISA, SDMT, VDT		↑	OXT plasma levels correlated with ↑ executive function	Fisher et al., 2021
	Premanifest and manifest	ELISA, PBA		↑	OXT plasma levels correlated with ↓ depressive-symptoms	Fisher et al., 2021
	Manifest	EIA, faux-pas		↑	OXT correlated with ↑ social cognition	Unti et al., 2018
	Premanifest	fMRI, emotional face matching task	Intranasal OXT adm.	↑	Ability to process disgust stimuli	Labuschagne et al., 2018
	Manifest	RIA		↓	OXT CSF levels	Hellem et al., 2022
		RIA, MMSE, MoCA, TASIT, EHt, RME		↓	OXT CSF levels correlated with ↑ cognitive impairment	Hellem et al., 2022
HD190QG (Mouse)		RT-PCR		↓	OXT mRNA	Kotliarova et al., 2005
		IHC		=	Number of OXT neurons	Kotliarova et al., 2005
BACHD (Mouse)		RIA		↓	OXT plasma level	Cheong et al., 2020
		RIA, EPM, FST, SIT		↓	OXT plasma levels with ↑ depressive-, anxiety-like and altered social behavior	Cheong et al., 2020
		FST	Intranasal OXT adm.	↓	Depressive-like symptoms	Cheong et al., 2020
		IHC, stereology		=	Number of OXT neurons	Soylu-Kucharz et al., 2016
		IHC, stereology	QA injection	=	Number of OXT neurons	Henningsen et al., 2021
R6/2 (MOUSE)		RT-PCR		↓	OXT mRNA levels	Kotliarova et al., 2005
		IHC, stereology		↓	Number of OXT neurons	Henningsen et al., 2021
		IHC, stereology	QA injection	=	Number of OXT neurons	Henningsen et al., 2021
AAV-MHTT (Mouse)		RT-PCR	mHTT AAV vector injection	↓	OXT mRNA	Hult et al., 2011
NP-3 (Rat)		OFT, EPM, FST	icv OXT injection	↓	Anxiety- and depressive-like symptoms	Khodagholi et al., 2022
		Western blot, ellman method	icv OXT injection	↑	OXTR, mGluR2, GSH levels	Khodagholi et al., 2022
		Western blot	icv OXT injection	↓	mGluR5 levels	Khodagholi et al., 2022

↓: decrease in symptomatic or abundance, ↑: increase in abundance, =: no change in neuronal population. adm, administration; AAV, adeno-associated virus; EHt, emotion hexagon test; EIA, enzyme inhibition assay; ELISA, enzyme-linked immunosorbent assay; EPM, elevated plus maze; FST, forced swim test; IHC, immunohistochemistry; icv, intracerebroventricular injection; mHTT, mutant huntingtin; MoCA, Montreal cognitive assessment; MMSE, mini mental state examination; OFT, open field test; QA, quinolinic acid; RIA, radioimmunoassay; RME, reading the mind of the eyes; RT-PCR, real-time polymerase chain reaction; PBA, problem behaviors assessment; SDMT, symbol digit modalities test; SIT, social interaction test; TASIT, the awareness of social interference test; VDT, verbal fluency test.

of several changes including decreased levels of the OXT receptor, mGluR2 and glutathione as well as increased mGluR5 levels in the striatum, hippocampus, prefrontal cortex, and amygdala (Khodagholi et al., 2022). These results indicate that OXT might have a protective effect on these molecular changes in HD. However, the OXT neuronal population appear to be resistant to quinolinic acid induced toxicity (Henningsen et al., 2021), which is an excitotoxin that has been linked to a loss of medium spiny neurons in the striatum of HD (Beal et al., 1986, 1991; Ferrante et al., 1993). This suggests that the vulnerability of OXT expressing neurons in HD is not caused by excitotoxicity. The underlying mechanisms of OXT loss in HD are not known and need further study.

Effects of oxytocin on social cognition and psychiatric features in Huntington's disease

Oxytocin has previously been established to have an important role in social cognition. Clinical studies have revealed a link between OXT and social cognition in HD. In HD patients, the ability to process emotions such as disgust, fear, anger, sad, surprise, and happiness is reduced (Labuschagne et al., 2018). Interestingly, a higher baseline level of OXT in the plasma was associated with a better recognition of emotion facial expression in HD gene carriers at an early disease stage before any onset of motor signs and symptoms onset (premanifest HD) (Unti et al., 2018). Moreover, intranasal OXT treatment normalized the ability of premanifest patients to process disgust stimuli (Labuschagne et al., 2018). More recently, Hellem et al. (2022) reported that HD patients with social cognitive impairment had significantly lower OXT CSF levels, suggesting a correlation between OXT CSF levels and social cognitive function. OXT may also be associated with executive dysfunction in HD. A clinical pilot study revealed that premanifest HD patients with higher OXT plasma levels performed better at cognitive tasks including verbal functioning, visual spatial attention, processing speed and working memory (Fisher et al., 2021). With an unmet clinical need for HD biomarkers, both OXT CSF and plasma levels may give some indication of the status of social cognitive deficits in HD.

Oxytocin could also play a role for the neuropsychiatric features of HD. In clinical HD, a positive correlation between OXT plasma levels and depression in both motor manifest and premanifest HD patients has been observed (Fisher et al., 2021). In the BACHD mouse model, OXT plasma level is lower than in wild-type littermates with increased depressive-, anxiety-like and social behavior (Cheong et al., 2020). Moreover, acute intranasal OXT administration reduced depressive-like behavior in this mouse model with no effect on anxiety-like behavior (Cheong et al., 2020). Furthermore, pretreatment with OXT injections prior to icv NP-3 injection in rats prevented the development of anxiety-and depressive-like behavior (Khodagholi et al., 2022). These results suggest that OXT might have protective effects and should be further investigated as a potential treatment in preventing the development of depressive and/or anxious phenotype in HD.

Clinical features and neuropathology of frontotemporal dementia

Frontotemporal dementia is a group of NDDs that are characterized by progressive altered behavior and decline in executive functions. FTD is the second most common dementia after Alzheimer's disease (Ahmed et al., 2021b). Clinically it is subdivided into three main types including behavioral-variant frontotemporal dementia (bv-FTD), semantic dementia and progressive non-fluent aphasia (Neary et al., 1998; Hodges and Patterson, 2007). bv-FTD is the most common form and comprises over 50% of all FTD cases. The syndrome has an early age of onset with a mean around 50 years of age and disease duration of approximately 8 years. Affected individuals have a range of clinical symptoms such as behavioral disinhibition, hallucinations, apathy, executive dysfunction as well as changes in eating behavior with hyperorality (Woolley et al., 2007; Rascovsky et al., 2011). However, a central feature in this condition is the early progressive loss of empathy and social cognition (Rankin et al., 2005). As such, considerable amount of research has during the past two decades been devoted to this topic. Impaired recognition of the facial expression of emotions occurs at an early stage, which in turn complicates the engagement or response to social cues (Keane et al., 2002; Rosen et al., 2004). Regions in the brain that are thought to be involved in social cognition include frontal, temporal and parietal lobes, which are the regions with predisposition to neuropathological changes and atrophy in FTD (Kennedy and Adolphs, 2012; Ahmed et al., 2021b).

Psychiatric symptoms can often initially mask an FTD diagnosis, as several of the symptoms overlap with other psychiatric syndromes such as obsessive-compulsive disorder, bipolar disorder and major depressive disorder (MDD). Around 50% of patients with bv-FTD receive initially a psychiatric diagnosis (Woolley et al., 2011). Neuroimaging studies have revealed a loss of gray matter in both MDD and bipolar disease that overlap with the affected regions in FTD (Peet et al., 2021). This, therefore, poses a diagnostic difficulty in the clinical setting (Ducharme et al., 2020). Recently, post-mortem analysis on brain tissue from FTD cases have shown a correlation between psychiatric symptoms and a higher abundance of the transactive response DNA-binding protein 43 kDa (TDP-43) inclusion pathology (Scarioni et al., 2020).

Clinical features and neuropathology of amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a fast-progressing NDD associated with both upper and lower motor neuron dysfunction leading to muscle weakness and bulbar dysfunction (Taylor et al., 2016). The disease onset occurs commonly in mid-adulthood (at a mean age of 55 years) with death typically 3–5 years after diagnosis usually due to respiratory failure (Zarei et al., 2015; Taylor et al., 2016). ALS patients also exhibit a range of non-motor symptoms including altered energy metabolism and eating behavior (Dupuis et al., 2011; Ahmed et al., 2016, 2021b). Pathological findings have been observed in the frontal and temporal cortices as well as in the hypothalamus that may underlie some of these changes (Neumann et al., 2006; Gabery et al., 2021).

Psychiatric symptoms such as apathy and depression have also been described in ALS, which have been shown to precede the onset of motor symptoms (Mioshi et al., 2014; Caga et al., 2018, 2021). In particular, depression is reported before and after diagnosis (Turner et al., 2016). Recent studies indicate that social cognitive impairment and emotion facial expression processing deficits is present in ALS patients. Also, an increased atrophy of the fornix, the main white matter tract of the limbic system, has shown to correlate with increased behavioral changes in ALS patients (Gabery et al., 2021). A recent report has shown that ALS patients have more difficulty with recognition of facial expression of emotions such as disgust, anger, fear and sadness (Palumbo et al., 2022). These findings suggest that the OXT pathway might be affected in ALS.

Overlap between amyotrophic lateral sclerosis and frontotemporal dementia

In recent years, a growing amount of evidence point toward that ALS and a large proportion of FTD are part of a disease spectrum continuum (Clark and Forman, 2006). Approximately 15% of FTD patients develop ALS-associated motor signs and symptoms and 15–18% of ALS patients exhibit FTD-like symptoms (Burrell et al., 2011; Lattante et al., 2015; Taylor et al., 2016). This concept was potentiated further with the discovery of the C9ORF72 expansion causing both ALS and FTD (DeJesus-Hernandez et al., 2011; Hodges, 2012). Both conditions share overlap at the neuropathological level including cytoplasmic TDP-43 inclusions in both neurons and glia cells (Buratti and Baralle, 2008, 2012).

Changes in the oxytocin system in amyotrophic lateral sclerosis and frontotemporal dementia

For FTD and ALS, the symptomatology and the clinical presentation suggest involvement of key physiological functions of the hypothalamus, which might even precede the onset of the cognitive and motor symptoms development (Vercruysse et al., 2018; Ahmed et al., 2021a). Significant atrophy of the hypothalamus is present on structural magnetic resonance imaging (MRI) as well as on post-mortem analyses in patients with bv-FTD and ALS (Piguet et al., 2011; Gorges et al., 2017; Gabery et al., 2021). So far, only a few studies have investigated OXT in ALS and FTD.

Recently, a 33% loss of OXT-expressing neurons in post-mortem tissue from ALS patients was reported together with the presence of TDP-43 inclusions in OXT-expressing neurons (Gabery et al., 2021). In bv-FTD, promising results have been observed during pharmacological treatments with OXT mainly targeting loss of empathy and the ability to process facial expression of emotions. So far, two small randomized controlled trials with intranasal OXT treatment have shown safety and tolerability as well as significant improvement in neuropsychiatric inventory scores assessing agitation, depression, apathy and irritability (**Table 2**; Jesso et al., 2011; Finger et al., 2015). However, larger randomized control trials are required before more definitive conclusions of the potential positive therapeutic effects of OXT can be made.

Furthermore, using blood oxygen level dependent signal during functional MRI, intranasal OXT treatment showed enhanced activity in limbic regions associated with processing of facial expression of emotions (Oliver et al., 2020). However, to date, no studies have investigated OXT in animal models of ALS or FTD. Nevertheless, these findings together highlight the potential of OXT as symptomatic treatment for deficits.

Similarities across Huntington's disease and the spectrum of amyotrophic lateral sclerosis and frontotemporal dementia disorders

The role of OXT has evolved from solely being related to parturition and breastfeeding to be able to modulate aspects of social behavior as well as emotional regulation. As these functions are affected early on in HD and the spectrum of ALS/FTD, OXT may play an important role (**Figure 1**). Impairments in social cognition as well as a reduced ability to recognize facial expression of emotions in all three conditions have been established (Craufurd et al., 2001; Christidi et al., 2018; Keech et al., 2018; Palumbo et al., 2022). This could be associated with OXT, in particular in HD and FTD in which direct correlations of OXT levels has been found (Jesso et al., 2011; Labuschagne et al., 2018; Unti et al., 2018; Hellem et al., 2022). Moreover, hypothalamic pathology has been identified in all three conditions with a selective OXT loss in HD and ALS. Histopathological findings such as HTT inclusions in HD as well as presence of TDP-43 inclusions in OXT-expressing neurons suggest a selective vulnerability of this neuronal population to the presence of mutant HTT and TDP-43 (Gabery et al., 2010, 2021). To date, no studies have investigated the number of OXT cells in FTD. Collectively, these findings could indicate a mechanistic overlap across all three NDDs.

Furthermore, pharmacological administration with exogenous OXT improved processing of facial expression of emotions in both HD and FTD, thus supporting the possibility of a therapeutic application of OXT in the future. However, chronic administration of OXT at least in rodents lead to anxiety, via alternative splicing of *Crfr2a* (Winter et al., 2021), which needs to be considered in the development of clinical applications.

TABLE 2 Summary of oxytocin (OXT) results in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD).

Tissue	Condition	Analysis	Treatment		Results	References
Clinical ALS/FTD	ALS	IHC, stereology		↓	Number of OXT neurons	Gabery et al., 2021
	FTD		Intranasal OXT adm.		Safe and well tolerated	Finger et al., 2015
	FTD	Facial expression recognition task, neuropsychiatric inventory scale	Intranasal OXT adm.	↑	Emotion recognition Improvement in neuropsychiatric inventory score	Jesso et al., 2011
	FTD	fMRI, Bold	Intranasal OXT adm.	↑	Increased activity in limbic regions	Oliver et al., 2020

↓: decrease in neuronal population, ↑: improvement in capacity. IHC, immunohistochemistry; fMRI, functional magnetic resonance imaging; BOLD, blood oxygenation level dependent.

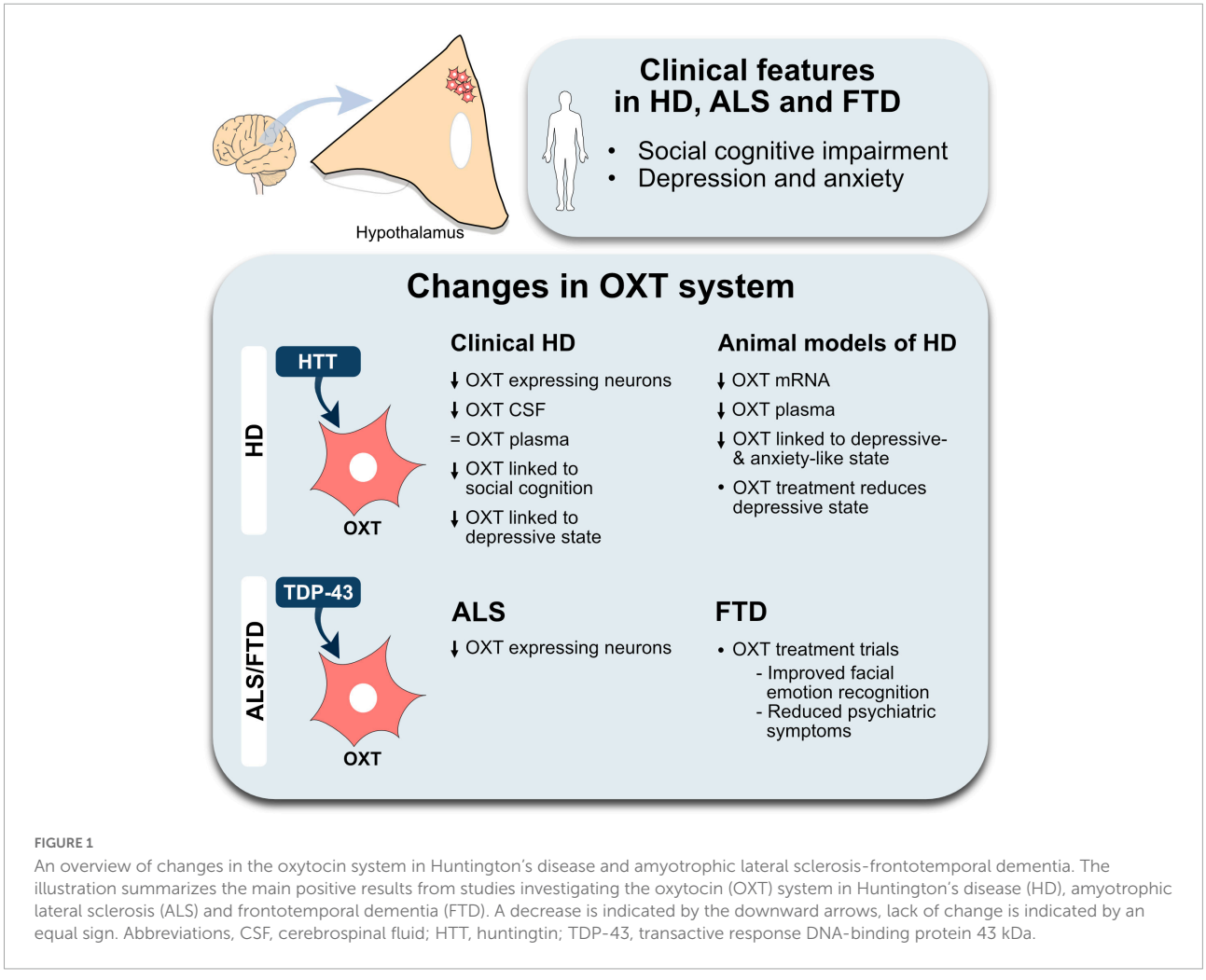

FIGURE 1
An overview of changes in the oxytocin system in Huntington's disease and amyotrophic lateral sclerosis-frontotemporal dementia. The illustration summarizes the main positive results from studies investigating the oxytocin (OXT) system in Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). A decrease is indicated by the downward arrows, lack of change is indicated by an equal sign. Abbreviations, CSF, cerebrospinal fluid; HTT, huntingtin; TDP-43, transactive response DNA-binding protein 43 kDa.

Conclusion

In this review, we provided a summary of the main results implicating changes in the OXT system related to HD, ALS and FTD in the literature. Across all three conditions, the impairments in social cognition and neuropsychiatric behavior occur early in the disease progression, prior to the onset of motor disturbances. OXT neuropathology may at least in part explain the development of these early features. There is an unmet need for biomarkers to track early disease progression in HD, ALS, and FTD. Levels of OXT in both CSF and plasma have been shown to track certain social cognitive

features, rendering OXT a potential biomarker candidate. Also, initial pharmacological intervention with OXT shows promising results. However, more experimental studies are needed to further determine the causative role of OXT in the development of the social and psychiatric impairments in HD, ALS, and FTD.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Oro-mucosal administration of oxytocin using medicated lollipops alters social attention, similar to intranasal and lingual routes: Implications for therapeutic use

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A key functional effect of intranasal administration of the neuropeptide oxytocin is on top-down control of social attention. However, an oro-mucosal administration route may be better tolerated for chronic therapeutic use and evidence suggests that some functional effects of oxytocin can be mediated via peripheral routes. The current study investigated if oxytocin administered orally using medicated lollipops can both increase blood oxytocin concentrations and influence social attention and state anxiety. In a randomized, double-blind, clinical trial adult male participants received oral oxytocin (24IU) or placebo 30-min before completing a well-established anti-saccade paradigm which can assess treatment effects on both top-down and bottom-up attention. Oxytocin administration modulated top-down social attentional processing by increasing anti-saccade error rates on both social and non-social stimuli although it only increased response latencies for social cues. Anti-saccade errors were also positively associated with the proportionate increase in plasma oxytocin concentrations. A comparison analysis showed that oral oxytocin administration increased blood concentrations to a similar degree as given by lingual spray, although less than when given intranasally. Importantly, attentional and anxiolytic effects of oxytocin in the anti-saccade task were similar across intranasal, lingual, and oral administration routes. These findings demonstrate that oral administration of oxytocin, similar to via intranasal and lingual routes, can modulate top-down social attention and state anxiety and support its potential for therapeutic use. They also provide further evidence that functional effects

of exogenously administered oxytocin can be mediated indirectly either by crossing the blood brain barrier or producing receptor mediated vagal stimulation, as opposed to via direct entry into the brain.

KEYWORDS

social attention, oxytocin, top-down attention processing, anti-saccade task, oro-mucosal administration

Introduction

The hypothalamic neuropeptide oxytocin (OXT) has been demonstrated repeatedly to play an important role in social cognition and motivation in both animal models and humans (Kendrick et al., 2017). Studies on the functional effects of OXT in humans have primarily used an intranasal administration route based on evidence that it may be able to directly enter the brain via the olfactory and trigeminal nerves (see Lee et al., 2020; Quintana et al., 2021; Yao and Kendrick, 2022). While some small initial studies in young children with autism spectrum disorder have reported beneficial therapeutic effects of chronic daily intranasal OXT treatment (Yatawara et al., 2016; Parker et al., 2017) a large-scale (n = 277) study across a wider age-range (3–17 years) and using an escalating dose strategy of up to 80IU per day did not (Sikich et al., 2021). However, inverted U response curves for OXT and potential receptor desensitization resulting from daily dosing regimes may have contributed to variable findings (see Yao and Kendrick, 2022; Martins et al., 2022). Indeed, a more recent study has reported that using less frequent dosing with intranasal OXT (24IU every other day for 6 weeks), to reduce potential receptor desensitization effects, and given as an adjunct to positive social interactions, improved social symptoms in 44% of young autistic children using the stringent clinical reliable change index (Le et al., 2022). Another chronic dose-response study using intranasal administration of a more stable form of OXT in adults has also reported some positive effects on social symptoms in adults only when lower doses are used (Yamasue et al., 2022). Nevertheless, more large-scale clinical trials are clearly required before any therapeutic potential of oxytocin can be fully established.

There is still an ongoing debate as to the route whereby intranasal OXT produces its reported effects on brain and behavior (see Leng and Ludwig, 2016; Yao and Kendrick, 2022). Intranasal OXT administration results in increased peptide concentrations in the blood, following absorption by the capillaries in the highly vascularized nasal cavity, as well as in cerebrospinal fluid (Striepens et al., 2013). This has raised the question as to whether increased concentrations of OXT in the blood may be playing a role in observed functional effects, either by acting on its peripheral receptors and, for example, stimulating the vagal system or by binding to molecules which facilitate it crossing the blood brain barrier (BBB) (see Yao and Kendrick, 2022).

While initial studies in animal models concluded that the BBB is relatively impermeable to OXT (Mens et al., 1983; Kendrick et al., 1986), recent studies have demonstrated that it can be transported into the brain by binding to the receptor for advanced glycation end products (RAGE) in BBB endothelial cells (Yamamoto et al., 2019; Yamamoto and Higashida, 2020; Munesue et al., 2021), with *in vitro* studies also reporting the presence of this potential transport system in humans (see Higashida et al., 2022). Compared to wild-type controls, RAGE knock-out mice do not exhibit increased OXT in the brain following intranasal or subcutaneous administration (Yamamoto et al., 2019; Munesue et al., 2021). Intravenous injection of labeled OXT can also enter the cerebrospinal fluid of monkeys within 60 min (Lee et al., 2018). In humans, both intravenous and intranasal OXT mediate a decrease in regional cerebral blood flow (rCBF) in the left amygdala and anterior cingulate cortex in adult males which is associated with increased peripheral plasma OXT concentrations (Martins et al., 2020). Additionally, OXT may influence brain function by stimulating the vagus via its peripheral receptors in the heart and gastrointestinal system (Yao and Kendrick, 2022). A number of animal model studies have reported brain or behavioral effects of acute peripheral OXT administration (intravenous, intraperitoneal, or subcutaneous) (Liberzon et al., 1997; Juif and Poisbeau, 2013; Smith et al., 2019) and RAGE knockout mice in contrast to wild type controls do not show functional effects following peripheral OXT administration (Yamamoto et al., 2019) and exhibit an impaired post-partum maternal behavior (Gerasimenko et al., 2021). In humans, we have recently reported that OXT administered via lingual spray can enhance brain reward responses and arousal in response to emotional faces more effectively than following intranasal administration and effects were associated with increases in blood concentrations (Kou et al., 2021). Effects of OXT on social attention and reducing state anxiety are also equivalent following intranasal or lingual routes of administration (Zhuang et al., 2022). Additionally, early studies in autistic adults have reported that intravenous oxytocin improved social cognition and repetitive behaviors (Hollander et al., 2003, 2007). Overall, there is therefore increasing evidence that peripheral

administration of OXT can produce both functional brain and behavioral effects and may be associated with the magnitude of peripheral concentration changes, although at this point it is still unresolved as to the precise mechanism(s) whereby increased peripheral concentrations of OXT influence brain and behavior.

Autistic individuals often exhibit attentional neglect of social stimuli or fail to detect salient social cues or direct attentional resources to them appropriately (Chita-Tegmark, 2016). A large number of studies in humans have demonstrated that intranasal OXT enhances attention toward social relative to non-social stimuli and salient cues such as eye-gaze in both healthy (Eckstein et al., 2019; Xu et al., 2019) and autistic individuals (Andari et al., 2016; Le et al., 2022). Our previous finding that lingually administered OXT has similar effects on modulating top-down attention to social and non-social cues as intranasal administration in an anti-saccade attentional task (Zhuang et al., 2022), suggests that an oral administration route for OXT might be used therapeutically. An intranasal administration route is potentially problematic therapeutically, especially for chronic treatment, since a number of factors can influence dosing efficiency, including application technique, size of the nasal cavity and nasal congestion. Furthermore, in young children, intranasal administration by others is not well tolerated. There is increasing interest in oro-mucosal administration strategies for pharmaceutical agents which are likely to be degraded by acidic conditions/peptidases in the gastrointestinal tract (Bastos et al., 2022). Ideally, the oro-mucosal administration should permit sufficient time for absorption of the pharmaceutical agent by the blood vessels and mucosa in the oral cavity before entering the gastrointestinal system. With OXT lingual administration, this can be achieved in adults by giving multiple sprays and instructing individuals not to swallow immediately, however for young children this is more problematic. A potential more suitable alternative for children is to use a medicated lollipop approach where the pharmacological agent, OXT in this case, is freeze-dried onto the surface of the lollipop and can slowly dissolve into the mouth during licking. We therefore took the novel step of using this approach to administer OXT in adults as a proof of principle study to determine both its efficacy for increasing blood OXT concentrations and for modulating top-down social and non-social attention.

To allow comparison with previous intranasal (Xu et al., 2019) and lingual spray (Zhuang et al., 2022) OXT administration studies, the current oral OXT administration study also used an adapted version of the emotional anti-saccade paradigm to examine its effects in modulating top-down and bottom-up social and non-social attentional processing. In this paradigm, effects on volitional top-down attention are evidenced by errors and saccade latencies when subjects are required to look away from stimuli (anti-saccades) or on automatic bottom up attention when subjects are required to look toward stimuli (pro-saccades). The weaker effects of OXT on non-social top-down attention observed in previous studies (Xu et al., 2019; Zhuang et al., 2021, 2022) might have been due to greater complexity of faces compared to simple oval shapes. We therefore adapted the paradigm to include images of houses inside the oval shapes which are classically used as controls for face images (Arkush et al., 2013; Oruc et al., 2018). The current study also measured blood concentrations of OXT before and after oral administration both in the main study and at more frequent time intervals in a separate pilot study on a different cohort of subjects. As in previous studies (Xu et al., 2019; Zhuang et al., 2022), we also measured effects of OXT on reducing state anxiety. Overall, we hypothesized that oral OXT administered via medicated lollipops would produce similar effects on top-down social attention as with intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) routes and that these would be associated with blood OXT concentrations. We also hypothesized that we would observe greater effects on top-down attention involving the more complex non-social stimuli. Finally, we hypothesized that orally administered OXT would produce a similar profile of increased concentrations in blood as lingual administration (Kou et al., 2021) and would reduce state anxiety similar to both intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) OXT.

Materials and methods

Participants, validation of oral administration approach and questionnaires

Seventy-two healthy male college students aged 18–30 years (Mean ± SEM = 21.15 ± 0.23) were recruited in a randomized, double-blind, placebo-controlled study (see **Figure 1**). An *a priori* power analysis showed that this would achieve 80% power for $\alpha = 0.05$ and a medium effect size ($f = 0.25$) (G*Power). Participants randomly received either oro-mucosal treatment with OXT using commercial sugar-free lollipops (24IU, $n = 35$, age: Mean ± SEM = 21.42 ± 0.37) or placebo (PLC) treated sugar-free lollipops ($n = 35$, age: Mean ± SEM = 20.9 ± 0.27). One surface of the lollipop was coated with OXT (24IU OXT dissolved in 0.1 ml sterile water, 0.9% sodium chloride and glycerol and then freeze-dried) or PLC (0.1 ml of same solution but without OXT and then freeze-dried). Random allocation to treatment groups was computer generated. See **Supplementary Figure 1** for consolidated standards of reporting trials (CONSORT) flow chart. All subjects were required not to consume caffeine or alcohol for 24 h prior to the experiment. Only male participants were included to match with previous oral and intranasal OXT studies using the same task and given the objective of establishing whether oral OXT might be effective therapeutically in autism, which is primarily a disorder affecting males (Xu et al., 2019; Kou et al., 2021). Exclusion criteria for all participants

were as follows: (i) Has had or is suffering from a neurological or psychiatric disorder; (ii) Use of any psychotropic drugs, including nicotine. All participants volunteering to take part were informed about details of the experiment before signing an informed consent form. All experimental procedures in this study followed the latest version of the Declaration of Helsinki and were also approved by the ethics committee of the University of Electronic Science and Technology, and pre-registered on the clinical trial website (NCT: https://www.clinicaltrials.gov, ID: NCT05444738).

In order to validate our oral OXT administration protocol using a medicated lollipop approach a pilot study on 15 adult male subjects (oral OXT lollipop: n = 10, oral PLC lollipop: n = 5) was performed. This investigated the pharmacodynamics of the 24IU medicated lollipop on plasma and saliva OXT concentrations over a period of 2 h. Blood samples were taken every 15 min via an indwelling catheter, two baselines before oral administration and eight samples following it; saliva samples were taken by a passive drool method before administration and 30 and 120 min after. In order to ensure that OXT freeze-dried on the surface of the lollipop dissolved in the mouth and absorbed by capillaries we asked subjects to lick, but not bite, the lollipop for 3 min.

To control for potential confounding effects of between-group differences in mood, personality and past experiences before treatment, all subjects in the main experiment first completed a set of validated questionnaires in Chinese. These included measures of depression [Beck Depression Inventory-II (BDI)–Beck et al., 1996], anxiety [State-Trait Anxiety Inventory (STAI)–Spielberger et al., 1971; Liebowitz Social Anxiety Scale (LSAS)–Mattick and Clarke, 1998], autistic traits [Autism Spectrum Quotient (ASQ)– Baron-Cohen et al., 2001 and Social Responsiveness Scale-2 (SRS-2)–Constantino and Gruber, 2012], early life experience [Childhood Trauma Questionnaire (CTQ)–Bernstein et al., 1998], alexithymia [Toronto Alexithymia Scale (TAS-20)–Bagby et al., 1994], emotion regulation [Emotional Regulation Questionnaire (ERQ)–Garnefski and Kraaij, 2007], behavioral response control [Behavioral Activation and Inhibition Scale (BAS/BIS)–Carver and White, 1994], and mood [Positive and Negative Affect Schedule (PANAS-18)–Watson et al., 1988]. Subjects then had a 5 ml blood sample taken by venipuncture for measurement of baseline OXT and received either OXT or PLC via a lollipop. A second blood sample was taken 30 min after administration to measure increased plasma OXT concentrations. After a short break, subjects were seated comfortably in front of an eye-tracking machine (Eye-link 1000) and after a brief practice of the anti-saccade task started the main task 40–45 min after oral treatment. Immediately after the task, subjects completed the PANAS and STAI questionnaires again to assess potential treatment and task effects of mood and state anxiety. Subjects were finally asked to guess which treatment they had received and analysis revealed that they were unable to do better than chance ($\chi^2 = 0.19$, $p = 0.66$).

Anti-saccade paradigm

An adapted version of the anti-saccade paradigm from our previous studies was used (Xu et al., 2019; Zhuang et al., 2021, 2022), with a total of 576 trials in 14 blocks. The first two blocks presented non-social stimuli (one anti-saccade and one pro-saccade block with 48 trials per block). However, in contrast to our previous studies where only a simple empty oval shapes were used here we used oval shapes incorporating pictures of houses taken from different angles and varying shades of gray in order to better match the complexity of the social facial stimuli (**see Figure 1**). The next 12 blocks presented social stimuli (emotional faces of angry, fear, happy, sad, and neutral of four males and four females) including six pro-saccade and six anti-saccade blocks with eight stimuli per block. Each block started with the presentation of cue words ("Toward"–i.e., pro-saccade or "Away"–i.e., anti-saccade) for 2,000 ms, followed by a "+" fixation on the screen (duration: 1,000–3,500 ms jittered). Next, a stimulus appeared on either the left or right side of the screen randomly for 1,000 ms. If the cue word was "Toward," the subject had to make a saccade toward the stimulus and if "Away" they needed to make a saccade away from it as quickly as possible. Subjects were required to complete the task quickly while maintaining accuracy. A 30 s break was allowed at the end of each block. Subjects initially received 32 practice trials (16 social and 16 non-social) on the task to reduce avoid potential problems with higher error-rates in initial trials (see Smyrnis et al., 2002).

Eye movement recording and processing

Eye movement data recording was carried out using an EyeLink 1000 Plus system (SR Research, Ottawa, ON, Canada) in monocular mode with a 2,000 Hz sampling rate and a 1,024 × 768 screen resolution. The fixed standard distance from the subject's eyes to the screen was set to 57 cm (using a fixed chin rest), and a nine-point calibration was conducted prior to start each block to obtain high quality eye-tracking data. The EyeLink Data Viewer 3.1 was used to export and pre-process the raw eye movement data. In line with previous studies, trials with latencies <70 or >700 ms and saccade velocity lower than 30°/s were discarded (García-Blanco et al., 2013; Xu et al., 2019; Zhuang et al., 2021, 2022). Seven subjects could not complete the experiment due to technical problems (OXT: 4; PLC: 3) and were therefore excluded. An error was defined as subjects making their first saccade in the opposite direction to the one they had been instructed to do. Finally, the mean error rate

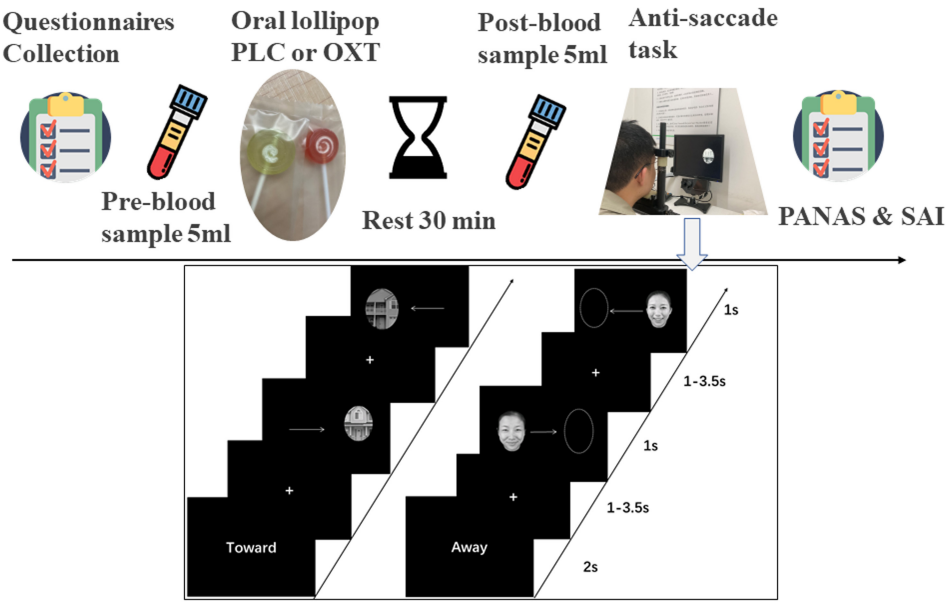

FIGURE 1
Experimental procedure for questionnaires, oral oxytocin administration and blood sampling **(top)** and the emotional anti-saccade paradigm **(below)**. "Toward" indicates the pro-saccade task where participants have to make a saccade toward the stimulus and "Away" indicates the anti-saccade task where participants have to make a saccade away from the side where the stimulus appears.

and latencies of correct saccade trials during both anti- and pro-saccade conditions were calculated and served as primary behavioral indices.

Blood sampling and oxytocin assays

Blood sampling and plasma OXT measurement. Five-milliliter venous blood samples were collected into EDTA tubes (two tubes for pre-treatment, two tubes for post-treatment) and immediately cooled and centrifuged at 1,600 × *g* for 15 min at 4°C. Sampling, handling, and OXT assay protocols are as in previous studies (see Kou et al., 2021; Le et al., 2022). Samples were run in duplicate and were subjected to a prior extraction step followed by an ELISA (ENZO Life Sciences, NY, USA). There has been some controversy concerning the validity of ELISA results for plasma OT (Leng and Ludwig, 2016) but we incorporated both the recommended extraction step and recovery of spiked samples to address this issue and our mean basal concentrations are in the expected normal range (i.e., <10 pg/ml).

Statistical analyses

Statistical analyses were either performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) or, where Shapiro–Wilk tests indicated a non-normal distribution, using nparLD software (Noguchi et al., 2012) for R-based non-parametric tests. To determine the effects of OXT, 2 (social/non-social stimuli) × 2 (pro-/anti-saccade) × 2 (OXT/PLC) ANOVAs were used for both error rates and response latencies. To further explore the effect of OXT on individual emotional expressions, 6 (anger/fear/happy/neutral/sad/shape) × 2 (pro-/anti-saccade) × 2 (OXT/PLC) ANOVAs were conducted on both error rate and response latencies. In addition, we performed correlation analyses between plasma OXT concentration changes (%) and behavior using Pearson to establish whether functional effects of oral OXT on modulating social attention and state anxiety (SAI) were associated with them. Correlations between SAI scores and performance on the anti-saccade task were also analyzed.

In a secondary analysis, a comparison across the effects of OXT administered intranasally (Xu et al., 2019), lingually (Kou et al., 2021), and orally (medicated lollipop) on both anti-saccade error rates and response latencies was performed using ANOVAs. In line with recent recommendations in the field (Quintana, 2022), the robustness of non-significant findings was additionally assessed using Bayesian analysis (JASP, version 0.14.1.0).[1] In, addition, we also conducted an exploratory analysis of changes in plasma OXT concentrations following administration of 24IU OXT by intranasal, lingual or oral routes using a non-parametric ANOVA due to a non-normal distribution of the data. For parametric ANOVAs,

1 https://jasp-stats.org

appropriate Bonferroni-corrected comparisons were employed within SPSS to control for multiple comparisons or for R-based non-parametric analyses Bonferroni-corrected Mann–Whitney *U*-tests were conducted for multiple comparisons.

Results

Effects of oral oxytocin administration *via* medicated lollipop on plasma and saliva oxytocin concentrations (pilot experiment)

Effects of oral administration of 24IU OXT by medicated lollipop (n = 10) on proportionate increases in plasma and saliva OXT concentrations were compared to those following PLC (n = 5). For plasma samples, data were not normally distributed and so a non-parametric ANOVA-type analysis was performed with treatment (OXT/PLC) and time-point (0/15/30/45/60/75/90/105/120 min) as factors. There were significant main effects of both treatment ($F_{1,\ 6.90}$ = 5.59, p = 0.05) and time-point ($F_{3.10,\ 8}$ = 2.82, p = 0.036) although not the treatment × time-point interaction ($F_{2.32,\ 8}$ = 1.22, p = 0.306). Exploratory *post-hoc* tests using Mann–Whitney showed that the percentage increase in OXT was significant in the OXT vs. PLC group at both 15 min (z = 2.511, p = 0.0121) and 30 min (z = 2.7557, p = 0.006) post-administration time points. Wilcoxon tests were also used to compare between baseline (time-point: 0) and other time-points within the OXT group and p-values Bonferroni-corrected. OXT concentrations in the OXT group were significantly increased at both 15 (p = 0.001) and 30 (p = 0.001) min time-points (**see Supplementary Figure 2**). A similar analysis of OXT concentrations in saliva (time-points, −15, +30, and +120 min) revealed large significant increases at both +30 min (>30-fold) and +120 min (5-fold) (both z = −2.886, p = 0.004, Wilcoxon) compared to baseline (**see Supplementary Figure 2**).

Potential confounders

Independent t-tests showed no significant differences between OXT and PLC groups across questionnaire scores before treatment (all ps > 0.05–see Table 1) indicating that the two groups were well-matched.

Oral oxytocin effects on saccade error rate and response latency

For error rates, data were not normally distributed and so non-parametric statistics were used for analysis. The treatment (OXT/PLC) × condition (social/non-social) × task (pro-/anti-saccade) mixed ANOVA-type on error rate showed a significant treatment × task interaction ($F_{1,\ 8}$ = 11.47, p = 0.007). *Post hoc* comparisons (Mann–Whitney U-test) indicating that OXT only increased error rates in the anti-saccade but not pro-saccade task (anti-saccade: PLC: Mean ± SEM = 15.1% ± 1.70, OXT: Mean ± SEM = 21.6% ± 1.7, z = 3.45, p = 0.001; pro-saccade: PLC: Mean ± SEM = 1.10% ± 0.20, OXT: Mean ± SEM = 0.85% ± 0.18, z = 0.99, p = 0.3222) (see Figure 2A). There was also a significant main effect of task ($F_{1,\ 8}$ = 770.68, p < 0.001), with higher error rates for anti-saccades compared to pro-saccades, and a condition × task interaction ($F_{1,\ 8}$ = 4.13, p = 0.042). *Post-hoc* tests showed that errors were higher for pro-saccades in the non-social condition (z = 3.585, p = 0.001). No other significant main or interaction effects of condition were found (all ps > 0.131).

In a mixed non-parametric ANOVA including stimuli as a factor, no significant three-way interaction was found for treatment (OXT/PLC) × stimuli (angry/sad/fearful/happy/neutral/shape) × task (pro-/anti-saccade) on error rates ($F_{4.39,\ 8}$ = 1.15, p = 0.332), indicating no differential treatment effects across the individual social and non-social stimuli. Task and stimuli main effects and a

TABLE 1 Mean ± SD questionnaire scores in OXT and PLC groups before and after attention task.

Questionnaires	OXT	PLC	*t*-value	*P*-value
Before task				
PANAS_P	22.34 (6.88)	20.88 (6.32)	0.895	0.374
PANAS_N	22.66 (5.37)	21.24 (5.79)	1.020	0.311
STAI (state)	39.87 (7.75)	40.09 (8.80)	−0.106	0.916
STAI (trait)	42.10 (7.05)	43.47 (8.58)	−0.692	0.492
BDI-II	7.50 (7.43)	10.15 (6.87)	−1.496	0.140
LSAS (avoid)	20.06 (11.23)	22.79 (11.73)	−0.957	0.342
LSAS (fear)	24.41 (12.36)	26.42 (12.92)	−0.643	0.522
BAS-reward responsiveness	6.85 (1.95)	7.15 (1.75)	−0.669	0.506
BAS-drive	7.75 (2.14)	8.06 (1.98)	−0.607	0.546
BAS-fun seeking	9.81 (2.19)	9.88 (2.41)	−0.116	0.908
BIS-behavioral inhibition	15.22 (2.32)	15.49 (2.70)	−0.425	0.672
ERQ	46.00 (6.06)	45.76 (7.75)	0.140	0.889
ASQ	21 (4.09)	21.273 (5.61)	−0.223	0.824
TAS	49.78 (8.34)	53.39 (9.23)	−1.654	0.103
CTQ	41.53 (8.42)	40.67 (6.13)	0.475	0.637
Post-task				
PANAS_P	16.68 (3.75)##	16.67 (3.40)##	0.012	0.990
PANAS_N	16.23 (3.10)##	16.06 (2.76)##	0.226	0.822
STAI (state)	34.07 (6.79)##	38.13 (8.50)	−2.068	0.043*

PANAS, positive and negative affect schedule; STAI, State-Trait anxiety inventory; BDI, Beck Depression Inventory; LSAS, Liebowitz Social Anxiety Scale; BAS/BIS, behavioral inhibition/activation system scale; ERQ, Emotion Regulation Questionnaire; ASQ, Autism Spectrum Quotient; TAS, Toronto Alexithymia Scale; CTQ, Childhood Trauma Questionnaire. *p < 0.05 OXT vs. PLC group (t-test) and ##p < 0.01 vs. pre-task (paired t-test).

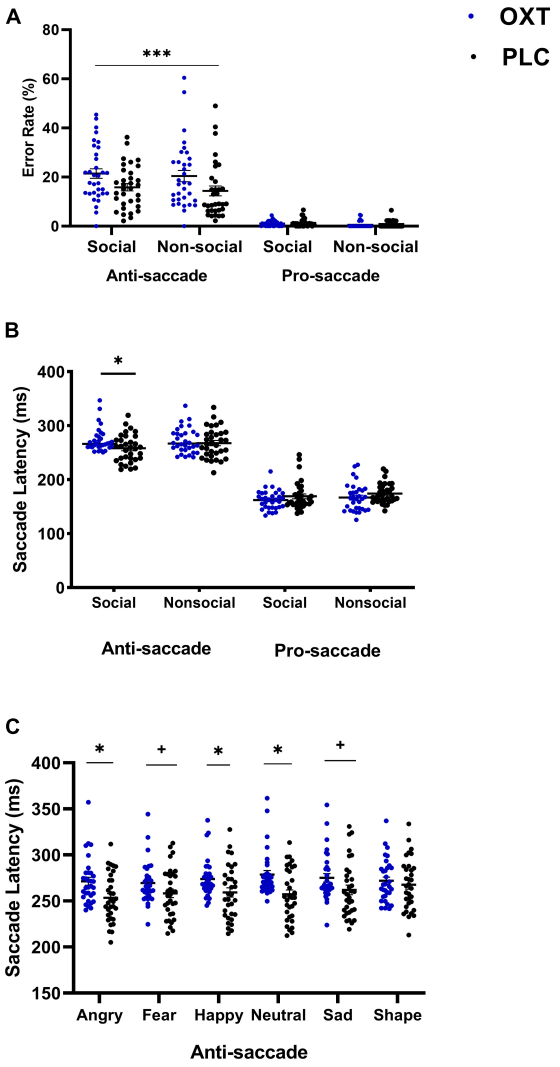

FIGURE 2
The effects of oral (lollipop) oxytocin (OXT) on error rates and saccade latencies in the anti-saccade task. Oral OXT increased **(A)** anti-saccade and pro-saccade error rates compared for OXT and PLC groups and for social and non-social stimuli (***$p < 0.001$ treatment × task interaction, indicating that OXT increased anti- but not pro-saccade errors for both social and non-social stimuli), and **(B)** for anti-saccade and pro-saccade response latencies for social and non-social stimuli **(C)** increased anti-saccade response latencies were seen across face emotions, and differed significantly from non-social stimuli. For panels **(B,C)**,*$p < 0.05$ and two-tailed and +$p < 0.05$ one-tailed *post hoc* Bonferroni-corrected treatment effect for OXT vs. PLC.

treatment × task interaction were all significant (all *ps* < 0.024), with the *post hoc* comparisons again showing a greater number of errors in the anti-saccade task following OXT ($z = -5.24$, $p < 0.001$).

For response latency, the condition (social/non-social) × treatment (OXT/PLC) × task (pro-/anti-saccade) mixed parametric ANOVA revealed a significant three-way interaction ($F_{1, 63} = 4.19$, $p = 0.045$, $\eta_p^2 = 0.062$). *Post hoc* Bonferroni-corrected comparisons indicated that response latencies in the anti-saccade task for social stimuli were significantly longer in the OXT than in the PLC group ($F_{1, 63} = 6.84$, $p = 0.011$, $\eta_p^2 = 0.098$, see Figure 2B). There was also a two-way treatment × task interaction ($F_{1, 63} = 9.33$, $p = 0.003$, $\eta_p^2 = 0.129$). However, *post hoc* analysis showed the interaction effect was primarily driven by task rather than treatment with both treatment groups showing faster response latencies for pro-saccades relative to anti-saccades (OXT: anti-saccade: Mean ± SEM = 272.81 ± 4.18, pro-saccade: Mean ± SEM = 164.52 ± 3.53, $p < 0.001$, Cohen's $d = 4.89$; PLC: anti-saccade: Mean ± SEM = 262.82 ± 4.11, pro-saccade: Mean ± SEM = 171.608 ± 3.47, $p < 0.001$; Cohen's $d = 3.68$).

The mixed ANOVA including stimuli as a factor revealed a significant three-way (stimulus × treatment × task) interaction ($F_{5, 315} = 2.63$, $p = 0.042$, $\eta_p^2 = 0.04$). The *post hoc* analysis indicated that anti-saccade response latencies in the OXT group were longer for angry ($p = 0.006$), fear ($p = 0.073$), sad ($p = 0.063$), happy ($p = 0.025$), and neutral ($p = 0.002$) expression faces but not for non-social shapes ($p = 0.498$). There were no differences between individual stimuli (see Figure 2C). In addition, there was a significant task × treatment interaction ($F_{1, 63} = 11.22$, $p = 0.001$, $\eta_p^2 = 0.15$) with *post-hoc* tests indicating that anti-saccade latencies were longer in the OXT compared to the PLC group (OXT: Mean ± SEM = 273.77 ± 4.18, PLC: Mean ± SEM = 259.62 ± 4.12, $p = 0.02$, Cohen's $d = 0.55$). The main effects of stimuli and task were also significant ($F_{5, 315} = 5.26$, $p = 0.001$, $\eta_p^2 = 0.08$; $F_{1, 63} = 1057.74$, $p < 0.001$, $\eta_p^2 = 0.94$) with pairwise comparisons of stimuli showing saccade latencies for angry ($p = 0.030$) and fear ($p = 0.020$) faces were faster than those for shapes.

Oral oxytocin effects on anxiety and mood

After treatment and performing the task there was a significant reduction in state anxiety (SAI) scores in the OXT compared to the PLC group (*t*-test, $p = 0.043$) (see Table 1). Paired *t*-tests conducted on pre- compared to post-task SAI scores showed that SAI scores were significantly decreased in the oral OXT group ($t = -3.30$, $p = 0.0026$) but not the PLC group ($t = -1.251$, $p = 0.22$). For mood scores both PANAS positive and negative scores were significantly reduced in both the OXT (positive $t = -5.14$, $p < 0.001$; negative $t = -2.49$, $p < 0.001$) and PLC (positive $t = -3.62$, $p = 0.001$; negative $t = -4.55$, $p < 0.001$) groups but there were no differences between treatments (see Table 1).

Plasma oxytocin concentration changes in the main experiment and association with attention and state anxiety

A 2 × 2 mixed parametric ANOVA was performed with plasma OXT concentration as the dependent variable, and time point (time 0 and +30 min) and treatment group (OXT/PLC) as independent variables. Results showed a significant main effect of time point ($F_{1,\ 63} = 21.76$, $p < 0.001$, $\eta_p^2 = 0.26$) but not treatment ($F_{1,\ 63} = 0.007$, $p = 0.93$) and a treatment × time point interaction ($F_{1,\ 63} = 14.75$, $p = 0.001$, $\eta_p^2 = 0.19$, see Figure 3A). The Bonferroni-corrected *post-hoc* tests revealed a significantly greater increase in plasma OXT concentration in the OXT compared to the PLC group ($p < 0.001$). A further mixed ANOVA with SAI score as the dependent variable and time (before/post-task) and treatment (OXT/PLC) as factors revealed a significant main effect of time ($F_{1,\ 62} = 9.74$, $p = 0.003$, $\eta_p^2 = 1.36$) with individuals in both treatment groups reporting reduced SAI scores after the test. A similar ANOVA analysis on PANAS positive ($F_{1,\ 62} = 26.56$, $p < 0.001$, $\eta_p^2 = 0.3$) and negative ($F_{1,\ 62} = 52.25$, $p < 0.001$, $\eta_p^2 = 0.46$) scores also revealed main effects of time due to a reduction in scores post-task (see Table 1). There were no significant time × treatment interactions for SAI or PANAS scores (all $ps > 0.142$).

Pearson correlation analysis indicated that both OXT ($r = 0.27$, $p = 0.15$) and PLC ($r = 0.43$, $p = 0.02$) groups had a positive correlation between the percentage changes in OXT concentrations 30-min after treatment and mean anti-saccade errors, although this only reached significance in the PLC group. There was no difference between the two groups however (Fisher's $z = -0.651$, $p = 0.258$) and so to increase statistical power, we therefore combined treatment groups and observed a robust positive correlation between percentage changes in OXT concentrations and anti-saccade errors ($r = 0.411$, $p < 0.001$) (see Figure 3B) but not latencies ($r = 0.077$, $p = 0.542$) or post-task reductions in state anxiety ($r = -0.214$, $p = 0.095$). There were no significant associations with post-task reductions in PANAS scores ($ps > 0.553$) or between task performance and pre- or post-task SAI scores (all $rs < -0.21$, $ps > 0.25$).

Comparison of different routes of oxytocin administration on attention control and state anxiety

A total of 201 subjects from the three studies were included in this analysis resulting in an estimate of 78% power achieved by the 3-factor ANOVAs (G*Power) for a medium effect size ($f = 0.25$) and $\alpha = 0.05$. Given that significant effects of all three routes of OXT administration (intranasal, lingual, and oral) were on top-down attention control (i.e., anti-saccade errors and response latencies) we only compared the relative efficacy of the different routes in the anti-saccade task. A non-parametric route (intranasal/lingual/oral) × treatment (OXT/PLC) × condition (social/non-social) mixed ANOVA-type test on anti-saccade error rate showed significant main effects of condition ($F_{1,\ 8} = 61.50$, $p < 0.001$), treatment ($F_{1,\ 185.79} = 22.48$, $p < 0.001$) and route ($F_{2,\ 185.79} = 10.60$, $p < 0.001$) and a route × condition interaction ($F_{1.99,\ 8} = 5.45$, $p = 0.004$). *Post hoc* Bonferroni-corrected Mann–Whitney *U*-tests showed anti-saccade error rates were higher for oral compared to lingual administration for social cues ($z = -3.045$; $p < 0.05$) and compared to lingual ($z = -4.287$; $p < 0.001$) and intranasal ($z = -3.922$; $p < 0.001$) administration for non-social cues. No other significant main or interaction effects were observed (all $ps > 0.595$). Given that OXT administration increased both social and non-social anti-saccade error rates we additionally compared its efficacy across routes specifically for social anti-saccade error rates on social stimuli. A Scheirer–Ray–Hare test for route (intranasal/lingual/oral) × treatment (OXT/PLC) was performed using the R-package "rcompanion," and results showed significant main effects of treatment ($H = 9.40$, $p = 0.009$) and route ($H = 16.16$, $p < 0.001$). Bonferroni-corrected Dunn tests showed oral administration produced higher anti-saccade error rates compared to lingual ($p_{adj.} = 0.008$), but the interaction between them was not significant ($H = 0.14$, $p = 0.93$) (see Figure 4A).

To further investigate potential administration route-dependent effects of OXT effect on specific stimuli a mixed ANOVA with stimuli (angry/fear/happy/neutral/sad/shapes) and route (intranasal/lingual/oral lollipop) and treatment (OXT/PLC) as factors was performed for anti-saccade error rates. There were main effects of stimuli ($F_{4.07,\ 8} = 20.51$, $p < 0.001$), treatment ($F_{1,\ 184.19} = 22.25$, $p < 0.001$) and route ($F_{2,\ 184.19} = 6.29$, $p = 0.002$), and a stimuli × route interaction ($F_{7.97,\ 8} = 2.89$, $p = 0.003$). The *Post hoc* Bonferroni-corrected tests indicated that error rates for shape stimuli following oral administration were significantly higher than for lingual ($z = -4.287$, $p < 0.001$) and intranasal ($z = -3.922$, $p < 0.01$). There were no other significant interactions (all $ps > 0.638$). Overall, these results suggest that OXT evoked similar increases in anti-saccade errors across different facial expressions following all three routes of administration. However, the inclusion of more complex non-social stimuli in the current oral administration study increased the number of anti-saccade errors compared to the previous lingual and intranasal studies using simpler shape stimuli.

A similar route × treatment × condition mixed ANOVA analysis for anti-saccade response latencies only revealed a condition × treatment interaction ($F_{1,\ 195} = 18.98$, $p < 0.001$, $\eta_p^2 = 0.089$). *Post hoc* Bonferroni-corrected tests indicated that response latencies were significant longer in the OXT than PLC group for the social stimuli condition (see Figure 4B). There were no

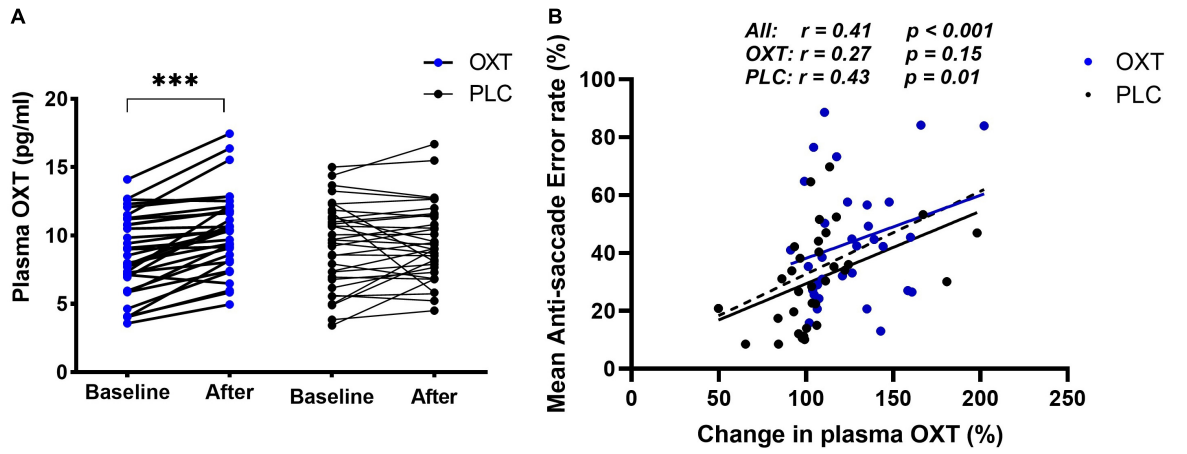

FIGURE 3
Effect of oral oxytocin (OXT) on plasma concentration of OXT in the main experiment **(A,B)** correlations between % anti-saccade errors and % change in plasma OXT 30 min after oral OXT or PLC administration. The correlation data points and regression lines for OXT (blue) and PLC (black) groups are shown both separately and combined (dashed line). ***$p < 0.001$ *t*-test.

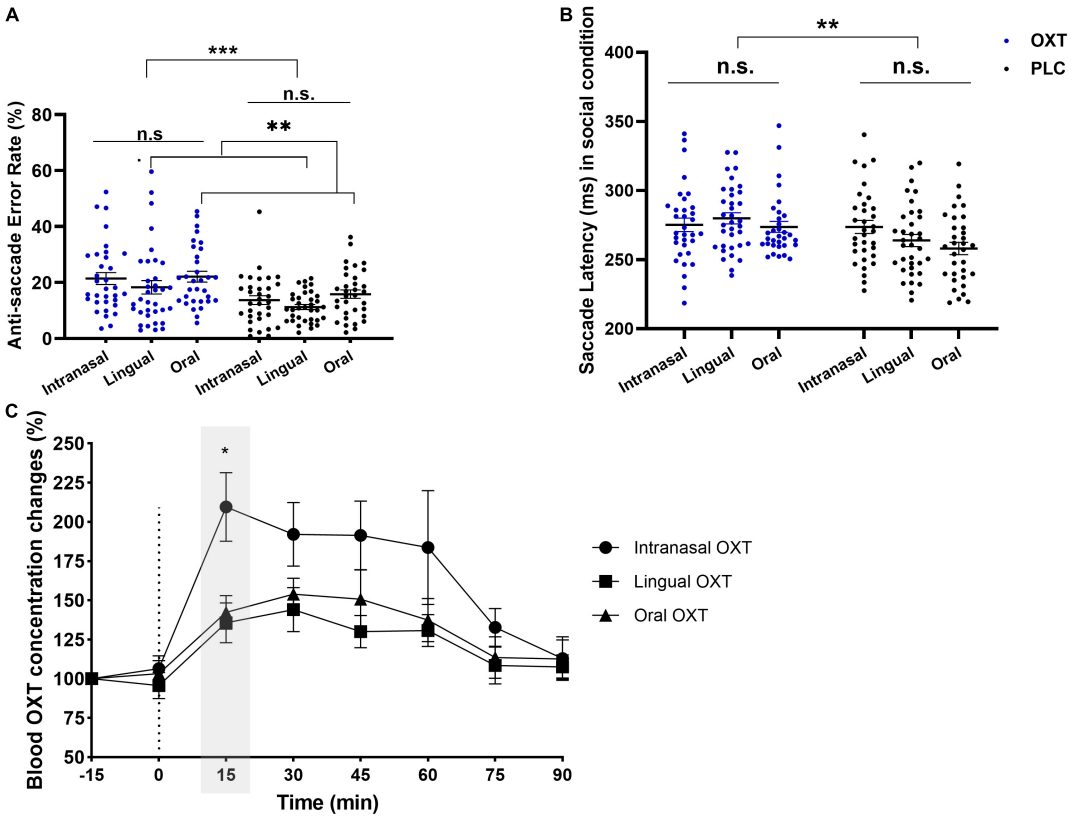

FIGURE 4
The comparative results of intranasal, lingual, and oral on error rates, saccade latencies, and peripheral OXT concentrations. **(A)** Significant treatment ($H = 9.40$, $p = 0.009$) and route ($H = 16.16$, $p < 0.001$) main effects to social cues on anti-saccade errors were observed, and oral administration produced higher errors than lingual ($p_{adj.} = 0.008$). **(B)** Bonferroni-corrected pairwise comparisons of condition × treatment ($F_{1, 195} = 18.98$, $p < 0.001$, $\eta_p^2 = 0.089$) showed longer anti-saccade latencies to social cues in OXT group compared to PLC ($p = 0.002$). **(C)** Changes in peripheral OXT concentration only showed a time main effect ($F_{4.95, 8} = 52.43$, $p < 0.001$), and the exploratory Bonferroni-corrected multiple comparison showed OXT concentration in intranasal was significantly higher than lingual ($z = 2.413$; $p_{Bonferroni-corrected} < 0.05$) at 15 min. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

other significant main or interaction effects (all *ps* > 0.126). A stimuli × treatment × route ANOVA again revealed a main effect of treatment ($F_{1, 195} = 6.250$, $p = 0.013$, $\eta_p^2 = 0.031$) and stimuli × treatment interaction ($F_{5, 975} = 12.48$, $p < 0.001$, $\eta_p^2 = 0.060$). *Post hoc* Bonferroni-corrected tests showed response latencies in the OXT group were longer than in the PLC group across all stimuli (all *ps* < 0.032). No other significant main effects or interactions were observed (all *ps* > 0.116).

A route × treatment ANOVA performed on pre- vs. post-task differences in SAI scores also revealed a main effect of treatment ($F_{2, 192} = 3.296$, $p = 0.035$ one-tailed, $\eta_p^2 = 0.016$) and no significant route × treatment interaction ($F_{2, 192} = 0.497$, $p = 0.609$) indicating an absence of differences between the routes of OXT administration.

In accordance with recent recommendations in the field (Quintana, 2022) we additionally examined the robustness of the non-significant findings for the comparison between different routes of OXT administration by performing Bayesian ANOVAs on anti-saccade errors and latencies for social stimuli. Results showed a satisfactory moderate fit for anti-saccade errors ($BF_{01} = 5.29$) and latencies ($BF_{01} = 6.84$). Similarly, for SAI scores the Bayes analysis revealed a moderate fit ($BF_{01} = 8.10$). Thus, overall this Bayesian analysis confirmed the lack of any administration route-dependent effects of OXT on top-down attention or state anxiety.

Exploratory comparison of changes in peripheral oxytocin concentrations following intranasal, lingual or oral administration

A comparison of changes plasma in OXT concentrations over time with different routes of administration was also carried out, with data for intranasal ($n = 15$) and lingual ($n = 10$) routes from a previous report (Kou et al., 2021). The route × time non-parametric ANOVA showed a significant main effect of time ($F_{4.95, 8} = 52.43$, $p < 0.001$). No other effects were significant (all *ps* > 0.211). The Bonferroni-corrected multiple comparison showed OXT concentrations following intranasal administration were significantly higher than after lingual ($z = 2.413$; $p < 0.05$) administration (see **Figure 4C**).

Discussion

In an initial pilot experiment, we confirmed that administration of OXT orally using a medicated lollipop approach significantly increased plasma OXT concentrations at 15 and 30 min after administration and concentrations in saliva were greatly increased after both 30 min and 2 h. The profile of increased plasma OXT concentrations was similar to that previously reported following lingual administration, although lower than initially (15 min) after intranasal administration (Kou et al., 2021). In the main experiment investigating the effects of oral OXT on visual attention results showed that compared with oral PLC it increased anti-saccade error rates to social and non-social cues, but only increased response latencies to social cues, with similar treatment effects across the different face emotions. Plasma OXT concentrations were again significantly increased 30 min after oral OXT administration and overall percentage concentrations changes were positively associated with anti-saccade errors. Finally, a comparison analysis with previous studies reporting effects of intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) administration of OXT revealed no significant differences between the three routes of administration on either anti-saccade error rates or response latencies suggesting that they had similar effects on top-down attention. Overall, the findings from this study support the therapeutic potential for oral administration of OXT using a medicated lollipop approach both for increasing peripheral OXT concentrations and for influencing top-down attention.

Both a validation pilot experiment and the main experiment confirmed that oral administration of OXT using a medicated lollipop approach significantly increased plasma OXT concentrations. The pilot study, where samples were taken at 15 min intervals for 2 h after oral administration, showed that plasma OXT concentrations rose significantly after 15 min and peaked at 30 min (around a 50% increase) but thereafter returned to baseline. In the main experiment plasma OXT concentrations were also increased at 30 min after administration. Parallel measurements in saliva revealed an expected very large increase in OXT concentrations after 30 min (30-fold) which remained increased after 2 h (5-fold), confirming the efficacy of the approach for producing large and long-lasting increases in the oral cavity and thus also influencing blood levels for a long period. Comparisons of the magnitude and time-course of increased OXT concentrations across the same dose (24IU) administered via oral, lingual and intranasal routes revealed no difference between oral and lingual although intranasal administration produced the greatest initial concentration changes (after 15 min). While peripheral basal OXT concentrations may not reliably reflect those in the brain, a recent meta-analysis has shown that peripheral changes evoked by both stress and intranasal OXT administration do more accurately reflect similar changes in the brain (Valstad et al., 2017).

The anti-saccade paradigm used in the current and previous studies can reveal treatment effects on both top-down (shifting attention away from a stimulus–indexed by anti-saccade errors and latencies) and bottom-up attention (shifting attention toward a stimulus–indexed by pro-saccade errors and latencies).

Consistent with the previous results for intranasal (Xu et al., 2019) and lingual spray (Zhuang et al., 2021) administration, OXT modulated top-down attention by increasing anti-saccade error rates for both social and non-social stimuli but only increasing anti-saccade latencies for social stimuli. In support of our hypothesis, there was also a positive overall association between changes in plasma OXT concentrations and anti-saccade errors, suggesting that they reflect functional effects in line with our previous study (Kou et al., 2021). However, interestingly the changes in plasma OXT concentrations were more significantly correlated with anti-saccade errors in the PLC than in the OXT group, suggesting that the pattern of endogenous OXT changes in the blood preceding the anti-saccade task are also influencing task performance. Both marked increases and decreases in endogenous levels were observed in some individuals in the PLC group (see **Figure 3A**), due perhaps to stress-related effects of blood sampling and/or anticipation of performing the eye-tracking task. Indeed, a meta-analysis has reported that stronger associations between OXT and cortisol concentrations occur in individuals anticipating having to perform a task (Brown et al., 2016). Overall, these findings suggest that OXT can interfere with control of top down attention for both social and non-social stimuli in terms of accuracy (Hovey et al., 2020) but its overall influence is strongest for social stimuli (face emotions), evidenced by increased response latencies, indicating an overall greater impact of social stimuli on weakening top-down attention control. Thus, OXT administration makes it more difficult for individuals to shift their attention away from social stimuli in particular. This finding is consistent with those from a previous studies using other paradigms (Averbeck, 2010; Yao et al., 2018).

Oral OXT also significantly reduced post-task SAI scores similar to our previous findings with lingual (Zhuang et al., 2022) and intranasal (Xu et al., 2019) administration and scores were significantly different between the OXT and PLC groups after the task. There were also significant reductions in PANAS mood scores in both OXT and PLC groups, which may reflect experiment fatigue. It is still unclear whether post-task reductions in state anxiety we have observed following OXT treatment in the current study as well as following intranasal and lingual administration (Xu et al., 2019; Zhuang et al., 2022) are due to an anxiolytic effect of the peptide *per se* or some form of interaction with the anti-saccade task. However, in confirmation of findings with lingual administration of OXT (Zhuang et al., 2022) we found no significant correlations between SAI scores and performance on the attention task and thus the two effects of OXT may be independent. Future experiments investigating anxiolytic effects of oral OXT will need to use other more typical paradigms specifically designed for inducing increased anxiety.

A comparative analysis of the effects the three routes of OXT administration on increased anti-saccade error rates and response latencies did not reveal any significant route-dependent differences. A Bayes analysis confirmed the lack of route-dependent significant differences with a moderate fit. This suggests that oral administration of OXT via a medicated lollipop has a similar effect on top-down attention as intranasal and lingual sprays. Similarly, the reduction in state anxiety following oral OXT was also similar across the three different routes of administration and confirmed by Bayes analysis showing a moderate fit. Thus, overall the functional effects of exogenously administered OXT on both top-down attention and state anxiety appear to be route-independent.

One minor difference between the results of the current experiment and those previously reported following intranasal and lingual oxytocin is that more anti-saccade errors were made in response to the non-social stimuli. The non-social stimuli in the current experiment were adapted to better match the stimulus complexity with the face expressions used and this appears to have increased the difficulty in shifting attention away from them. However, most importantly the modulatory effects of OXT were similar to those found after intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) administration.

A major topic of discussion regarding the functional effects of exogenously administered OXT concerns the route(s) by which functional effects are produced. On the one hand, intranasal OXT can enter the brain directly through the olfactory and trigeminal nerves to exert its functional effects (see Yao and Kendrick, 2022). However, it can also produce functional effects after entering the peripheral blood system through the highly vascularized nasal cavity (as well as dripping down into the oral cavity). Following entry into the peripheral blood system, OXT may potentially influence brain and behavior either by binding to RAGE and crossing the BBB or via stimulation of vagal projections via its receptors in the heart and gastrointestinal system (Quintana et al., 2021; Yao and Kendrick, 2022), although this remains to be fully established. On the other hand, administration of OXT via oral or lingual spray routes can only produce functional effects via increasing concentrations in peripheral blood (Tabbaa and Hammock, 2020; Yao and Kendrick, 2022). Given that all three delivery routes have in common only peripherally mediated effects, and produce very similar effects on top-down attention and anxiety, this argues strongly that endogenously administered OXT is acting primarily by increasing peripheral concentrations. This is supported by a previous finding that both intranasal (Xu et al., 2019) and lingual (Zhuang et al., 2022) administration of OXT can influence neural responses to emotional faces. However, in this case the patterns of functional effects observed following intranasal and lingual administration on both brain and behavior were different, suggesting that exogenously administered OXT may exert some distinct functional effects following direct entrance into the brain or indirectly after entering peripheral blood. The temporal and spatial patterning of influences on regional OXT

receptors via these different routes will also be somewhat different. Thus, it is possible that the route via which exogenously administered OXT produces functional effects may be influenced by both pharmacodynamic factors such as dose (Spengler et al., 2017; Quintana et al., 2021) or task modality (Horta de Macedo et al., 2014) or stimulus salience (Koch et al., 2014; Hovey et al., 2020). Future studies will need to further clarify dose, task and context-dependent influences on effects of direct- compared to indirectly mediated functional effects of exogenously administered OXT on both brain and behavior.

The present study has several limitations. First, only male participants were included in line with previous studies investigating effects of intranasal and lingual oxytocin (Xu et al., 2019; Zhuang et al., 2022), and to avoid potential influences of the menstrual cycle on OXT concentrations. However, sex-dependent differential effects of OXT have been found in several previous studies (Rilling et al., 2014; Gao et al., 2016; Bredewold and Veenema, 2018), so future studies will need to examine effects of oral OXT in female subjects. Secondly, while post-task reductions in state anxiety levels were consistent across different routes of OXT administration future experiments need to confirm anxiolytic effects using other tasks. Thirdly, since positive associations between task performance and changes in plasma OXT following oral treatment occurred in both the OXT and PLC groups, particularly in the latter, it is difficult to differentiate between endogenously and exogenously derived functional effects which would require larger sample sizes and a dose-response approach. Lastly, the sample sizes of the groups in the exploratory comparative analysis of peripheral OXT concentrations were small, and the levels of peripheral OXT concentrations and their trends under the three routes of administration need validation in larger sample sizes.

In conclusion, the current study has validated the use of an oral administration route for OXT using a medicated lollipop approach both for increasing blood and saliva concentrations of OXT and for producing functional effects on top-down attention. Importantly, the effects of oral OXT both on top-down attention and state anxiety were similar to those found following intranasal or lingual administration routes and suggest its potential use therapeutically, particularly in young children in the context of autism. Additionally, these findings support the view that important functional effects of exogenously administered OXT can be mediated via increased peripheral concentrations as opposed to via direct entry into the brain which can only occur via an intranasal route.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Electronic Science and Technology of China Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

KK designed the study and provided the critical revisions. DX and QL collected the data. DX and YZ completed the ELISA analysis. DX, QZ, SY, and WZ analyzed the data. DX drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.1022101/full#supplementary-material

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Missing pieces in decoding the brain oxytocin puzzle: Functional insights from mouse brain wiring diagrams

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The hypothalamic neuropeptide, oxytocin (Oxt), has been the focus of research for decades due to its effects on body physiology, neural circuits, and various behaviors. Oxt elicits a multitude of actions mainly through its receptor, the Oxt receptor (OxtR). Despite past research to understand the central projections of Oxt neurons and OxtR- coupled signaling pathways in different brain areas, it remains unclear how this nonapeptide exhibits such pleiotropic effects while integrating external and internal information. Most reviews in the field either focus on neuroanatomy of the Oxt-OxtR system, or on the functional effects of Oxt in specific brain areas. Here, we provide a review by integrating brain wide connectivity of Oxt neurons and their downstream circuits with OxtR expression in mice. We categorize Oxt connected brain regions into three functional modules that regulate the internal state, somatic visceral, and cognitive response. Each module contains three neural circuits that process distinct behavioral effects. Broad innervations on functional circuits (e.g., basal ganglia for motor behavior) enable Oxt signaling to exert coordinated modulation in functionally inter-connected circuits. Moreover, Oxt acts as a neuromodulator of neuromodulations to broadly control the overall state of the brain. Lastly, we discuss the mismatch between Oxt projections and OxtR expression across various regions of the mouse brain. In summary, this review brings forth functional circuit-based analysis of Oxt connectivity across the whole brain in light of Oxt release and OxtR expression and provides a perspective guide to future studies.

KEYWORDS

oxytocin, neural circuit, oxytocin receptor (OxtR), wiring diagram, mice

Introduction

Oxytocin (Oxt) was originally identified in 1906 as the primary molecule involved in parturition and lactation (Dale, 1906). Further studies over the past centenary identified this nonapeptide's role in regulating multiple other behaviors both in the central and peripheral nervous systems (Lee et al., 2009; Jurek and Neumann, 2018; Lefevre et al., 2021; Wang et al., 2022). As further studies elucidate this molecule's impact on brain and body systems, efforts to explore and establish the brain circuit level mechanisms of Oxt's functional control have proliferated. However, most prior effort has been focused on specific behaviors with selected brain areas. Although these divide-and-conquer approaches have been critical in establishing the role of Oxt in individual brain regions, uniting these studies to gain a broad circuit-based understanding of the multitude of Oxt functions that modulate brain processing has been challenging. Here, we provide an integrated view to link Oxt's influence on connected neural circuits with the different behaviors Oxt evokes. Thus, we aim to present new insights into the relationship between Oxt's anatomy and function.

Oxytocin: A historical perspective

Sir Henry H Dale, a British physiologist, initially discovered that extracts from pituitary glands (from oxen) when administered intravenously facilitated contractions of the uterus (Dale, 1906). In 1909, gynecologist William Blair Bell performed investigations that proved that pituitary extracts facilitated uterine contractions and helped with fetal delivery (Bell, 1909). In the following year, another study demonstrated a role for the same extract in milk ejection in animals (Ott and Scott, 1910). With the advancement in biochemical methods, the chemical structure of the molecule Oxt was identified in 1953 (Tuppy, 1953) and synthesized by Vincent du Vigneaud in 1954 (du Vigneaud et al., 1954). Further studies in the following years identified the neurons that produced Oxt (Bargmann and Scharrer, 1951) and the receptor that Oxt binds to (Gimpl and Fahrenholz, 2001). For more details, we refer to previous papers describing the long history of Oxt starting as a facilitator of parturition to how it reached its current status of a social hormone that functions within the brain (Lee et al., 2009; Carson et al., 2013; Froemke and Carcea, 2017; Jurek and Neumann, 2018).

Neuroanatomy and functions of Oxt neurons

Oxt is synthesized mainly in the paraventricular hypothalamus (PVH) and the supra optic nucleus (SO) along with a smaller number of neurons in the accessory nuclei of the hypothalamus and extended amygdala (Freda et al., 2022; Son et al., 2022). In addition, our recent study identified a dense cluster of Oxt neurons in the tuberal nucleus area (TU) of the hypothalamus in the mouse brain (Son et al., 2022). Oxt functions mainly through a single Oxt receptor (OxtR) that is expressed on the target tissues throughout the body, and enriched in most parts of the brain (Gimpl and Fahrenholz, 2001; Assinder, 2022). Oxt elicits its actions through OxtRs in the peripheral system to regulate gastric motility, heart rate, breathing, vasodilation and regulation of blood glucose levels via insulin (Filipov and Kasakov, 1978; Higa et al., 2002; Mack et al., 2002; Welch et al., 2014; Pozo and Claret, 2018). In the central nervous system, Oxt is known to regulate multiple aspects of social behaviors including recognition, memory, pair bonding and maternal bonding (Nagasawa et al., 2012; Oettl et al., 2016; Ophir, 2017; Raam et al., 2017). Oxt is also known to exert its effects on sleep, reward systems, and several aspects of sensory systems ranging from olfaction and taste to vision and hearing (Hung et al., 2017; Grinevich and Stoop, 2018; Raymond et al., 2021). Not surprisingly, dysfunctional Oxt signaling has been implicated in several neurological disorders, most notably autism spectrum disorder (ASD) and even Alzheimer's Disease (Ishunina and Swaab, 2002; Yamasue and Domes, 2018; Szczepanska-Sadowska et al., 2022).

Mismatch between Oxt projections and OxtR: Implications on Oxt release mechanisms

The widespread expression of OxtRs compared to relatively fewer areas of Oxt neuronal projections throughout the brain has been a puzzling problem in the field over the past few decades. This led to multiple hypotheses on the release mechanisms of Oxt (Chini et al., 2017). But recent literature suggests most OxtR enriched areas contain at least sparse projections in the rat brain (Grinevich et al., 2016). In our recent publication, we quantified and compared Oxt projections and OxtR density in the whole mouse brain. Except for regions within the thalamus and medulla, our analysis revealed no significant quantitative correlation between Oxt projection and OxtR density in most brain areas (Son et al., 2022). For example, most regions within the cerebral cortex of the mouse brain are enriched with OxtRs, but the Oxt projection fibers are sparse. However, Oxt modulates multiple behaviors by its effect in the cerebral cortex. For example, Oxt reduces GABAergic inhibition in cortical areas like the auditory areas (AUD) and piriform areas (PIR) to enhance the auditory and olfactory responses (Marlin et al., 2015; Mitre et al., 2016). Another example is the main olfactory bulb (MOB) which has abundant OxtRs but very minimal to null Oxt projections. Oxt addition to

the MOB resulted in enhanced neuronal activity. Conversely, many hindbrain areas (hindbrain reticular nuclei) have Oxt projections and little to no OxtRs in the mouse brain. This suggests that Oxt signaling mechanisms could be different from the canonical synaptic transmission with direct projection. For example, Oxt uptake to the MOB is postulated to occur via a trans ventricular pathway [cerebrospinal fluid (CSF)-Subarachnoid-lymphatic system] (Veening et al., 2010). This is a very feasible pathway considering the distance between MOB to Oxt producing neurons, and the presence of Oxt fibers along the sides of the 3^{rd} ventricle (Son et al., 2022). Further studies are required to confirm ventricular release of Oxt and the brain regions that uptake Oxt from the trans ventricular pathway.

Another hypothesis postulates that Oxt released into the blood stream is further transported to the CSF through the receptor for advanced glycation end-products (RAGE) (Yamamoto et al., 2019). This hypothesis is relevant for the uptake of externally administered Oxt to reach the brain, whether or not endogenous Oxt follows this pathway is still debated in the field. To add to the complexity, Oxt is also released from somata and dendrites (Ludwig, 1998). This release is mostly evoked by other peptides. Oxt itself can exert a feed forward activation of PVH and SO Oxt producing neurons, in turn resulting in further Oxt release (Moos et al., 1984; Neumann et al., 1996; Hirasawa et al., 2004). Oxt is also released *en passant*, a synapse independent mechanism, resulting in the release of a small number of vesicles at a specific target region. This is a diffusion based slow release of Oxt resulting in 60-90s delayed responses (Chini et al., 2017). Site specific dendritic release explains the mismatch between CSF concentrations and site specific concentrations of Oxt (Ludwig and Leng, 2006). It is also believed that dendritic release of Oxt causes excitation of nearby (100 um) neurons of a different nature, thus mediating population level cross talk between neurons at a specific site (Son et al., 2013). All these evidence cumulatively suggest site specific release as well as diffusion based and CSF based transport of Oxt, that can explain the mismatch between Oxt fibers and OxtRs. Hence, it is important to carefully analyze the brain areas that are enriched with projection fibers to understand the site-specific release associated functions of Oxt.

In subsequent sections, we link neural connectivity and the diverse functional effects of Oxt with OxtR expression and broadly classify brain regions with Oxt connections into three major functional modules; **internal state control, somatic visceral control and cognitive control** (Son et al., 2022). These modules are clustered based on known functions of regions (All abbreviations can be found in **Table 1**). Each module is further divided into three inter-connected circuits to process distinct information. Here, we will review individual circuits with their function and contribution of Oxt signaling to shape signal processing. Moreover, we compare whole brain Oxt projections with OxtR density and highlight the main areas of apparent discrepancies to discuss the functional relevance of Oxt in these mismatched areas.

Oxytocin associated circuitry in internal state control

Internal state can be defined as the combination of cellular and metabolic activities that modify the sensory information representation and the communication between body and brain (Kanwal et al., 2021). The main characteristic that delineates the internal state node is the regulation of baseline neural conditions that attenuate other responses within the body. This means that while internal state control does not regulate fast responses to stimuli, this control can create a predisposition to certain responses. As such, alterations to the internal state have broad influence on levels of attention, alertness and aggression, sleep, arousal and more (**Figure 1**).

Internal state module: Attention

Attention can be defined as the cognitive and behavioral processes that allow one to preferentially select relevant information present in the environment as well as avoid irrelevant information (Sarter et al., 2001). Most of the brain regions in the attention circuit receive Oxt projection fibers and express OxtRs to modulate the behavioral response. The two major attention systems in the brain include the cholinergic system of the basal forebrain (BF) and norepinephrine system of the locus ceruleus (LC).

Multiple areas of the BF- diagonal band nucleus (NDB), substantia innominata (SI), magnocellular nucleus (MA) and medial septal nucleus (MS) release acetylcholine upon receiving an attention relevant cue in the rat brain (Záborszky et al., 2018; Laszlovszky et al., 2020). Although there is no direct evidence to prove that Oxt modulates attention in rodent studies, hypothalamic Oxt neurons send their long-range projections to both the BF and the LC (Son et al., 2022). Moreover, the BF is an area that is also enriched in OxtRs, suggesting the possibility of Oxt modulation of the BF attention circuit (Newmaster et al., 2020). In human postmortem samples of Autism Spectrum Disorder (ASD) patients, Oxt binding to OxtR was found to be reduced in the Nucleus Basalis of Meynert (NBM), a subset of neurons in the SI, suggesting the role of Oxt in disease progression of ASD (Freeman et al., 2018). Recent clinical studies also point toward the role of Oxt in modulation of social attention. Intranasal Oxt administration improved socially directed gaze and increased attention allocation to familiar faces (Freeman et al., 2018; Marsh et al., 2021). Moreover, intranasal Oxt enhanced the attention allocation to faces in autistic individuals (Kanat et al., 2017).

TABLE 1 List of abbreviations.

Abbreviations	Full names
AI	agranular insular area
AOB	accessory olfactory bulb
AON	anterior olfactory nucleus
ARH	arcuate hypothalamic nucleus
AUD	auditory areas
BF	basal forebrain
BMA	basomedial amygdalar nucleus
BST	bed nucleus of stria terminalis
CEA	central amygdalar nucleus
CP	caudoputamen
CU	cuneate nucleus
DMH	dorsomedial nucleus of the hypothalamus
DMX	dorsal motor nucleus of the vagus nerve
DR	dorsal raphe nucleus
GPe	globus pallidus, external segment
GPi	globus pallidus, internal segment
GU	gustatory areas
IC	inferior colliculus
LC	locus ceruleus
LG	lateral geniculate complex
LHA	lateral hypothalamic area
LPO	lateral preoptic area
LS	lateral septal nucleus
MEPO	median preoptic nucleus
MG	medial geniculate complex
MO	somatomotor areas
MOB	main olfactory bulb
mPFC	medial prefrontal cortex
MY	Medulla
NTS	nucleus of the solitary tract
OT	olfactory tubercle
PAG	periaqueductal gray
PB	parabrachial nucleus
PGRN	paragigantocellular reticular nucleus
PIR	piriform area
PPN	pedunculopontine nucleus
PRN	pontine reticular nucleus
PRT	pretectal region
PVH	paraventricular hypothalamic nucleus
RM	nucleus raphe magnus
SC	superior colliculus
SCH	suprachiasmatic nucleus
SLC	subceruleus nucleus
SNr	substantia nigra, reticular part
SOC	superior olivary complex
SS	somatosensory areas
STN	subthalamic nucleus
TH	Thalamus
VII	facial motor nucleus
VIS	visual areas
VMH	ventromedial hypothalamic nucleus
VPL	ventral posterolateral nucleus of the thalamus
VPM	ventral posteromedial nucleus of the thalamus
VPMpc	ventral posterolateral nucleus of the thalamus, parvicellular part

The LC sends adrenergic projections to the medial prefrontal cortex (mPFC), thalamus (TH), BF and many other brain areas (Sara, 2009; Chandler et al., 2019). Oxt is known to increase LC adrenergic receptor responsiveness and thus enhance salience of received cues in rats (Petersson et al., 1998). Optogenetic activation of PVH-Oxt neurons in rat brain resulted in downstream activation of LC-noradrenaline followed by an enhanced attention to novel objects suggesting that Oxt directly regulates attention by modulating LC responses (Wang et al., 2021). The LC also receives monosynaptic inputs from another attention relevant area called the pedunculopontine nucleus (PPN), an area with abundant Oxt neuronal fibers. This suggests multiple levels at which Oxt can modulate attention responses, at either the PPN or LC. Oxt at the PPN can modulate adrenergic response from the LC, thus acting as a neuromodulator of another neuromodulator.

There are several other brain areas along with the BF and LC, that are relevant in the attention circuit. For example, the claustrum (CLA) in primates is an area relevant for top-down control of attention with its extensive connections to the neocortex (Mathur, 2014; Atlan et al., 2018; Zingg et al., 2018). The mouse CLA predicts upcoming movement in between intertrial intervals (Chevée et al., 2022). Interestingly, Oxt neurons project to the CLA-Endopiriform complex in the mouse brain, an area with high density of OxtRs, the functional relevance of which has yet to be explored (Dubois-Dauphin et al., 1992; Newmaster et al., 2020; Biggs and Hammock, 2022).

Internal state module: Threat, alert, and defense states

Fear is a combined response constituting physiological (cardiovascular, respiratory) and behavioral (freeze, fright, startle) counterparts experienced due to an exposure to possible threats that can affect one's survival (Olivera-Pasilio and Dabrowska, 2020). The brain receives external threat (predator) cues to the limbic forebrain and extended amygdala (bed nuclei of stria terminalis, BST; lateral amygdalar nucleus, LA; medial amygdalar nucleus, MEA and central amygdalar nucleus, CEA). Once a threat cue is received, the immediate response is arousal- which activates the downstream defense cascade. Arousal is the state of being awake and alert- mostly regulated

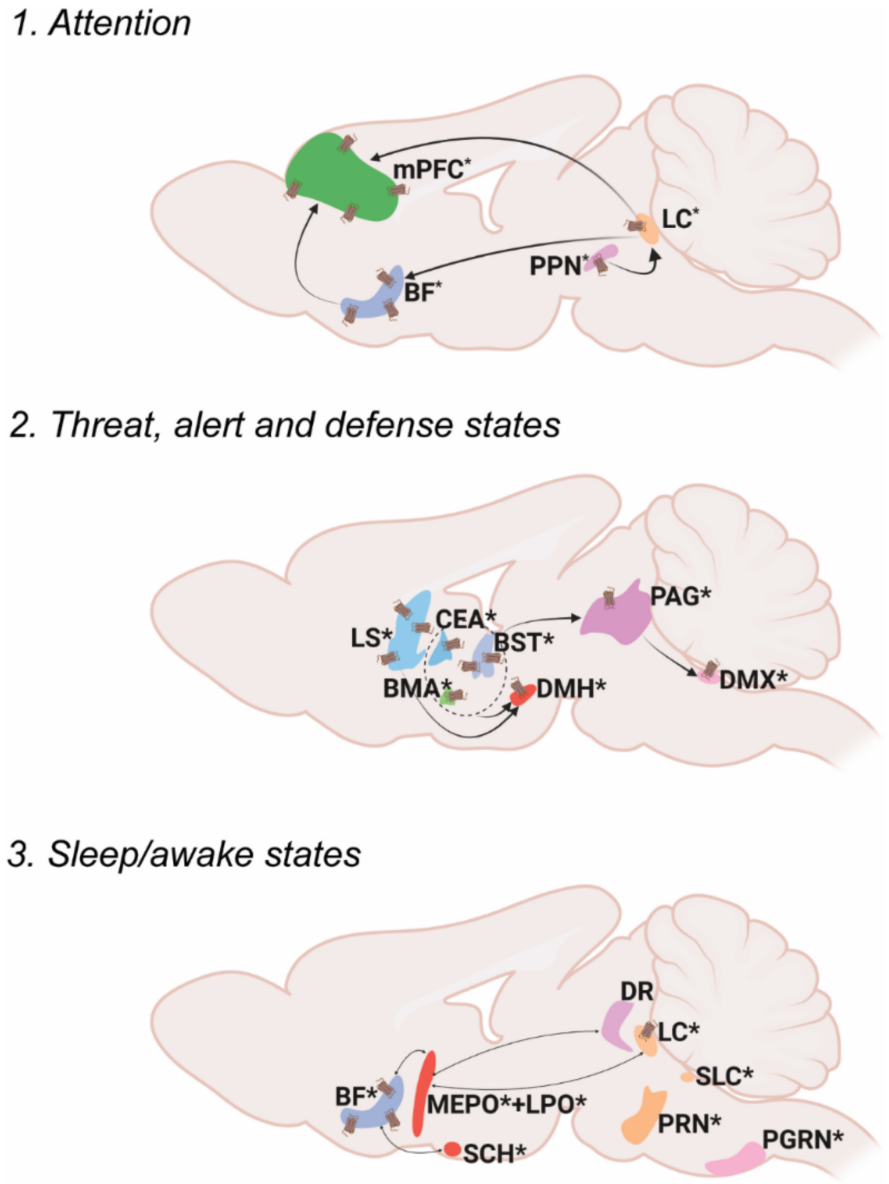

FIGURE 1
Oxt associated circuitry in internal state control. Pathways depicting three different functional circuits: 1. Attention, 2. Threat, alert and defense states, 3. Sleep/awake states. * denotes the presence of Oxt projection fiber in the specified area. Receptor symbol depicts presence of OxtR on the area mentioned. For abbreviations, refer **Table 1**.

by the hypothalamus (ventromedial hypothalamic nucleus, VMH and dorsal premammillary nucleus, PMd)- by increasing the tone in the sympathetic (visceromotor) and autonomic (striated muscles) nervous systems. The next step in the fear response cascade invokes the flight or fight response, resulting in specific motor patterns of flight or fight: attack, run, freeze etc. (Kozlowska et al., 2015). The skeletal muscle activation for fight and attack is mediated through the periaqueductal gray (PAG) whereas visceromotor output (for example, increasing cardiac output) is mediated via the dorsal motor nucleus of the vagus nerve (DMX) (Kozlowska et al., 2015; Deng et al., 2016). Alternatively, the freezing response may occur, which puts on hold the flight or fight response- activated mainly through the vagal pathway from the DMX by inhibiting sympathetic activation (Roelofs, 2017; Roelofs and Dayan, 2022).

Oxt neurons send projections to all these areas, controlling many aspects of fear response. For example, Oxt released from the PVH to the extended amygdala (the CEA and the BST), is critical for regulating fear/threat responses (Duque-Wilckens et al., 2020; Olivera-Pasilio and Dabrowska, 2020). Oxt in the CEA reduces cued fear whereas in the BST, Oxt facilitates cued fear responses and avoids diffuse threats (Knobloch et al., 2012;

Francesconi et al., 2021). Oxt acts mainly by the strong binding of Oxt to OxtRs in the BST and this also creates an anxiogenic effect (Martinon et al., 2019). The brain processes contextual threat cues (predator exposure) slightly different than other threat cues (predator odor). The lateral septum (LS) processes contextual cues and sends responses to the hypothalamus (Cezario et al., 2008). Oxt signaling in the LS regulates social fear during lactation (Menon et al., 2018). Altogether, Oxt can exert differential effects on multiple brain areas after gauging the input threat due to its vast connectivity to interconnected brain areas in the fear circuit.

Internal state module: Sleep/awake states

Sleep can be defined as a fast reversible state of immobility accompanied by reduced neurophysiological and behavioral responses to environmental stimuli (Raymond et al., 2021). Sleep is mainly categorized into REM (rapid eye movement) sleep and NREM (non-rapid eye movement) sleep. Although the complete sleep circuit is unclear, main brain areas and molecules/neurotransmitters that mediate REM and NREM sleep have been identified. The REM/NREM sleep transitions regulate only the short stretches of sleep as opposed to the whole night's sleep regulated through different brain centers (Scammell et al., 2017).

One of the earliest identified sleep promoting areas is the preoptic area (Von Economo, 1930). The NREM active lateral preoptic area (LPO) and median preoptic nucleus (MEPO) neurons are GABAergic and inhibit the attention/alert/wake promoting centers consisting of the BF, dorsal raphe (DR), and LC. These neurons also produce galanin, a neuropeptide very highly associated with sleep regulation (Ma et al., 2019). All the attention/alert centers are also reciprocally connected to the ventrolateral preoptic nucleus (VLPO) to inhibit galanin neurons during awake states. The brain areas active during REM sleep include pontine areas- the subceruleus nucleus (SLC), the pontine reticular formation (PRN), and the paragigantocellular nucleus (PGRN). Most of the sleep active neurons are reciprocally connected with inhibitory neurons in the alert/attention centers and selective activation of one group determines the sleep/wake state (Scammell et al., 2017). The transition between sleep to wake states based on day-night cycles is majorly controlled by the circadian system/biological clock possessed by most animals. The central pacemaker that regulates circadian rhythm is the suprachiasmatic nucleus (SCH). SCH activity oscillates with day-night cycles based on the transcriptional regulation of a group of circadian genes (Eban-Rothschild et al., 2018).

While Oxt has been implicated in this system, Oxt's role in sleep regulation remains relatively understudied. Oxt neurons project to all the previously mentioned major nodes that control REM, NREM and circadian aspects of sleep. Despite the lack of evidence for the exact mechanism of sleep regulation by Oxt, there are several clinical studies implicating better quality sleep with increased Oxt levels in humans. For instance, increased endogenous Oxt in postpartum women facilitates sleep (Comasco et al., 2016). Oxt administration in obstructive sleep apnea patients shortened the duration of apnea (Jain et al., 2017). Although evidence suggests that Oxt improves sleep quality, this could also be attributed to the anxiolytic abilities of Oxt indirectly enhancing sleep (Comasco et al., 2016). However, Oxt levels in sleep deprived Syrian Hamsters were increased in the SO suggesting an endogenous pathway that activates Oxt to regulate sleep. In male rats, intracerebral Oxt administration under stress free conditions enhanced sleep (Lancel et al., 2003). Since Oxt is connected to the main sleep regulatory brain areas and clinical studies show positive sleep regulation, further research understanding the mechanisms by which Oxt modulates sleep could help improve our knowledge of disorders like insomnia, sleep apnea, narcolepsy etc. along with other psychological disorders in which sleep is perturbed.

Oxytocin regulation of somatic/visceral control

Oxt in the somatic/visceral control module share abilities that regulate a host of homeostatic activities and can be further subdivided into three groups: pain controlling areas, areas involved in sensory motor regulation and areas regulating body physiology and metabolism (**Figure 2**).

Somatic/visceral module: Pain

Pain is a distressing sensation and an emotional experience often associated with either actual or potential tissue damage, with the major intention of starting the body's defense mechanisms to react toward the causal stimuli and thus prevent further tissue damage. The ascending pathway carries pain information from the peripheral (dorsal root ganglion) to the central nervous system (PNS and CNS, respectively) while the descending pain pathway brings responses from CNS to the peripheral reflex organs (Yam et al., 2018).

Ascending pain pathways include spinothalamic pathways that relay pain information from the spinal cord to different thalamic areas followed by thalamocortical pathways which relay information from thalamus to the cortical centers (e.g., somatosensory cortex) that process different aspects of pain perception. The medial thalamus (mediodorsal nucleus of thalamus, MD; parafascicular nucleus, PF; central lateral nucleus of the thalamus, CL) sends the emotional and motor related information to the mPFC (e.g., anterior cingulate cortex, ACC). The lateral thalamus (ventral posterolateral nucleus of the thalamus, VPL) conveys sensory pain

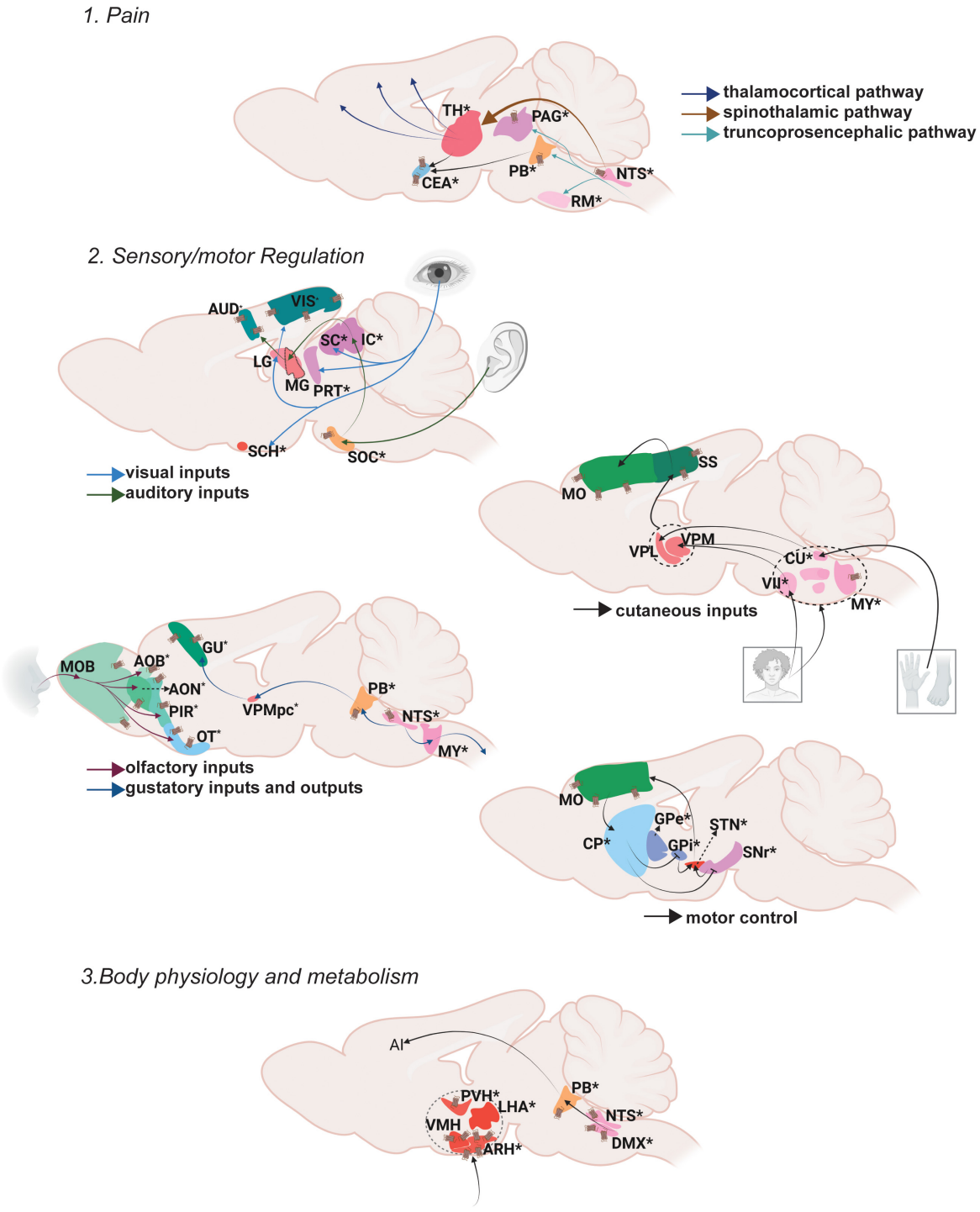

FIGURE 2
Oxt regulation of somatic/visceral Control. Pathways depicting three different functional nodules.1. Pain, 2. Sensory/motor regulation, 3. Body physiology and metabolism. For further details refer, **Figure 1** legend. For abbreviations, refer **Table 1**.

information to the somatosensory cortex (SS), and the posterior thalamus (lateral posterior nucleus of the thalamus, LP; supragenicular nucleus, SGN) relays pain perception and intensity information to the posterior insular cortex (Purves et al., 2001; Khera and Rangasamy, 2021; Mercer Lindsay et al., 2021). Another pathway that carries pain information is the truncoprosencephalic projections that include parabrachial nucleus (PB) connections to the amygdala

and further to the cingulate and the insular cortices (Barik and Chesler, 2020; Kuner and Kuner, 2021). The ascending information also passes through the PAG in the midbrain and rostroventral medulla (RVM) in the hindbrain where the PAG integrates the descending output to the spinal cord (Basbaum et al., 2009). Overall, a vast majority of brain areas especially in the thalamus regulate various aspects of pain processing.

Oxt exerts its effects on both ascending and descending brain regions that modulate pain. Oxt neurons send projections to multiple thalamic areas (Medial: subparafascicular area, SPA; parafascicular nucleus, PF; lateral peripeduncular nucleus, PP) to regulate the ascending pain pathway. Oxt neurons also send projections to the PB and various amygdalar nuclei to modulate the pain inputs. In the descending pathway, Oxt neurons project to the nucleus raphe magnus (RM) to further modulate pain responses (Lefevre et al., 2021; Son et al., 2022). Even though Oxt innervates only a few areas that regulate pain, it exerts an effect on brain regions of both the ascending and descending pathway resulting in multi-level regulation of pain.

Oxt is known to have analgesic effects, both from preclinical and clinical studies. In rats, partial sciatic nerve ligation induced pain results in increased Oxt synthesis (Nishimura et al., 2019). Moreover, Oxt modulates the GABAergic tone of the insular cortex and thus exerts an analgesic effect in mice (Gamal-Eltrabily et al., 2020). In clinical studies, intranasal Oxt administration attenuated pain in patients with lower back pain, and in women with chronic pelvic pain (Schneider et al., 2020; Flynn et al., 2021). These data strongly suggest analgesic effects of Oxt, but further investigation is required to understand the mechanism by which Oxt elicits these effects.

Somatic/visceral module: Sensory/motor regulation

Sensorimotor integration is defined as the ability to integrate different sources of sensory stimuli in the central nervous system and transform this into goal directed motor functions (Machado et al., 2010). The motor system is controlled mainly via the basal ganglia circuit that functions through motor activity in the whole body, mainly the forelimbs and hindlimbs.

The visual inputs from the retina reach the lateral geniculate nucleus (LG) in the thalamus from which the information is sent to the visual cortex (VIS). Visual information is passed on to the suprachiamatic nucleus (SCH) of the hypothalamus from the retina to direct attention to the visual stimuli (Peirson et al., 2018). The pretectum (PRT) also receives visual information from the retina and SCH to modulate visuomotor behaviors (Levine and Schwartz, 2020). Oxt projects to the VIS, PRT and SCH (Son et al., 2022). The superior colliculus (SC), a midbrain area extensively innervated by Oxt neurons, also receives visual input from retina as well as processed information from the VIS especially while tracking objects (Zubricky and Das, 2022). There is no direct evidence to prove the effect of Oxt on vision. Social attention measured by changes in eye gazes are facilitated upon intranasal Oxt administration (Freeman et al., 2018). Whether this can be attributed to effects of Oxt on vision or attention is not clear.

Auditory inputs received via the cochlea are sent to the superior olivary nucleus (SOC) followed by the inferior colliculus (IC). The IC is the relay station where ascending and descending auditory pathways converge. From the IC, auditory signals are passed to the AUD through the medial geniculate nucleus (MG) (Morgan et al., 2020). The posterior intralaminar thalamic nucleus (PIL) functions as an integrator of auditory information before it is passed to the AUD (Smith et al., 2019). Oxt neuronal projections reach all the relevant brain regions for auditory processing (SOC, IC, PIL, AUD). Studies in rodents demonstrated that Oxt can induce plasticity in AUD which help facilitate parent responses to infant cries (Schiavo et al., 2020). A recent study identified that the PIL responds to pup calls to mediate maternal behavior (Valtcheva et al., 2021). Clinical studies so far have only correlative evidence suggesting Oxt regulates auditory responses. In humans, listening to their mother's voice decreased infant pain scores while increasing Oxt levels above baseline (Filippa et al., 2021). Intranasal Oxt administration in ASD patients has significantly improved the ability to select speech sounds from background noise (Lin et al., 2014; Yoshimura et al., 2018).

Olfactory inputs arise from the olfactory epithelia and reach the main MOB. From the MOB, it projects to the taenia tecta (TT), anterior olfactory nucleus (AON), PIR, olfactory tubercle (OT) and entorhinal cortex (ENT). Vomeronasal inputs that carry pheromone information also start from the olfactory epithelium, but flow to the accessory olfactory bulb (AOB) and further to the bed nucleus of stria terminalis (BST), nucleus of the lateral olfactory tract (NLOT) and various amygdaloid nuclei. Processed olfactory information is passed to multiple brain regions depending on the action to be performed (De Castro, 2009; Canavan et al., 2011). Despite the high density of OxtRs, Oxt neurons have limited projection to olfactory brain regions (Newmaster et al., 2020; Grinevich and Neumann, 2021; Son et al., 2022). However, stimulation of Oxt neurons as well as injection of Oxt in the MOB resulted in increased neuronal activity (Yu et al., 1996). This increased activity is attributed to the binding of Oxt to OxtR in the MOB (Vaccari et al., 1998). These data suggest that Oxt can powerfully modulate olfactory signal processing in the olfactory bulb even without direct projection. There is also evidence that OxtR activation in the MOB increases the signal to noise ratio for odorant evoked responses (Oettl et al., 2016). These suggest a highly sensitive and projection fiber independent activity of Oxt on OxtRs.

Taste inputs received through the taste receptors reach the brain through the nucleus of the solitary tract (NTS). From the NTS, there are three distinct pathways that relay taste information: the reflex pathway for either enhancing or

reducing ingestion, the lemniscal pathway for taste perception and discrimination, and the visceral-limbic pathway mostly for regulating homeostatic and motivational states. The reflex pathway involves NTS signals conveyed to medullary and reticular formations that further innervate the cranial motor nuclei (Martin and Sollars, 2017). The lemniscal pathway from the NTS relays through the PB and further to the gustatory cortex (GU) via the ventral posterior medial nucleus of the thalamus (VPMpc). This pathway also transitions the sensation from somatosensory lingual to gustatory representation in the brain through the signals received in the agranular insular cortex (Stapleton et al., 2006). The visceral-limbic system connects the NTS to BF areas, the lateral hypothalamus (LH), the BST and the amygdala. Among these areas that control multiple facets of taste perception, discrimination and memory, Oxt innervates the NTS, PB, GU and BST. Thus, Oxt could modulate reflex, leminscal and visceral-limbic gustatory pathways by either exerting its effect on one specific node or on multiple nodes of these pathways. So far there is no direct evidence for Oxt controlling taste perception and discrimination.

The cutaneous afferents from both the forelimbs and the hindlimbs reach the thalamus either through direct spinothalamic pathways or from the spinal cord via the cuneate nucleus (CU). Tactile information is processed in different areas of the ventral posterior complex of the thalamus: the ventral posterolateral nucleus of the thalamus (VPL) –from the foot and hand (dorsal root ganglion-cuneate nucleus-RVM) and the ventral posteromedial thalamus (VPM) -from the face (through spinal trigeminal nucleus-VII). From the thalamus this information is passed to the somatosensory cortex that then delivers the processed information to the motor cortex (Qi et al., 2014a). Oxt projections reach areas in the medulla- spinal trigeminal nucleus (spinal nucleus of the trigeminal caudal part, SPVC and interpolar part, SPVI -sensory associated) that receive temperature, touch and pain information from the face through the facial motor nucleus (VII -motor related) and reticular formation (gigantocellular reticular nucleus, GRN; parvicellular reticular nucleus, PARN; lateral reticular nucleus, LRN) responsible for motor movements of head and face (Patel and Das, 2021). Despite Oxt projections, OxtRs are present in multiple somatosensory control areas within the mouse brain including the somatosensory and motor cortices extensively (Newmaster et al., 2020). It is yet to be explored whether Oxt directly affects tactile information processing.

The integration of visual, auditory and somatosensory inputs occurs in the multisensory midbrain, the superior colliculus (SC), which also receives direct projections from Oxt neurons. The heavy inputs from the SC to Oxt neurons transmit visual information required for learning of pup retrieval in virgin female mice, a process that requires integration of multiple inputs (Carcea et al., 2021). Although OxtRs are not reported so far in the mouse brain SC, there is a report suggesting presence of OxtRs in the superficial layers of the SC in primates (rhesus monkeys) (Freeman et al., 2014; Newmaster et al., 2020).

Motor control is a well-studied area which mainly involves the basal ganglia circuit. The dorsal striatum (caudatoputamen, CP), the globus pallidus (GP), and the subthalamic nuclei (STN) as major stations of the basal ganglia receive motor inputs from cortical and sub cortical areas. There are three main pathways that control different aspects of locomotion. The direct pathway relays signal from the motor cortex that results in active motor responses. The motor cortex sends excitatory inputs to the CP, which in turn results in inhibition of the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr), activating the thalamus and resulting in motor activity. The indirect pathway mediates inhibitory outflow and thus reduces the motor activity. Inputs from the motor cortex reach the globus pallidus externa (GPe) that inhibits the STN, resulting in the activation of the GPi and SNr, causing inhibition of motor activity. The hyperdirect pathway is a direct relay signal from the motor cortex to STN inhibiting ongoing motor activity (Schroll and Hamker, 2013). Oxt projects to all the areas in the mouse brain motor circuit including the CP, GP, SN and STN and has the capability to modulate all three motor pathways (Son et al., 2022). For example, locomotor activity was reduced upon Oxt addition or OxtR inhibition in the SNc. Oxt modulates this locomotor activity by influencing the nigral glutamatergic tone in rats (Angioni et al., 2016).

Somatic/visceral module: Body physiology and metabolism

Body physiology is the branch of biology that deals with regulating the normal function of organs. Metabolism can be defined as the sum total of all reactions within the body that converts food to energy (Sánchez López de Nava and Raja, 2022). Major brain areas that integrate glucose sensing to regulate metabolism include the paraventricular hypothalamic nucleus (PVH), ventromedial hypothalamic nucleus (VMH), lateral hypothalamic area (LHA) and arcuate hypothalamic nucleus (ARH) (McCormack et al., 2020). There are multiple reviews that extensively explain the role of Oxt in energy metabolism (Cezario et al., 2008; Song et al., 2014; Lawson, 2017; Ding et al., 2019; Onaka and Takayanagi, 2019; McCormack et al., 2020; Kerem and Lawson, 2021). For instance, OxtRs are enriched in the ARH and these neurons control satiety (Fenselau et al., 2017). Moreover, Oxt in the NTS regulates food seeking and motivation (Wald et al., 2020).

Body physiology and metabolism is not only regulated by nutrient/glucose uptake, but also by fluid intake and homeostasis. Fluid intake and regulation is maintained mainly through the projections from NTS to PB and downstream areas- the CEA, MEPO, vascular organ of lamina terminalis (OV) and anteroventral periventricular nucleus (AVPV)

(Zimmerman et al., 2017). Fluid intake is also directly regulated via Oxt through its projections to the PB, specifically by neurons that express OxtRs (Ryan et al., 2017). More evidence for Oxt regulation of fluid intake can be found at Arletti et al., 1990; Ryan, 2018

Cardiovascular activity is also regulated by Oxt that is released from the brain (Petersson, 2002). The NTS and DMX are very closely situated brain regions that regulate cardiovascular activity. They both control baroreflex control of the heart. Oxt inputs via neuronal terminals present at the solitary-vagal complex increase vagus outflow and thus result in a slower heart rate (Higa et al., 2002; Karelina and Norman, 2009). Both of these areas are also enriched with OxtRs in rodents (Barberis and Tribollet, 1996). There are several reviews that explain the cardiovascular control of Oxt in detail (Gutkowska and Jankowski, 2012; Jankowski et al., 2020; Szczepanska-Sadowska et al., 2021; Wang et al., 2022).

Oxytocin regulation of cognitive control

Cognitive control refers to the selection of emotions, behaviors and thoughts based on social context and current requirements along with avoiding inappropriate actions (Miller and Cohen, 2001). The cognitive control node involves Oxt's regulation of mental processes—from learning and memory to reward and value assessment—giving rise to a wide array of social and sexual behaviors (**Figure 3**).

Cognitive control module: Learning and memory

Memory is defined as the process of encoding, storing and retrieving information (Squire, 2009). Memory can be subdivided into explicit memory, implicit memory and working memory.

Explicit memories include events that happened in the past (episodic) as well as general information and facts (semantic). Episodic memory mainly functions through neocortex (perirhinal area; PERI)-entorhinal area (ENT) -hippocampal circuits (dentate gyrus; DG, areas within Ammon's horn; CA3, CA1, subiculum; SUB) (Bird and Burgess, 2008). The hippocampus is also connected to the retro splenial cortex (RSP) and thalamic nuclei (anterior thalamic nucleus; ATN and midline thalamic nuclus; MTN) to further facilitate the process of memory storage and retrieval (Ophir, 2017).

Memory modulation by Oxt is studied specifically in the context of social memory (Lin and Hsu, 2018). OxtRs are enriched in the CA2 area of the mouse brain, especially in the pyramidal neurons (Young and Song, 2020). Oxt fibers that reach CA2 neurons enhance the rate of signal transfer in the hippocampus by creating burst firing, which in turn results in short term plasticity and feedforward activation on CA1 neurons (Tirko et al., 2018). OxtRs in the CA2/3 area are also required for discrimination of social stimuli, but not required for non-social stimuli (Raam et al., 2017). Impaired social recognition was also observed in a CA2 specific OxtR knockout mouse (Lin et al., 2018). The ENT receives sparse projection from Oxt neurons and is enriched with OxtRs. Oxt inputs are required for ENT to CA2 plasticity that regulates long term social recognition memory in mice (Lin et al., 2018). The supramammillary nucleus (SUM) that has OxtRs, is also required for the formation of short term and long term social recognition memory (Rajamani et al., 2022). These are the major areas that show relevant social memory effects with perturbed Oxt signaling. Oxt fibers also reach other memory relevant thalamic nuclei like the ATN and nucleus of reuniens (RE).

Cognitive control module: Reward and value assessment

Reward is an act of pleasant or positive affective experience (White, 2011). The main reward system in the brain is the dopaminergic mesolimbic pathway. Once a stimulus that indicates reward is received, dopamine is released from the ventral tegmental area (VTA) to the nucleus accumbens (ACB). From the VTA to ACB forms the mesolimbic pathway and the VTA to PFC forms the meso-cortical circuits, the most relevant pathways for reward. The serotonergic dorsal nucleus raphe (DR) neurons project on the VTA to modulate reward responses (Qi et al., 2014b). Thus, dopaminergic VTA and serotonergic DR together function to shape the reward responses that are sent either to the ACB or different cortical areas- the mPFC areas- the infralimbic area (ILA) and anterior cingulate area (ACA) along with the orbital area (ORB) and agranular insular area (AI). The DR also projects to the ACB directly to modulate reward responses.

Social reward is mainly regulated by Oxt's effect on reward circuitry. Oxt released in the VTA promotes prosocial behaviors. Optogenetic activation of Oxt-PVH neurons resulted in activation of reward specific VTA dopamine neurons that project to the ACB. This circuit is necessary to elicit social reward (Hung et al., 2017; Borland et al., 2019). DR serotonergic inputs to the OxtR positive ACB are also required for social reward. Ablation of OxtRs in the ACB resulted in impaired social reward processing (Dölen et al., 2013). Pair bonding observed in female prairie voles is also driven through Oxt in the ACB along with dopamine receptor 2 (Liu and Wang, 2003; Borie et al., 2022). There were reports suggesting changes in OxtR levels leading to pair bonding in prairie voles (Ophir et al., 2012; King et al., 2016). A more recent study postulates that OxtR are not required for social attachment in prairie voles using a CRISPR knockout model of OxtR, that has to be further evaluated in the light of previous literature

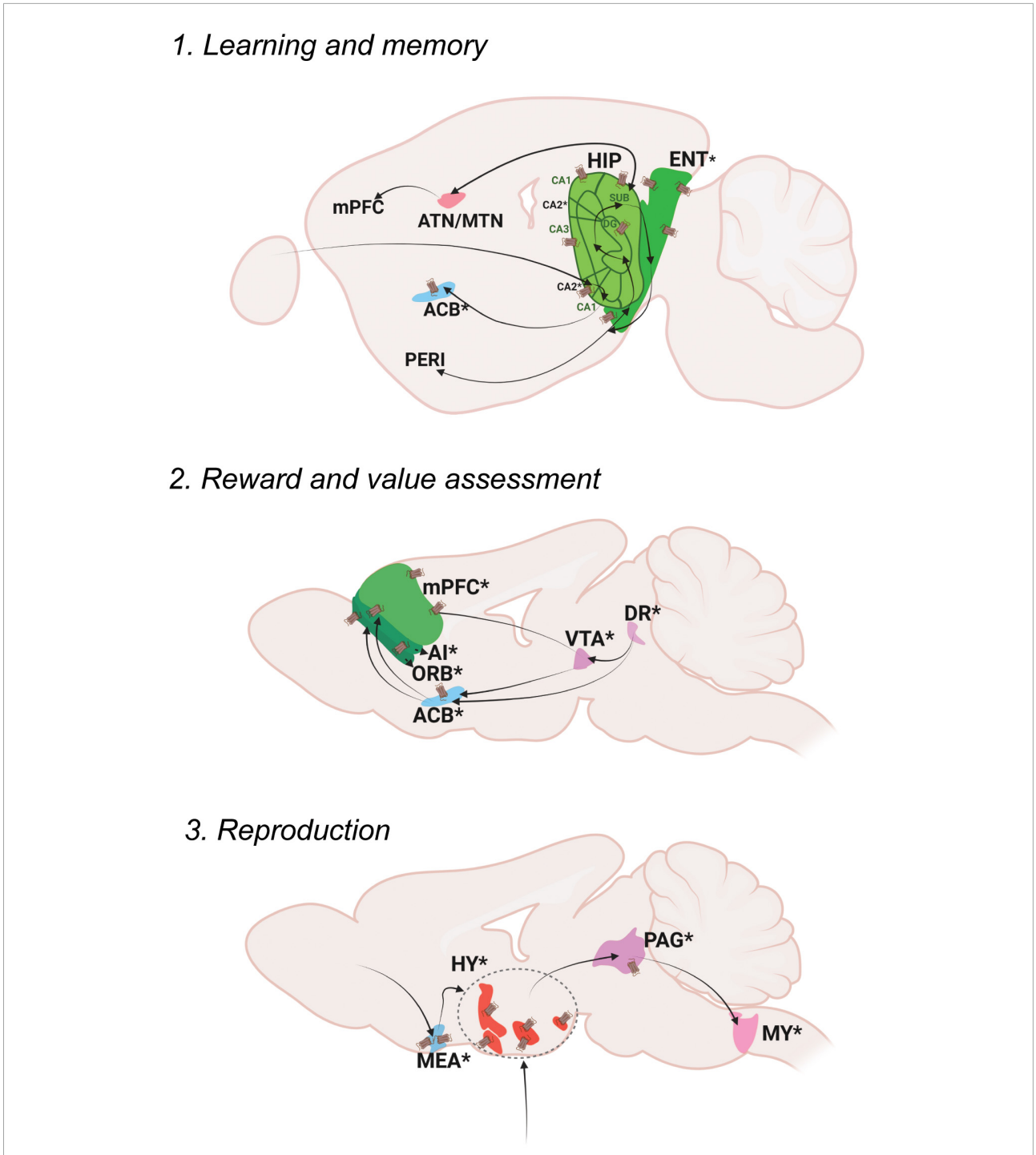

FIGURE 3
Oxt regulation of Cognitive Control. Pathways depicting three different functional nodules: 1. Learning and memory, 2. Reward and value assessment, 3. Reproduction. For further details refer, **Figure 1** legend. For abbreviations, refer **Table 1**.

(Berendzen et al., 2022). Oxt present in the ACB during a critical period during development establishes social reward learning (Nardou et al., 2019). Similar reward associated behaviors are mediated through Oxt in the mPFC. Oxt inputs to the mPFC result in the development, and support improvement of helping behaviors (Yamagishi et al., 2020; Li et al., 2021). Oxt injections in the mPFC (specifically the anterior cingulate area; ACA) of rhesus monkeys enhanced context dependent prosocial behaviors (Jiang and Platt, 2018). These suggest that Oxt can act throughout the dopaminergic VTA, serotonergic

DR and PFC to regulate different levels of reward processing. Transcriptomic analysis of PVH-OXT neurons projecting to social reward brain regions are disrupted in an ASD mouse model and showed enrichment of ASD risk genes (Lewis et al., 2020). These reports suggest an exquisite role of Oxt in the development and maintenance of social reward memories, the perturbation of which results in ASD like phenotypes.

Cognitive control module: Reproduction

Reproduction is a basic instinct crucial for survival of a species that can be defined as the process by which genetic material is transmitted from one generation to the next (Ishii and Touhara, 2019). Reproduction includes sexual activity, pregnancy, parturition, and lactation. Sexual activity in rodents follows mainly three steps: approach, investigation and mating. Approach and investigation results in the activation of olfactory and vomeronasal pathways. In male mice, pheromone signals from female mice are received in the AOB area and transmitted to the medial amygdala (MEA). The MEA inputs are then passed to the regulatory centers of reproduction in the hypothalamus- the preoptic area, the ventromedial hypothalamus (VMH) and the ventral premammilary nucleus (PMv). From the hypothalamus, signals are transmitted to the ventral midbrain followed by brainstem areas and the spinal cord that results in erection and ejaculation. In female mice, estrogen acts at the VMH and PAG, which is connected to the midbrain reticular nucleus (MRN) and then further through the reticulospinal tract to the spinal cord, that results in lordosis (Hashikawa et al., 2016).

Oxt acts at multiple brain areas to regulate different aspects of reproduction. During pregnancy and parturition, the role of hypothalamic release of Oxt is well discussed (Veening et al., 2010). Hypothalamic Oxt release is also important for lactation (Perkinson et al., 2021). Oxt fibers reach the MEA, multiple regions of the pre-optic area- medial preoptic area (MPO), medial preoptic nucleus (MPN), posterodorsal preoptic nucleus (PD), periventricular hypothalamic nucleus, preoptic part (PVpo), anteroventral preoptic nucleus (AVP) as well as the VMH and PMv. The MEA is also enriched with OxtRs. Oxt in the MEA alters sex preferences in male mice and is required to discriminate female mice from other male mice as well as female scent from male scent (Yao et al., 2017). It is also shown that Oxt is required in males for sexual experience based long term changes in MEA activity (Li et al., 2017). Oxt also plays a relevant role in regulating sexual behaviors through its actions in the preoptic area. OxtRs are expressed in the MPO, an area that mediates copulatory behaviors, with a sexual dimorphism of more OxtRs in males than females (Sharma et al., 2019). A further study from our lab identified sexual dimorphism in the anteroventral periventricular nucleus (AVPV), an area situated very close to the MPO (Newmaster et al., 2020). Intracerebral injections of Oxt in the MPO resulted in increased sexual behavior in male rats (Gil et al., 2011) and increased sexual receptivity in female rats (Caldwell et al., 1989). Moreover, Oxt in the MPO of monogamous mandarin voles resulted in better paternal care and OxtR antagonists reduced the total duration of paternal care as well as increased the latency to initiate paternal care (Yuan et al., 2019). All these reports suggest a major role for Oxt in the MPO in sexual and caregiving behaviors. The VMH is an estrogen receptor enriched area known for reproductive and metabolic regulation in female mice (Correa et al., 2015). Oxt mRNA was found to be higher in the VMH during certain stages of the estrous cycle in female rats suggesting a potential role of Oxt in luteinizing hormone release (Bale et al., 1995).

In mice, Oxt from the PVH to VTA induces erection (Melis et al., 2007). During pregnancy, increased Oxt binding to OxtRs was found in the SON, PVH and MPO (Bealer et al., 2006). A blockade in the binding of Oxt to OxtRs resulted in reduced milk yields upon suckling in rats and in marmosets (Lipschitz et al., 2003; Taylor and French, 2015). There is clinical evidence also suggesting a potential treatment possibility with Oxt for fertility and reproductive disorders. Oxt levels increase during sexual arousal and ejaculation in both men and women (Cera et al., 2021). Deficiencies in the Oxt system result in impotence and decreased libido whereas increased Oxt enhanced sexual behaviors (Magon and Kalra, 2011). Overall, Oxt plays multiple roles in reproduction, by exerting effects on the peripheral system as a hormone and within the CNS as a neuromodulator.

Conclusion

In this review, we addressed functional circuits in the brain and explained the specific areas at which Oxt can exert its effect to modulate particular behaviors. We explained the neural circuits responsible for nine different functions and at what levels Oxt can act within each circuit. Oxt neuronal fibers reach all the major brain areas involved in most of the functional circuits. An exception to this is the thalamic regions (VPM, VPL, LG), the major relay station for sensory circuits and pain circuits to the cortex, that neither receive projection fibers, nor have OxtRs. We were also able to identify cross talk between multiple functional circuits and illustrate how Oxt can modulate different behaviors by acting at one brain area. For example, the PAG mediates fight and attack responses as well as receiving pain information. Another region that receives both pain and visual inputs is the PB. Social reward and memory areas in the brain are also heavily interconnected with each other and Oxt exerts effects on most areas within these two circuits to impact social memory (Nardou et al., 2019). Thus, Oxt can exert its effects

at multiple levels of a functional circuit and alter the responses of more than one circuit due to its modulatory effects on crosstalk nodes. We hope that our review linking Oxt projection areas with functional circuits helps further research to unveil underexplored areas where Oxt can exert specific behavioral effects.

Author contributions

SM and YK conceptualized the manuscript. SM wrote the initial manuscript and figures and further developed the manuscript with RB. YK handled the funding and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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We used BioRender.com to create illustrations in **Figures 1-3**.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The modulation of emotional and social behaviors by oxytocin signaling in limbic network

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Neuropeptides can exert volume modulation in neuronal networks, which account for a well-calibrated and fine-tuned regulation that depends on the sensory and behavioral contexts. For example, oxytocin (OT) and oxytocin receptor (OTR) trigger a signaling pattern encompassing intracellular cascades, synaptic plasticity, gene expression, and network regulation, that together function to increase the signal-to-noise ratio for sensory-dependent stress/threat and social responses. Activation of OTRs in emotional circuits within the limbic forebrain is necessary to acquire stress/threat responses. When emotional memories are retrieved, OTR-expressing cells act as gatekeepers of the threat response choice/discrimination. OT signaling has also been implicated in modulating social-exposure elicited responses in the neural circuits within the limbic forebrain. In this review, we describe the cellular and molecular mechanisms that underlie the neuromodulation by OT, and how OT signaling in specific neural circuits and cell populations mediate stress/threat and social behaviors. OT and downstream signaling cascades are heavily implicated in neuropsychiatric disorders characterized by emotional and social dysregulation. Thus, a mechanistic understanding of downstream cellular effects of OT in relevant cell types and neural circuits can help design effective intervention techniques for a variety of neuropsychiatric disorders.

KEYWORDS

oxytocin, oxytocin receptor (OTR), intracellular cascades, social behavior, emotional behavior, threat response, stress response

Introduction

Well-known for its role in reproductive behaviors, the highly conserved neuropeptide oxytocin (OT) is a key modulator of neural activity in a distributed network of cells within the limbic forebrain. OT modulation of the limbic forebrain network is critical for mediating behavioral and physiological responses to internal

and external stimuli – prominent among these are aversive stress/threat and appetitive social exposure. A wide range of behaviors modulated by OT include the threat and/or stress-induced defensive responses such as freezing and pro-active coping, and social exposure-elicited behaviors such as social interaction, aggression, mating, and maternal care (Carter, 1998; Ferguson et al., 2000; Mantella et al., 2003; Pedersen et al., 2006; Neumann, 2008; Bartz et al., 2011). OT modulation is important for conferring salience of emotional and social behaviors (Carter, 1998; Ferguson et al., 2000; Ciocchi et al., 2010; Bartz et al., 2011; Knobloch et al., 2012; Hasan et al., 2019). The pleiotropic effects of OT on these behaviors are thought to be driven by cascading molecular signaling in specific neural circuits across the brain (**Figure 1**).

Oxytocin (OT) binds almost exclusively to its membrane-bound oxytocin receptor (OTR), which is a G-protein coupled receptor that can associate with one of several G proteins that mediate distinct physiological responses downstream of OT-OTR interaction in a cellular context and circuit-specific manner (Tomizawa et al., 2003; Wang and Hatton, 2007; Lin et al., 2012; Chini et al., 2017). The knowledge of various signaling pathways underlying context and experience-dependent behavioral responses induced by OT is crucial for understanding the heterogeneity of the downstream effects elicited by OT across the limbic forebrain. The critical challenge in oxytocin research is establishing causal relations between the specific behavioral effect and the underlying molecular mechanisms and circuits. The objective of this review is to provide a framework for the role that OT plays in modulating physiological responses relevant to emotional and social behaviors at different levels of the organization – from signaling inside cells to specific cell types and neural circuits, based on rodent studies. We describe here the cellular and molecular mechanisms that underlie the neuromodulation by oxytocin and how OT signaling in specific neural circuits within the limbic forebrain mediates emotional and social behaviors. In light of the array of modulatory effects that OT exerts on complex behaviors in humans and animal models, we discuss how OT signaling has been a prime focus for understanding pathophysiology and therapeutic potential in neuropsychiatric disorders.

Oxytocin signaling inside cells

In mammals, OT is synthesized in the hypothalamus, particularly in the paraventricular nucleus (PVN), the supraoptic nucleus (SON), and accessory magnocellular nuclei (AN) (Stoop, 2012). OT is released from these nuclei as a neurohormone with both paracrine and synaptic functions; therefore, oxytocin release has a dual mechanism, reaching different cortical and subcortical regions where the oxytocin receptor (OTR) is expressed (Jiménez et al., 2015; Mitre et al., 2016; Jurek and Neumann, 2018). The release of OT from PVN and SON, *via* axonic fibers, stimulates numerous brain regions expressing the OTR (Knobloch et al., 2012; Mitre et al., 2016) and permits the precise time-dependent, local regulation of its basal levels in addition to volume transmission (Landgraf and Neumann, 2004). Aside from axonal release, the calcium-dependent release of OT from dendrites is triggered by vesicles primed for activity-dependent release, which could lead to a functional reorganization of neuronal networks harboring the OTR, thereby affording a substrate for sustained effects (Ludwig et al., 2002).

Oxytocin binds to its cognate receptor oxytocin receptor

The various effects exerted by OT are channeled through its only receptor, the oxytocin receptor (OTR), which belongs to the G-protein coupled receptor family (**Figure 1A**). In rare circumstances, OT can also bind to the receptor of closely related nonapeptide vasopressin, albeit with lower affinity (Wang and Hatton, 2007). The OTR is expressed in various cell populations within a distributed network across the brain and binds OT with an affinity of about 1–10 nM (Chini et al., 2017). This cell surface receptor transmits the OT signal intracellularly, enabling it to exert its effect on various cell functions. There are several well-established pathways downstream of OT-OTR interactions, which vary at the level of brain regions, cells, and molecules involved in other outcomes of these interactions. Context-dependent signaling is central to the variability of OTR activity, hence it is important to understand how cellular context influences OT-mediated activation of various intracellular signaling cascades and the recruitment of additional signaling partners. Along the temporal scale, the physiological effects exerted by oxytocin are both immediate and/or long-lasting. The immediate effects of oxytocin can be attributed to the specific signaling cascade it activates, leading to biochemical changes. The enduring effects exerted by OT, on the other hand, are due to its relatively long half-life and the cascading intracellular messenger pathways that lead to altered gene expression (Ludwig and Leng, 2006). Additionally, OT can transactivate members of the receptor tyrosine kinase family – TrkB, which is a receptor for brain-derived neurotrophic factor (BDNF) (Mitre et al., 2022) and epidermal growth factor receptor (EGFR) (Lin et al., 2012). OT-mediated TrkB transactivation leads to clustering of the scaffold protein gephyrin and mediates inhibitory responses. Moreover, *in vitro* and *in vivo* data suggest that G protein-coupled receptors, including OTR, can form heterodimers with other multiple G protein-coupled receptors, including dopamine D1 and D2, serotonin 2C, orexin, and melanocortin 3 receptors (MCR3), providing possible mechanisms for its many physiological effects (Ringuet et al., 2021).

Oxytocin and G protein signaling

Oxytocin receptor (OTR), a G-protein coupled receptor, binds to downstream coupling partners referred to as G proteins that contain three subunits – α, β and γ (Kamato et al., 2015). While all three subunits are crucial, the specificity of the downstream signaling is generally conferred by the engaged α subunit, which can be $G\alpha_q$, $G\alpha_s$, $G\alpha_i$, and others. OTRs have been shown to couple to $G\alpha_q$ and $G\alpha_{i/o}$ subtypes of G proteins, which have contrasting effects on cellular activity and cAMP abundance. An important factor in determining the G protein coupling partner of OTR is the oxytocin concentration. At a low concentration of OT (∼ 2 nM), $G\alpha_q$ is the partner of choice, whereas, at a high OT concentration of ∼90 nM, OTR is coupled to $G\alpha_{oB}$. The coupling partners for the intermediate concentrations of OT (11 nM – 62 nM) include $G\alpha_{i3}$, $G\alpha_{oA}$, $G\alpha_{i1}$, and $G\alpha_{i2}$ (Busnelli et al., 2013).

Of physiological relevance, OTR couples predominantly to $G\alpha_{q/11}$ subunit. Downstream of $G\alpha_{q/11}$ coupling, OTR stimulates intracellular calcium (Ca^{2+}) mobilization through a phospholipase C (PLC)-dependent mechanism (Park et al., 1998; Gutkowska and Jankowski, 2012). PLC stimulates hydrolysis of the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacylglycerol (DAG), which in turn activates protein kinase C (PKC) and inositol 1,4,5-trisphosphate (IP_3). This cascade of molecular signaling stimulates the release of intracellular Ca^{2+} stores *via* IP_3 receptors and also activates other Ca^{2+}-activated kinases (Thibonnier et al., 1999; Viero et al., 2010). However, there is a lot of heterogeneity at the level of the physiological outcome of OT-OTR activation. For example, in neuronal cells – an increase in Ca^{2+} concentration leads to the formation of Ca^{2+}-calmodulin complexes which then activate neuronal isoforms of nitric oxide (NO) synthase. NO in turn stimulates the soluble guanylate cyclase to produce cGMP. In neurosecretory cells, rising Ca^{2+} levels regulate their firing pattern, thereby modulating cellular excitability and leading to transmitter release (Gimpl and Fahrenholz, 2001). Further, elevated Ca^{2+}-levels can induce alterations in gene expression, both at the levels of transcription and protein synthesis (translation). $G\beta\ \gamma$ subunits coupled to OTR are predominantly involved in the peripheral actions of the neuropeptide (Hoare et al., 1999; Zhong et al., 2003). In neurons, however, these subunits are implicated in modulating electrical activity including dissociated hippocampal neurons (Blumenstein et al., 2004) as well as in the brainstem and spinal cord (Yevenes et al., 2003).

Oxytocin receptor (OTR) coupling to different G proteins mediates diverse effects depending on the cellular context. Whole-cell patch-clamp recordings from the supraoptic nucleus in brain slices have demonstrated that OT induces $G\alpha_{q/11}$-mediated calcium mobilization which is followed by subsequent spike frequency reduction in response to the progressive elevation in OT concentration (Wang and Hatton, 2007). Similarly, in the midbrain, OT directly increases the firing rate of dopamine neurons in the ventral tegmental area (VTA), which is consistent with the concept that OTR is primarily coupled to $G\alpha_{q/11}$ protein (Xiao et al., 2017). Primary cerebellar neurons display OT-mediated modulation in the levels of neurexin and neuregulin. This involves the regulation of Rho GTPases and OTR coupling with $G\alpha_{q/11}$ (Zatkova et al., 2016). Finally, In the GN11 cell line which is derived from olfactory neurons, OTR coupling to $G\alpha_q$ has been shown to decrease inward rectifying potassium K + (IRK) currents, however, in contrast, the opposite effect of increasing K + involves OTR coupling to $G\alpha_{i/o}$ in a different sub-population (Gravati et al., 2010). Thus, intracellular OTR coupling to specific G proteins determines the cellular response and activity to OT-OTR binding.

Oxytocin and synapse dynamics

The effect of OT on synaptic activity and synapse formation has been well established (Bakos et al., 2018). Neurodevelopmental disorders, including autism spectrum disorders, have various synaptopathies that present with deficient oxytocin signaling (Bakos et al., 2015). The multiple properties of synapses modulated by OT include synapse formation (Blumenstein et al., 2004), synapse stabilization (Lestanova et al., 2016), synapse number (Ripamonti et al., 2017), and synaptic transmission (Jo et al., 1998). Disrupted synaptogenesis and synapse functionality can result in impaired neuronal connectivity, circuit formation, and stability (Zatkova et al., 2016). OT modulates synaptic features by acting on local synaptic sites and induces context-dependent signaling cascades. At the presynaptic membrane, activation of OTR leads to increased intracellular Ca^{2+} concentration, which may result in increased neurotransmitter release (Bakos et al., 2018). This increase in Ca^{2+} could be due to $G\alpha\ _q$-mediated activation of the phospholipase-C leading to inositol 1,4,5-trisphosphate receptor (IP3R) induced calcium release from intracellular sources (Lambert et al., 1994) and through inhibition of the potassium Kir7.1 channels, which induces calcium entry through the voltage-dependent calcium channel (York et al., 2017).

Oxytocin modulates long-term synaptic plasticity and protein synthesis

Oxytocin exerts its effects on emotional behaviors by recruiting converging pathways in the paraventricular nucleus that promote nascent protein synthesis (Blume et al., 2008; Knobloch et al., 2012), innervating for example the central amygdala, where OTR-expressing neurons express higher synaptic strength after proactive coping threat conditioning

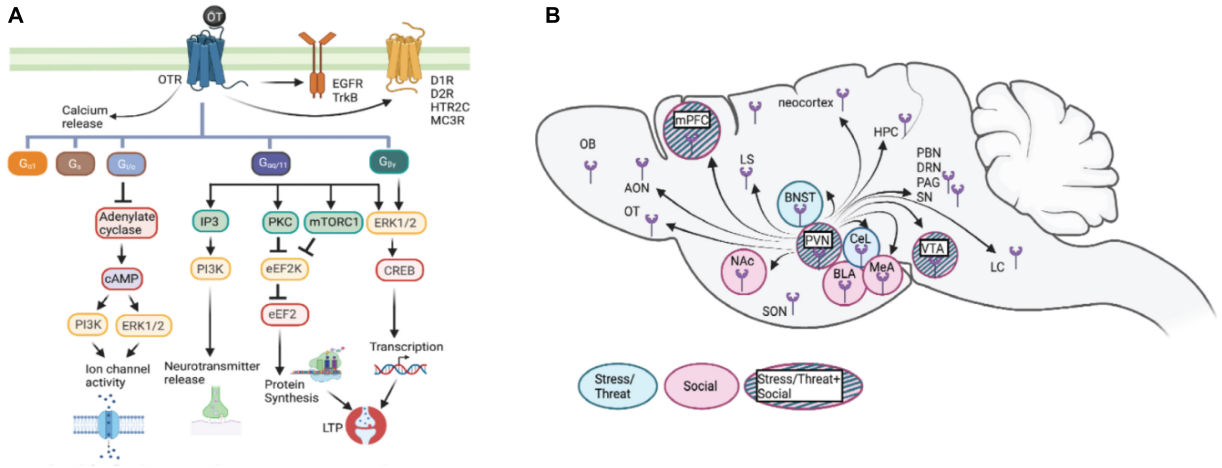

FIGURE 1
(A) Schematic representation of potential cascades involved in oxytocin signaling: OTR which is G-protein coupled receptor acts through various G-protein subunits, Gaq111 being the most common. This subunit either through calcium release or EGFR/TrkB transactivation brings about various downstream effects including neurotransmitter release, protein synthesis. Additionally binding of OT to its receptor also trans-activates some other receptors like dopamine receptors (01R, D2R), serotonin receptor (5HTR2c), orexin receptor (OXR) and melanocortin receptor (MC3R) forming heterodimers. Other subunits include Gpy; involved in LTP induction and protein synthesis, Gifo in regulating ion channel activity, Gs and Ga1 involved in cellular responses like proliferation and differentiation. **(B)** Diagram of oxytocin release in brain areas involved in stress/threat or social networks. Oxytocin stimulates the limbic forebrain through the presence of OTR and intracellular cascades, increasing the signal to noise ratio for stress/threat or social information. OT, oxytocin; OTR, oxytocin receptor; Gaq111, Gv0, Gs, Ga1; Gifo various G-protein subunits, EGFR, Epidermal growth factor; cAMP, cyclic adenosine monophosphate; IP3, Inositol 1,4,5 triphosphate; PKA, protein kinase A; pKC, Protein Kinase C; ERK, extracellular signal related kinases; eEF2, elongation factor 2; CREB, Cyclic AMP responsive element binding protein; LTP, Long term potentiation; 01R, Dopamine type1 receptor; D2R, Dopamine type 2 receptor; HTR2C, 5Hydroxytryptamine receptor 2C; MC3R, Melanocortin 3 receptor; OXR, Orexin receptor; ERK1/2, Extracellular signal-regulated kinase; mTORC1, mammalian target of rapamycin complex I; PVN, paraventricular nucleus; SON, supraoptic nucleus; mPFC, medial prefrontal cortex; OB, olfactory bulb; OT, olfactory tubercle; AON, anterior olfactory nucleus; BNST, base nucleus of the stria terminalis; CeL, centrolateral amygdala; BLA, basolateral amygdala; MeA, medial amygdala; Nae, nucleus accumbens; VTA, ventrotegmental nucleus; LS, lateral septum; HPC, hippocampus; LC, locus coeruleus; PAG, periaqueductal gray; SN, substantia nigra; PBN, parabrachial nucleus; ORN, dorsal raphe nucleus.

and freezing reduction (Terburg et al., 2018). Protein synthesis is tightly regulated at the level of initiation and elongation (Shrestha and Klann, 2022). OT promotes translation elongation by activating eukaryotic elongation factor 2 (eEF2) both in a hypothalamic cell line and *in vivo* within the PVN (Martinetz et al., 2019). Protein synthesis is required for long-term synaptic plasticity, which is a persistent change in the synaptic strength, manifested as either long-term potentiation (LTP) or long-term depression (LTD). OT has been shown to affect both forms of synaptic plasticity depending on the brain region. In the medial amygdala (MeA), OT strongly augments LTD induction in the afferents from the accessory olfactory bulb (AOB) (Gur et al., 2014). In the rat hippocampus, OT is involved in the maintenance of LTP, which is induced upon tetanic stimulation in the CA1 region. This effect of oxytocin is exerted via two pathways – the first pathway involves the conventional $G\alpha_{q/11}$-coupled phospholipase C pathway, whereas the second pathway involves transactivated EGFR (Wang, 2016) downstream signaling mediated by phosphatidylinositol 3 kinase (PI3K), extracellular signal-regulated kinase 1/2 (ERK1/2) and mammalian target of Rapamycin complex I (mTORC1) (Tomizawa et al., 2003; Lin et al., 2012). Importantly OTR-mediated mediated enhancement of LTP is dependent on new protein synthesis (Lin et al., 2012), indicating that OT triggers long-lasting effects on cellular physiology – which is particularly relevant for long-term social and threat-related memories.

Limbic forebrain-based oxytocin signaling network in stress/threat responses

Oxytocin-oxytocin receptor (OT-OTR) interactions mediate neuromodulatory influence on specific neural motifs within the emotional limbic forebrain for the acquisition and expression of stress/threat responses (**Figure 1B**). OT modulation serves the important function of fine-tuning the salience of neuronal network activity, mainly facilitating GABA-dependent increase in signal-to-noise ratio (Owen et al., 2013; Mitre et al., 2016; Oettl et al., 2016; Tirko et al., 2018), although its role in glutamatergic and astrocyte modulation has been addressed recently (Tirko et al., 2018; Wahis et al., 2021). This can be demonstrated at the level of behavior using a differential threat conditioning paradigm in which animals are exposed

to two different auditory stimuli, one that is associated with the imminence of a footshock (i.e., threat) and the other that predicts safety. Pavlovian threat conditioning generates cued freezing response to threat predictive stimulus whereas instrumental signaled active avoidance results in cued avoidance responses that dominate over freezing (LeDoux and Daw, 2018; Hasan et al., 2019). OT neuromodulation of pertinent neural circuits facilitates the discrimination between stimuli that predict threat and safety, respectively. Supported by human studies, OT has been shown to facilitate adaptive response to threats and to reduce maladaptive fear, notably in social contexts (Janeček and Dabrowska, 2019; Triana-Del Río et al., 2019; van den Burg and Hegoburu, 2020), and mainly through its OT releasing long-range axons that irrigate the limbic forebrain (Sofroniew, 1983; Knobloch et al., 2012). Although acute activation of OTR in the central nervous system promotes the attenuation of paralyzing threat responses (freezing), high doses of OT administered chronically elicit anxiety-like responses (Peters et al., 2014). This dose-dependent effect may be mediated by OT binding to arginine vasopressin (AVP) receptors, which have been associated with enhanced fear (Viviani et al., 2011; Jurek and Neumann, 2018).

Oxytocin (OT) signaling is also critical for the physiological and behavioral responses to different kinds of stressors, which can be broadly categorized into physical and psychological stressors. Physical stress represents potentially life-threatening bodily harm, such as electric footshock and forced swim stressors whereas psychological stress involves anticipation of pain or threat, for instance - maternal separation, immobilization, social defeat, and predation (Sandi and Haller, 2015). Depending on the context and the stressor type, OT either impedes the already operating stress response or is released simultaneously with the onset of a stressor to moderate the outcome of the stress response (Winter et al., 2021). OT signaling in brain regions within the limbic forebrain network, including the paraventricular thalamus, amygdala, prefrontal cortex, lateral septum, and bed nucleus of stria terminalis, orchestrate the neuromodulation of stress/threat responses (**Table 1**).

Oxytocin is released by paraventricular nucleus during stress/threat responses

Oxytocin (OT) is released from the PVN during or immediately after, acute stress. Available rodent models of stress partially mimic the stress-induced pathophysiological and behavioral changes as seen in humans. In the acute model, the stressor is applied once and for a short time, while chronic stress involves repeated application of stressful stimuli over an extended period (Daviu et al., 2019). OT modulation of the stress response is particularly evident during periods of high endogenous OT levels such as the peripartum period (Slattery and Neumann, 2008). During this period, OT reduces the levels of corticotropin-releasing factor (CRF) in the PVN and the sympathetic nervous system as a physiological response to labor-induced stress. CRF release in PVN is the primary inducer of the hypothalamic-pituitary-adrenal (HPA) axis that activates generalized stress responses. For instance, in lactating women, the increase in OT during lactation appears to dampen the subsequent stress-induced secretion of corticosteroid (CORT) (Cox et al., 2015). The bidirectional inflection of OT and CRF in the PVN could underlie one of the OT-dependent neural mechanisms of stress-buffering. The cellular architecture of PVN comprises magnocellular and parvocellular neurosecretory cells, that have distinct morphology, electrophysiological properties, and pathways. While the magnocellular PVN cells innervate numerous forebrain regions and release neurohormones into the blood from the posterior pituitary, parvocellular neurosecretory cells in PVN regulate the anterior pituitary via projections to the medial eminence. Evidence for a direct interaction between the OT and CRF systems is based on the observation that parvocellular CRF neurons in the PVN co-express OT but not OTR, whereas magnocellular CRF neurons co-express CRF receptor (CRFR2), OT, and OTR, allowing these CRF neurons to respond to OT release and vice versa (Arima and Aguilera, 2000; Dabrowska et al., 2011).

Furthermore, chronic administration of OT modulates the expression of the *crfr2* gene, leading to a reduction in CRFR2 membrane expression and eventually an anxiogenic phenotype (Winter et al., 2021). Additional anxiolytic mechanisms in the PVN related to OT include the stimulation of oxytocin secretion via GABA-B receptors (Marques de Souza and Franci, 2008) and activation of OT neurons via secretion of neuropeptide-S (Grund et al., 2017). Oxytocin also increases the pain threshold and stimulates various positive social interactions (Rahm et al., 2002; Uvnäs Moberg et al., 2020). During the acquisition of cued freeze suppression and/or extinction in threat conditioning paradigms, coordinated release of OT and glutamate from irrigated areas innervated by their axonal terminals to induce network plasticity in pertinent brain regions including the central amygdala, prefrontal cortex, lateral septum, and bed nucleus of the stria terminalis (BNST) (Knobloch et al., 2012; Hasan et al., 2019). Recent studies strongly suggest that the connectivity of the PVN to these areas involves experience-dependent control of spiking activity in the PVN, with hypothalamic OT neurons constituting a memory engram for the extinction of learned freezing responses (Hasan et al., 2019). Additionally, repeated exposure to OT produces long-lasting effects by affecting the activity of other transmission systems like dopamine, a mechanism that makes OT potentially clinically relevant. Interestingly, its function to modulate threat responses depends on the context and internal states. OT signals can either reduce or exacerbate such reactions, depending on the context,

TABLE 1 OT-OTR signaling in limbic network modulates neuronal activity and behavioral salience in circuits for stress/threat and social responses.

Component of limbic forebrain network	Role in stress/threat responses	Neuromodulation by OT-OTR
Paraventricular Nucleus of the Hypothalamus	Triggers and modulates stress responses through the production of Corticotropin releasing factor (CRF), Adrenocorticotropic hormone (ACTH or CORT), Oxytocin (OT) and Vasopressin (AVP). First relay of the hypothalamus-pituitary-adrenal axis (HPA) (Marques de Souza and Franci, 2008; Dabrowska et al., 2011; Cox et al., 2015; Gómez-Gómez et al., 2019)	OT has anti-stress and anxiolytic effects, by the inhibition of CRF & CORT production. OT release also responds to conditioned threat stimuli (Arima and Aguilera, 2000; Liu et al., 2016; Grund et al., 2017; Hasan et al., 2019; Duarte-Guterman et al., 2020)
Centrolateral Amygdala	Triggers and modulates conditioned threat responses, specially freezing in rodents (Ciocchi et al., 2010; Haubensak et al., 2010; Duvarci et al., 2011; Fadok et al., 2017; Shrestha et al., 2020b)	OT stimulates the OTR-expressing PKCd cells that inhibit the AVPr-expressing SOM cells, thus inhibiting the display of freezing behavior (Huber et al., 2005; Kirsch et al., 2005; Knobloch et al., 2012; Terburg et al., 2018; Ferretti et al., 2019; Gunduz-Cinar et al., 2020)
Prefrontal Cortex	Cognitive control of stress/threat responses through top-down modulation of subcortical areas, to initiate behavior and decision-making (Milad and Quirk, 2002; Gruene et al., 2015; Capuzzo and Floresco, 2020; Diehl et al., 2020; Scheggia et al., 2020)	OT reduces stress/threat responses (freezing) through OTR-expressing GABAergic cells. OT stimulates social buffering of freezing responses (Nakajima et al., 2014; Sabihi et al., 2014; Li et al., 2016; Jang et al., 2022)
Bed nucleus of stria terminalis	Integrates information by interfacing with other brain regions to regulate distinct aspects of motivated behaviors associated with stress, anxiety, depression, and decision-making (Janeček and Dabrowska, 2019; Mosley et al., 2021)	OT through OTR facilitates cued freezing but reduces freezing responses to un-signaled, diffuse threats, underlying discrimination among the type of threat (Martinon and Dabrowska, 2018; Francesconi et al., 2021)
Component of limbic forebrain network	**Role in social responses**	**Neuromodulation by OT-OTR**
Paraventricular Nucleus of the Hypothalamus	Increases arousal for relevant stimuli through neuroendocrine regulation (Smith and Wang, 2014; Peñagarikano et al., 2015)	Neuronal activity in OT neurons is positively correlated to social interaction (Smith and Wang, 2014; Peñagarikano et al., 2015)
Medial Amygdala	Increases behavioral salience for both positive and negative emotional stimuli (Arakawa et al., 2010; Senn et al., 2014)	Neuronal activity and synaptic plasticity in OTR-expressing neurons of the medial amygdala are positively correlated to social interaction (Choleris et al., 2007; Lukas et al., 2013; Gur et al., 2014)
Prefrontal cortex	Modulates social behavior and relays salience information to other brain areas (Jang et al., 2022; Musardo et al., 2022)	Neuronal activity from projections to and from the mPFC can be modulated by OT (Tan et al., 2019; Musardo et al., 2022).
Mesolimbic dopaminergic system	Integrates information for reward, reinforcement and motivated behaviors (Dölen, 2015; Wei et al., 2015)	OT stimulates OTR expressing cells in the ventro tegmental area and nucleus accumbens to increase reward salience for social stimuli, thus increasing social interaction (Hung et al., 2017; Peris et al., 2017; Kohli et al., 2019; Nardou et al., 2019)

social environment, and hormonal status (Bosch and Neumann, 2012).

Oxytocin modulates stress/threat responses in the amygdala

The centrolateral nucleus of the amygdala (CeL) is implicated in the acquisition, storage, expression, and extinction of threat-dependent memories (Ciocchi et al., 2010; Haubensak et al., 2010; Duvarci et al., 2011; Fadok et al., 2017; Terburg et al., 2018; Winter et al., 2021) and the ensuing physiological response of retrieving those memories: freezing behavior (Ciocchi et al., 2010; Viviani et al., 2011; Whittle et al., 2021) or adaptive signaled avoidance (Fadok et al., 2017; Terburg et al., 2018; van den Burg and Hegoburu, 2020). Two prominent neuronal populations in the CeL differ in their reactivity to threat-predictive conditioned stimuli (CS): one population exhibits excitatory (CeL-On) while the other population exhibits inhibitory (CeL-Off) responses to the CS following Pavlovian threat conditioning (Ciocchi et al., 2010; Haubensak et al., 2010; Duvarci et al., 2011). Moreover, these cell types have been genetically identified and manipulated using cre- driver lines in rodents: CeL-On cells have been shown to express somatostatin (Som +) (Li et al., 2013; Penzo et al., 2015), and CeL-Off cells correspond to PKCδ + neurons, which in turn express the oxytocin receptor (Haubensak et al., 2010; Shrestha et al., 2020b). Further research has shown that, under baseline conditions, CeL-Off (PKCδ +) neurons exert a tonic inhibitory influence on cells within the centromedial nucleus (CeM), the output nucleus of the amygdala. Excitation of CeL-On (Som +) cells during CS would cause inhibition of CeL-Off neurons, resulting in disinhibition of freezing output neurons within CeM (Ciocchi et al., 2010; Haubensak et al., 2010; Fadok et al., 2017). Therefore, both CeL-On and CeL-Off neurons project to the CeM and inhibit each other (Ciocchi et al., 2010; Haubensak et al., 2010). However, an alternative view indicates a higher level of complexity for this network,

in which connections between like neurons are stronger than those between different neuronal types (Hunt et al., 2017). Both CeL-Off (Som +) and CeL-On (PKCδ +) synapses are enhanced after Pavlovian threat conditioning for the expression of either freezing or active avoidance responses, respectively (Li et al., 2013; Penzo et al., 2014; Terburg et al., 2018). Therefore, these cell populations interact in a network with mutual inhibition and differentially encode memory acquisition with threat and safety cues by altering the cellular translation landscape (Shrestha et al., 2020b). In this study, blocking *de novo* protein synthesis in CeL-PKCδ interneurons disrupts the acquisition and consolidation of long-term inhibition of the conditioned freezing response and threat/safety discrimination (Shrestha et al., 2020b,a). Conversely, the inactivation of Som + neurons impedes the acquisition of freezing responses, while their optogenetic activation stimulates them. This also suggests that threat conditioning may disrupt competition between mutually inhibitory CeL neuron subtypes (Li et al., 2013; Penzo et al., 2014).

While OT can act on different subnuclei of the amygdala to induce freezing extinction/suppression (Gunduz-Cinar et al., 2020), the well-described mechanism of action has been done in the CeL – where PKCδ + cells are stimulated by OT and glutamate from the PVN and lateral amygdala (LA), respectively (Huber et al., 2005; Viviani et al., 2011; Terburg et al., 2018; Hasan et al., 2019). The coordinated release of OT and glutamate in CeL activates CeL-Off (PKCδ +) cells and subsequently inhibits CeL-On (Som +) cells, leading to the attenuation of conditioned freezing (Knobloch et al., 2012; Hasan et al., 2019; Wahis et al., 2021). Aside from OTR expression in PKCδ + inhibitory cells in CeL, recent reports suggest that a morphologically distinct subpopulation of astrocytes in CeL express OTR and these cells strongly mediate the anxiolytic and positive reinforcement effects of OT (Wahis et al., 2021). Consistent with this mechanism, OTR + cellular activation in CeL rescues adaptive avoidance behavior in rats deprived of inputs from the basolateral amygdala. In these animals, electrophysiological recordings showed an enhanced α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-dependent connectivity between the LA and CeL OTR + neurons but not OTR- neurons in high avoiders, i.e., animals that learned to avoid an imminent threat (Terburg et al., 2018). These findings highlight the role of OT within the centrolateral amygdala in modulating divergent defensive responses depending on the context and tone of threat/safety contingency (Ferretti et al., 2019).

Oxytocin modulates stress/threat responses in the prefrontal cortex

Neural network activity in the rodent medial prefrontal cortex (mPFC) has been associated with the acquisition of threat responses and their extinction. Along the dorsoventral axis, mPFC is divided into two subregions crucial for threat responses – the prelimbic cortex (PL) and the infralimbic cortex (IL). While PL promotes the expression of freezing, the IL is involved in its extinction (Milad and Quirk, 2002; Burgos-Robles et al., 2007; Sotres-Bayon and Quirk, 2010; Sierra-Mercado et al., 2011). Thus, these two subregions of the mPFC are differentially recruited during the perception of threat versus safety (Knapska et al., 2012; Cain, 2019). Consistent with these findings, functionally distinct neurons in the BLA project to either PL and IL regions, and mediate freezing acquisition and extinction, respectively (Senn et al., 2014; Vogel et al., 2016). mPFC networks are also responsible for the acquisition, expression, and extinction of adaptive avoidance via GABAergic modulation (Capuzzo and Floresco, 2020; Diehl et al., 2020).

Oxytocin (OT) plays an important role in modulating prefrontal GABAergic control of mPFC activity. This function of OT in mPFC circuits is crucial for extinguishing defensive threat reactions (freezing) in rodents and humans (Eckstein et al., 2015, 2019; Sabihi et al., 2017; Triana-Del Río et al., 2019). Among cortical interneurons, OTR is primarily expressed in Som + cells in the rodent mPFC (Nakajima et al., 2014; Li et al., 2016), however, OTR expression varies by sex and brain state. For instance, OTR expression increases in lactating females compared to virgins or male rodents (Mitre et al., 2016). In mPFC, OTR modulates stress responses in a sex-dependent manner, mainly through its interaction with CRF stress-dependent signaling (Li et al., 2016), and potentially with sex hormones like estradiol (Gruene et al., 2015). Also with ng this finding, in a subregion-specific manner, OT signaling reduces anxiety-like behavior through its action in PL but not in IL (Sabihi et al., 2014). Complementarily, blocking OTR in PL is anxiogenic in lactating dams but not in virgins. This mechanism appears to be GABA-dependent, as administration of OT in the PL was accompanied by increased activation of GABA neurons in the same area (Sabihi et al., 2017). This finding supports the observation that OTR is expressed primarily by PL SOM interneurons, which is also consistent with the idea that this cell population is responsible for controlling the discrimination of affective states in rodents (Scheggia et al., 2020).

Oxytocin modulates stress/threat responses in the bed nucleus of the stria terminalis

The bed nucleus of the stria terminalis (BNST) is evolutionarily and anatomically close to the CeL. Of the BNST cell types, type III consists mainly of OT-positive GABAergic neurons. In this area, OT modulates adaptive responses to threats and attenuates fearful reactions in animal models and human studies via a possible interaction with the CRF system (Janeček and Dabrowska, 2019; Mosley et al., 2021). Endogenous

OT excites BNST interneurons and inhibits CeL-driven BNST output neurons by releasing GABA (Francesconi et al., 2021). The aforementioned neuromodulatory mechanism serves to enhance threat memory for a discrete cue or landmark (freezing behavior), enabling accurate and rapid adaptive responses to the threat, for example, in stress-induced social vigilance and adaptive avoidance (Martinon and Dabrowska, 2018; Steinman et al., 2019; Duque-Wilckens et al., 2020).

Limbic forebrain-based oxytocin signaling network in social behaviors

In addition to stress/threat responses, OT also plays a vital role in modulating social behaviors in rodents. Animals engage in a variety of social behaviors including social interaction, pair bonding, sexual behaviors, maternal care, and aggression (Jurek and Neumann, 2018). Among these behaviors, appetitive social behaviors toward a conspecific are determined using assays to measure social approach/avoidance, which refers to the animal's tendency to engage in social interaction often in preference to exploring a non-social object. Motivation to engage in social approach/avoidance can be assessed as socially conditioned place preference (CPP). Social memory/recognition involves the initial sensing of a conspecific through sensory modalities followed by memory formation and recall of a previously encountered conspecific. Lastly, social threat-related responses to a conspecific involve identifying, recognizing a threat, and responding appropriately. There is compelling evidence that OT signaling plays an important role in mediating multiple aspects of social behaviors – encompassing social investigation, social motivation, social memory, and social threat.

Global manipulation of the OT system provides insight into its modulatory influence on social behaviors. Systemic administration of OT or OTR agonist (OT-A) increases time spent in social investigation and augments social preference in a social CPP task (Ramos et al., 2015; Sobota et al., 2015; Zhang et al., 2015; Kohli et al., 2019; Duarte-Guterman et al., 2020). Of note, this effect of OT is both sex-specific and age-dependent (Zhang et al., 2015; Dannenhoffer et al., 2018; Duarte-Guterman et al., 2020). Similarly, administration of an OTR antagonist decreases time spent in social investigation compared to vehicle-treated animals (Lukas et al., 2011). In a compelling study, investigators tested social discrimination in OT knockout (KO), OTR KO, and partial forebrain OTR KO mouse strains (OTR Fb KO). The transgenic subjects were all male mice of the C57BL/6J strain and tested with female Balb/c, C57BL/6J, and SW strains. Interestingly, OT KO and OTR KO mice showed impaired social memory in some strains and not others, whereas OTR Fb/Fb mice showed impaired social memory in all strains. This finding implies that OT plays a role in social recognition across different strains, who may exhibit distinct social cues and release diverse pheromones (Macbeth et al., 2009). While these studies elucidate the effects of the global OT system on social behaviors, brain region-specific manipulations of OT in the limbic forebrain have begun to reveal fascinating circuit mechanisms of this neuromodulator (**Figure 1B** and **Table 1**).

Oxytocin signaling through the paraventricular nucleus is essential for social behavior

Oxytocin (OT) signaling in the rodent hypothalamus has been strongly implicated in social behaviors. While OT is synthesized by multiple hypothalamic nuclei, the PVN OT network is particularly implicated in the social approach/avoidance and social recognition/memory. Activity in OT neurons in the PVN has been shown to increase during social interaction (Hung et al., 2017). In addition, OT mRNA abundance in PVN significantly decreased in mice that showed low levels of social interaction compared to mice that showed high levels of social interaction (Murakami et al., 2011). These findings demonstrate that OT activity in PVN is positively correlated with social behaviors. As previously discussed, chronic restraint stress leads to an increase in OT immunoreactive cells in the PVN. This effect of chronic stress is accompanied by an increase in social approach (Li et al., 2016). OT signaling within PVN is also associated with rewarding aspects of social investigation. For instance, in a social CPP test - mice that show social preference have higher OT gene expression in the PVN compared to controls (Liu et al., 2016). More direct evidence for the role of OT neurons in the PVN in social behavior comes from Resendez and colleagues (Resendez et al., 2020), who showed that chemogenetic activation of OT neurons in the mouse PVN enhances social investigation while chemogenetic inhibition of the same neurons abolishes social investigation. Two-photon calcium imaging of PVN OT neurons in behaving animals has further revealed that these neurons are activated by social stimuli and they differentially encode social and non-social stimuli (Resendez et al., 2020). Together, these findings indicate that OT signaling in the PVN affects the salience of social behaviors.

In addition, social stress increases the release of OT, following heightened PVN network activity. This leads to an increase in OT-OTR binding in networks such as the lateral septum, where OT modulates the expression and extinction of social-derived threat responses in lactating females, which appears to be augmented by sex hormones (Zoicas et al., 2014; Menon et al., 2018). Similarly, in the PVN of female rodents, increased OT release is correlated with high levels of maternal aggression (Bosch et al., 2005). Excessive or uncontrollable socially induced stress is associated with OT signaling impairments, which in turn correlate with high

levels of anxiety-like behavior. Consistent with these studies, exogenous OT promotes resilience to social stress (Hale et al., 2021; Shi et al., 2021), primarily through the involvement of projections from PVN OT neurons to the prelimbic cortex (He et al., 2019).

Oxytocin signaling in the amygdala modulates social recognition/memory

Electroencephalogram (EEG) studies have shown that chronic OT administration leads to a decrease in high-frequency bands in the amygdala concurrent with increased social interaction compared to vehicle control. This indicates that OT might reduce local circuit activity within the amygdala, as effects on long-distance connectivity would have altered lower frequency bands (Sobota et al., 2015). Magnocellular OT neurons in the PVN project to the CeL and CeM subnuclei of the amygdala (Sofroniew, 1983). Besides the central amygdala, OTRs are also expressed in the BLA and medial amygdala (MeA) (Eckstein et al., 2015). To investigate the odor-induced recruitment of brain regions, Arakawa and colleagues (Arakawa et al., 2010) conducted an odor investigation test where a rat was placed in a cage with bedding that had the odor of a conspecific. Following the test, the authors carried out immunohistochemistry for cFos, a marker of cellular activity. This study showed that conspecific odor increases IEG expression in several brain regions including the olfactory bulb, MeA, BNST, and PVN. The increase in IEG expression was accompanied by an increased level of OTRs in the MeA and PVN. Further, they showed that infusion of OTR antagonist in the MeA decreases odor investigation compared to vehicle control. These findings provided compelling evidence for OT signaling within MeA in integrating conspecific odor-induced social investigation.

Moreover, OTR mRNA levels are significantly lowered in MeA of mice that showed low levels of social interaction compared to mice that had high levels of social interaction (Murakami et al., 2011). Ferguson and colleagues (Ferguson et al., 2002) examined cFos expression in OT KO and wild-type mice during a social learning task and reported similar activation in the main and accessory olfactory bulbs, the piriform cortex, and the cortical amygdala. Interestingly, wild-type mice had more activation in MeA compared to KO mice. Further, the BNST and medial preoptic area, which receive direct input from MeA, failed to show an increase in cFos expression in OT KO mice. Additional evidence for the role of MeA in social recognition comes from a study in female rats where re local infusion of antisense oligonucleotides targeting OTR resulted in impaired social memory (Choleris et al., 2007). Acute administration of OT into the MeA before memory acquisition rescued social memory (Ferguson et al., 2000), implying that local OT and OTR signaling in MeA are both necessary and sufficient for social recognition. Similar findings were reported in another study where the infusion of OTR antagonist in MeA impaired social memory in adult but not juvenile male rats (Lukas et al., 2013).

Oxytocin (OT)-induced protein synthesis is thought to be important for the consolidation of social memories. A study using social discrimination tasks found that blocking protein synthesis before memory acquisition blocked long-term social memory in rats. *In vitro*, exogenous administration of OT has been shown to enhance theta burst stimulation (TBS)-induced LTD in the anterior olfactory bulb (AOB)-MeA pathway. *In vivo*, TBS administered to the AOB before memory acquisition leads to social recognition deficits (Gur et al., 2014). Together, these findings show that MeA plays a crucial role in social memory and that OT modulates synaptic plasticity that is associated with social memory. More recent studies show that OT signaling in another amygdala subnucleus, BLA, affects social behavior. Social recognition was impaired in female mice that underwent early life stress, which coincided with an increase in dendritic complexity as well as an increase in OTR density within the BLA (Wei et al., 2015). Further, optogenetic stimulation of OTR-expressing PFC neurons that project to the BLA eliminated social recognition (Tan et al., 2019). Though these early studies are promising, more investigation into OT signaling in the BLA is needed to understand how this brain area is contributing to social approach and social memory.

Oxytocin signaling in the prefrontal cortex modulates social interaction and social threat

Oxytocin (OT) signaling in mPFC has been shown to modulate social behaviors such as social recognition and social threat. A recent study showed that a subset of glutamatergic neurons in mPFC projecting to BLA express OTRs, separately from cortical interneurons. This study demonstrated that optogenetic stimulation of the mPFC-BLA pathway impairs social recognition (Tan et al., 2019). Another study demonstrated that social isolation for over a week leads to increased subsequent social interaction, which is accompanied by increased excitatory neurotransmission from the ventral tegmental area (VTA) afferent to the mPFC. Chemogenetic inhibition of OT neurons in PVN abolishes social isolation-dependent modifications of synaptic efficacy and behavior, indicating a crucial role of OT signaling across VTA and mPFC for motivated social behavior (Musardo et al., 2022). Additionally, gene deletion of an inhibitory subunit of NMDA receptor (GluN3A KO) results in a significant reduction in OTR expression within mPFC and impaired social interaction in KO mice, which is rescued with exogenous OT administration (Lee et al., 2018).

Oxytocin (OT) signaling in mPFC also plays a key role in integrating social and threat-related information for optimal behavior outcomes. In a phenomenon known as social buffering, stress and fear responses are attenuated by acute or chronic social exposure. Jang and colleagues showed that paired rats exhibit reduced threat responses in a passive avoidance task and that OT infusion in the prelimbic cortex within mPFC of social-deprived rats results in a similar reduction in threat responses (Jang et al., 2022). Interestingly, social buffering of stress/threat response requires nascent protein synthesis in mPFC (Jang et al., 2022). Hence endogenous oxytocin seems to be fundamental for mediating the buffering effects of social interactions to diminish threat reactions like freezing (Ferrer-Pérez et al., 2020; van den Burg and Hegoburu, 2020).

Oxytocin modulation of the mesolimbic dopamine system in socio-emotional behaviors

The mesolimbic dopamine system connects the ventral tegmental area (VTA) with the ventral striatum, which includes the nucleus accumbens (NAc) and the olfactory tubercle. VTA in the telencephalon is populated by dopaminergic neurons and plays a significant role in reward, motivation, cognition, and aversion. On the other hand, the ventral striatum is populated by medium spiny neurons that express receptors for dopamine released by afferents from VTA. OTR is highly expressed in the mesolimbic dopamine circuit, including in the medial and lateral subdivisions of VTA. At a cellular level, OTRs are expressed in glutamatergic and dopaminergic neurons whose fibers project to the NAc, prefrontal cortex, and amygdala (Peris et al., 2017).

Direct activation of PVN-VTA projecting OT neurons leads to an increase in social investigation. On the other hand, inhibiting PVN-VTA OT neurons leads to abolished social preference in a social CPP test, indicating that this projection is required for social reward (Hung et al., 2017). Whole-cell recordings in the midbrain dopamine system have revealed that bath application of OT increases the firing rate of dopamine neurons in VTA (Xiao et al., 2017). Studies carried out on OT signaling in the striatum have similarly elucidated an important role of OT in mediating social behaviors. For example, Zhang and colleagues (Zhang et al., 2015) investigated the effects of OT infusion in the striatum and found that both males and females increase social interaction following the treatment. The same study also performed proteomics of striatum and found that protein levels of calcineurin and GAD67 were significantly altered upon OT administration. Specifically, calcineurin levels increased whereas GAD67 levels decreased in the striatum, indicating a possible role of OT in modulating excitatory-inhibitory balance in the striatum. Moreover, OT directly influences dopamine release in the mesolimbic circuit. Intraperitoneal injection of OT in rats leads to an increase in persistent dopamine release in the NAc (Kohli et al., 2019). Bath application of OT caused long-term depression (LTD) in medium spiny neurons in the NAc whereas application of an OTR antagonist occluded the LTD. Further investigation revealed that this synaptic plasticity was caused by a decrease in the probability of presynaptic neurotransmitter release. At the behavior level, infusion of OTR antagonist within the NAc of male mice prevented the preference for a socially conditioned context in a social CPP test (Dölen et al., 2013). The effects of OT on the mesolimbic dopamine system appear to be age-dependent. Administration of an OTR antagonist into the NAc, but not BLA, decreases time spent in the investigation of the novel conspecific, which shows that OT in the NAc is essential for motivating social behavior (Smith et al., 2017). Therefore, OT acts on the mesolimbic dopamine system to modulate reward-processing related to the social approach.

In addition to its influence on social behaviors, the mesolimbic dopamine system is recruited during contextual threat responses and is associated with neural circuit function in brain areas where OTRs are also expressed – such as the amygdala, prefrontal cortex, VTA, and striatum. There is evidence that dopaminergic neurons increase their spiking activity during the extinction of freezing responses and prevent the renewal of such responses (Bouchet et al., 2018). Dopamine also gates the associative learning of fear to switch from danger to safety conditioning (Groessl et al., 2018; Luo et al., 2018). Concerning stress-response, subchronic social isolation stress leads to OT-mediated strengthening of excitatory neurotransmission from VTA to mPFC (Musardo et al., 2022). Thus, the interactions between the mesolimbic dopamine system and OT signaling seem to be important not only for social behaviors but also for mediating stress/threat responses.

Oxytocin dysfunction and therapeutic potential in neuropsychiatric disorders

Oxytocin signaling has been implicated in a wide range of neuropsychiatric disorders, due to its crucial role in emotional and social behaviors. Among these disorders, autism spectrum disorders (ASD) are characterized by repeated or restricted interests and deficits in social interaction and social communication. Interestingly, the same brain regions that have been associated with stress/threat and social responses in rodents show abnormal activity in ASD patients (Dichter, 2012). In rodent models of ASD, OT administration has been shown to ameliorate social deficits (Peñagarikano et al., 2015; Wang et al., 2018; Hörnberg et al., 2020; Cherepanov et al., 2021). In clinical studies, intranasal OT has been used to treat ASD. So far, results

have been mixed; some studies find that intranasal OT improves social deficits (Huang et al., 2021), while others report no effects on social deficits (Yamasue et al., 2020; Sikich et al., 2021). Some studies attribute the different responses to OT to differences in individual variability (Kosaka et al., 2016; Parker et al., 2017), though these results have also been challenged (Sikich et al., 2021). Further studies demonstrating the long-lasting effects of stress attenuation by OT are warranted, especially for social threats. This would provide the neurobiological basis for treatment options for social dysfunctions using exogenous OT (Neumann and Slattery, 2016).

Studies in animals strongly support the role of the OT-OTR system in the modulation of traumatic or threat memories (Triana-Del Río et al., 2019). In clinical studies, this system has been investigated in post-traumatic stress disorder (PTSD), an emotional disorder characterized by over-consolidation of traumatic/threat memories, generalization of fear, hyperactivity of the amygdala and attempts to avoid trauma-related cues. Findings from studies involving OT as a therapeutic strategy for PTSD show that an acute dose of intranasal OT increases neural responses to social reward (Nawijn et al., 2017), whereas repeated OT administration reduced symptoms of PTSD, which is correlated with decreased amygdala reactivity to fearful faces, and the attenuation of amygdala-PFC functional connectivity (Frijling, 2017). Intranasal administration of OT has been shown to trigger behavioral and neuronal responses related to threat memory processing in PTSD patients, suggesting that, similar to animal models, OT can amplify the acquisition and consolidation of threat/intrusive memories, on a comparable process of increasing the signal to noise ratio for relevant threat stimuli (Owen et al., 2013; Terburg et al., 2018). In these studies, the effects of exogenous OT are influenced by biological covariates, such as salivary cortisol, heart rate variability, sex, and PTSD polygenic risk scores (Schultebraucks et al., 2022). On the other hand, another group demonstrated that OT administration early after trauma did not attenuate PTSD symptoms in all trauma-exposed participants with acute distress; however, participants with high acute PTSD symptom severity did show beneficial effects of OT (van Zuiden et al., 2017). Following these efforts, Carmassi and colleagues (Carmassi et al., 2021) showed that baseline plasma OT levels are decreased in PTSD patients of both sexes compared to healthy controls. However, in another study, the change in peripheral OT levels did not differ by treatment condition and did not correspond to chana get in PTSD symptoms (Sippel et al., 2021).

Converging translational studies indicate that intranasal administration of OT reaches the brain to trigger physiological effects (Quintana et al., 2019, 2021; Winterton et al., 2021), correlated with a general OT-concentration increment in salivary, plasma, and cerebrospinal fluid samples (Striepens et al., 2013). However, it is still unknown if these effects reflect amplified endogenous OT release upon intranasal OT administration (as a result of positive feedback mechanisms) or the exogenously administered compound (Quintana et al., 2019, 2021). In clinical studies using OT, the statistical power is limited, thus, more systematization, larger sample sizes, and diversity in the sample populations are required, making emphasis on the exact duration of OT administration, its concentration, the dose-response effects, and the stress reactivity of the participants (Quintana et al., 2021; Winterton et al., 2021). Therefore, converging literature support the critical role of OT in social and emotional behaviors in both rodents and humans, but the therapeutic potential of OT on human neuropsychiatric disorders remains to be fully characterized.

Conclusion

While not comprehensive, we have highlighted here the studies that provide compelling evidence on how OT signaling in the limbic network modulates social and stress/threat-related behaviors. At the intersection of social behaviors and stress/threat response is social threat response when the conspecific partner is perceived as a threat. OT exerts an essential role in increasing the signal-to-noise ratio of sensory signals within a social context (Owen et al., 2013; Marlin et al., 2015; Tirko et al., 2018); this effect is potentiated when the social context becomes stressful or threatening context. OT provides resilience against social stress and socially derived threat responses. There are two prominent modulations of the OT system related to social threat, and both of them seem to relate to the increased OT release as a survival signal against the stress/threat context. First, OT is released during social buffering of acute stress responses. For example, OT signaling in the prelimbic cortex reduces freezing expression induced by acute social exposure (Jang et al., 2022), a phenomenon that has been observed in the neighboring anterior cingulate cortex (Burkett et al., 2016), and PVN (Smith and Wang, 2014), hence endogenous oxytocin seems to be fundamental for mediating the buffering effects of social interactions to diminish threat reactions like freezing (Ferrer-Pérez et al., 2020; van den Burg and Hegoburu, 2020). Secondly, social stress also increases the release of OT, as mentioned before for PVN network activity. This increases OTR binding in networks like the lateral septum, where OT modulates the expression and extinction of socially derived threat responses in lactating females, which appears to be tempered by sex hormones (Zoicas et al., 2014; Menon et al., 2018). In this brain area, OT signaling promotes rather exacerbated threat responses (freezing) and aggression responses to social threats (Guzmán et al., 2013; Meyer et al., 2020), similarly, in the PVN of rodent females, increased OT release is correlated to high levels of maternal aggression (Bosch et al., 2005). Excessive or uncontrollable socially induced stress is associated with OT signaling impairments, which are also correlated to high levels of anxiety-like behavior. This is described as the nucleus accumbens (Hou et al., 2020) or

the mPFC (Shi et al., 2021). To counterbalance this effect, exogenous oxytocin promotes resilience to social stress (Hale et al., 2021; Shi et al., 2021), primarily through the involvement of projections from PVN OT neurons to PL (He et al., 2019). Therefore, coordinated regulation of neural circuits across the limbic forebrain is necessary for OT-mediated behavioral and physiological responses to social, stress, and threat-related stimuli when presented in isolation or together.

The crucial challenge in oxytocin research is determining how context-dependent intracellular signaling responses elicit a particular behavioral or physiological response. OTR-induced cellular responses and the signaling mechanisms in behaviorally relevant neural circuits may provide a better understanding of these effects. Behavioral neuroscience will significantly benefit from this knowledge. This knowledge of signaling cascades and secondary messengers will further aid in treatments using oxytocin and its analogs which will facilitate the design of better therapeutic interventions for neuropsychiatric disorders involving oxytocin.

Author contributions

RT-D, SR, JG, and PS: manuscript writing and proofreading. JL and EK: manuscript proofreading. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The oxytocin receptor represents a key hub in the GPCR heteroreceptor network: potential relevance for brain and behavior

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In the last 10 years, it has become increasingly clear that large numbers of axon collaterals extend from the oxytocin (OXT) hypothalamic axons, especially the parvocellular components, to other brain regions. Consequently, the OXT signaling system forms, like other monoamine axons, a rich functional network across several brain regions. In this manuscript, we review the recently indicated higher order G-protein coupled heteroreceptor complexes of the oxytocin receptor (OXTR), and how these, *via* allosteric receptor-receptor interactions modulate the recognition, signaling, and trafficking of the participating receptor protomers and their potential impact for brain and behavior. The major focus will be on complexes of the OXTR protomer with the dopamine D2 receptor (D2R) protomer and the serotonin 2A (5-HT2AR) and 2C (5-HT2CR) receptor protomers. Specifically, the existence of D2R-OXTR heterocomplexes in the nucleus accumbens and the caudate putamen of rats has led to a postulated function for this heteromer in social behavior. Next, a physical interaction between OXTRs and the growth hormone secretagogue or ghrelin receptor (GHS-R1a) was demonstrated, which consequently was able to attenuate OXTR-mediated Gαq signaling. This highlights the potential of ghrelin-targeted therapies to modulate oxytocinergic signaling with relevance for appetite regulation, anxiety, depression, and schizophrenia. Similarly, evidence for 5-HT2AR-OXTR heteromerization in the pyramidal cell layer of CA2 and CA3 in the dorsal hippocampus and in the nucleus accumbens shell was demonstrated. This complex may offer new strategies for the treatment of both mental disease and social behavior. Finally, the 5-HT2CR-OXTR

heterocomplexes were demonstrated in the CA1, CA2, and CA3 regions of the dorsal hippocampus. Future work should be done to investigate the precise functional consequence of region-specific OXTR heteromerization in the brain, as well across the periphery, and whether the integration of neuronal signals in the brain may also involve higher order OXTR-GHS-R1a heteroreceptor complexes including the dopamine (DA), noradrenaline (NA) or serotonin (5-HT) receptor protomers or other types of G-protein coupled receptors (GPCRs).

KEYWORDS

G protein-coupled receptors, oligomerization, heteroreceptor complexes, oxytocin, dopamine, ghrelin, serotonin

Introduction

Oxytocin (OXT) is classically described as a nona-neuropeptide released from nerve terminals in the posterior pituitary into the blood circulation to control parturition uterine contractions, social bonding, and nursing milk letdown (Jurek and Neumann, 2018). This OXT neuropeptide in the posterior pituitary is mainly synthesized in the magno- and parvocellular paraventricular hypothalamic neurons and in the supraoptic neurons (Onaka and Takayanagi, 2019). It should be noted that species differences exist, e.g., in voles OXT is also expressed in the bed nucleus of the stria terminalis (Ross and Young, 2009) and, in glutamatergic neurons of the human prefrontal cortex (Zhong et al., 2022). The oxytocin neuropeptide binds its receptor the oxytocin receptor (OXTR), a G-protein coupled receptor (GPCR), expressed in the periphery and central nervous system (Jurek and Neumann, 2018; Froemke and Young, 2021). Over the last decades, it has become increasingly clear that the hypothalamic oxytocin neurons send projections and especially axon collaterals into many brain areas possessing oxytocin receptors (OXTR), suggesting its function extends to complex behaviors, including the production of food intake and social and emotional behaviors (Jurek and Neumann, 2018; Froemke and Young, 2021). Oxytocin signaling involves among other areas, the limbic system, the central and basolateral amygdala, the midbrain serotonin neurons, and other regions of the lower brain stem also including projections into the spinal cord (Eliava et al., 2016). Moreover, extrahypothalamic regions have also been shown to possess oxytocin neurons (Knobloch and Grinevich, 2014). Overall, oxytocin neurotransmission operates *via* volume transmission similar to other neuropeptides (Borroto-Escuela et al., 2015a), and secreted oxytocin in the blood circulation functions as a peptide hormone.

An important integrative molecular mechanism in the cellular plasma membrane is represented by GPCR heteroreceptor complexes (dimers or higher order complexes) that *via* allosteric receptor-receptor interactions modulate the recognition, signaling, and trafficking of the participating receptor protomers with an impact on other participating proteins (Fuxe et al., 2010a, 2014; Borroto-Escuela et al., 2014, 2015b, 2017; Fuxe and Borroto-Escuela, 2016).

In this review, we will deal with the discovered OXTR heteroreceptor complexes and their function, in which the dopamine D2R protomers (Romero-Fernandez et al., 2013; de la Mora et al., 2016), 5-HT2AR and 5-HT2CR protomers (Chruścicka et al., 2019, 2021; Wallace Fitzsimons et al., 2019) participate and discuss their potential relevance in brain and behavior. They will give a major contribution to the oxytocin field since through the allosteric receptor-receptor interactions in the OXTR heteroreceptor complexes the OXTR protomer can modulate and be modulated y the other participating receptor protomers like the D2R, 5-HT2AR, and 5-HT2CR. The integrative activity of the OXTR becomes substantially enlarged with modulation among others of the monoamine receptors.

Neuroanatomy of the oxytocin pathways and their axon collaterals

Oxytocin positive neurons

The oxytocin immune-reactive nerve cell bodies only exist in the magnocellular and parvocellular areas of the paraventricular hypothalamic nucleus and in the supraoptic nucleus except for the bed nucleus of the stria terminalis (Liao et al., 2020; Froemke and Young, 2021). Most of the oxytocin positive axons in the magnocellular pathway pass *via* the median eminence into the posterior pituitary where the oxytocin nerve terminals release oxytocin into the blood capillaries to act as hormones. However, the oxytocin peptide is also released from cell bodies and dendrites into the extracellular space to act *via* volume transmission (Fuxe et al., 2010b; Borroto-Escuela et al., 2015a) to synchronize the firing of the oxytocin networks in the

hypothalamus and favor waves of oxytocin release into the blood as demanded in nursing and parturition (Froemke and Young, 2021).

In the last 10 years, it has become established that a rich network of axon collaterals is formed from the oxytocin hypothalamic axons, especially the parvocellular ones, which project to different brain regions, including nucleus accumbens and caudate putamen (Jurek and Neumann, 2018; Froemke and Young, 2021). The oxytocin collaterals form rich networks in the brain, like those from the monoamine axons do (Fuxe, 1965a,b), in many areas of the brain like the hippocampus, limbic regions, dorsal and ventral striatum, amygdala, the lower brain stem and the spinal cord (Onaka and Takayanagi, 2019; Froemke and Young, 2021). The introduction of using oxytocin-Cre mice in which the Cre recombinase is expressed under the oxytocin promotor combined with oxytocin nerve cell-specific viruses carrying a Cre-dependent promotor for, e.g., a fluorescent protein, allowing for the necessary sensitivity for proper mapping of the widespread distribution of oxytocin and its receptors (Froemke and Young, 2021).

Oxytocin receptors in the brain

The areas receiving oxytocin nerve terminals contain low to moderate densities of oxytocin receptors (OXTR) as studied with receptor autoradiography and experiments performed on mouse line with fluorescence-labeled OXTR (Yoshida et al., 2009; Froemke and Young, 2021). It is of interest that in the cerebral cortex the OXTRs appear to be found to a substantial degree on the inhibitory GABA interneurons showing somatostatin or parvalbumin immunoreactivities (Nakajima et al., 2014). A recent review has in fact been written on the role of OXT signaling at the synaptic connections (Bakos et al., 2018). OXTR exists at the presynaptic and postsynaptic levels of excitatory and inhibitory synapses modulating their synaptic transmission. OXT can improve postsynaptic and presynaptic glutamate transmission (Osako et al., 2001) and depress spontaneous GABA inhibitory postsynaptic currents involving a presynaptic mechanism. Furthermore, it is of interest that OXT *via* a certain class of prefrontal cortical interneurons can modulate female sociosexual behavior (Nakajima et al., 2014). It seems likely that the OXTRs modulation of brain networks takes place mainly through volume transmission which is true for other neuropeptides in the brain, including galanin and neuropeptide Y (Fuxe et al., 2010b; Borroto-Escuela et al., 2015a). However, it is also possible that the oxytocin GPCR heterocomplexes formed, while mainly located in extra-synaptic membranes, can also exist in synaptic membranes.

The major change in evolution of mammals, regarding the hormonal role of the OXT-OXTR system, may have been the appearance of an increasing number of oxytocin axon collaterals that are formed from hypothalamic neurons that innervate large parts of the brain. In this way, neuroendocrine information can reach large parts of the central nervous system (Jurek and Neumann, 2018) including the spinal cord and through the formation of heterocomplexes that integrate this information into the brain networks involved, especially for social behavior, food intake, and neuroendocrine events. See also the excellent review of Froemke and Young, which discusses the most recent findings on the neurocircuitry of oxytocin mainly in the context of social behavior (Froemke and Young, 2021). This integrative mechanism may be disturbed in mental diseases like depression and anxiety (Perez de la Mora et al., 2022).

Recently, the crystal structure of the human OXTR was established in a complex with the OXTR antagonist retosiban which is in clinical use for counteraction of labor (Waltenspuhl et al., 2020). It is of interest that the OXTR has a dependence on allosteric modulators like cholesterol and magnesium (Mg^{2+}) for full activation (Klein et al., 1995a,b; Perez de la Mora et al., 2022). In the crystal structure, it was possible to observe that the cholesterol was bound in a pocket produced by transmembrane helices IV and V (Waltenspuhl et al., 2020). This feature gives a structural foundation for understanding how levels of cholesterol can allosterically influence the overall function of the OXTR (Waltenspuhl et al., 2020). In addition, the existence of two conserved residues with negative charges of transmembrane helices I and II of the OXTR were also identified (Waltenspuhl et al., 2020). These residues can be a site for the Mg^{2+} *via* electrostatic interactions, which may allow the development of allosterically enhanced agonist binding. This has provided a structural basis for the allosteric modulation produced by cholesterol and Mg^{2+} in the OXTR, which may be true also for other GPCRs, especially the vasopressin receptor and is poised to have important functional consequences for receptor functioning. Similarly, this concept has relevance for the allosteric receptor-receptor interactions in OXTR and other types of heteroreceptor complexes (Borroto-Escuela et al., 2012).

Oxytocin heteroreceptor complexes

An extensive literature now supports the fact that Class A and B GPCRs function not only as monomeric entities but can crosstalk with other GPCRs and can even form dimers or higher-order oligomers (Terrillon and Bouvier, 2004; Borroto-Escuela et al., 2012, 2014; Schellekens et al., 2013a; Navarro et al., 2018; Milligan et al., 2019; Nemoto et al., 2022). In particular, the OXTR has been reported to be able to form homomers (Cottet et al., 2010; Busnelli et al., 2016) as well as to form dimers with other GPCRs, including with the highly related vasopressin V1a and V1b (Terrillon et al., 2003), the GHSR (Wallace Fitzsimons et al., 2019), the D2 (de la Mora et al., 2016), the 5HT2A (Chruścicka et al., 2019) and the 5HT2C (Chruścicka et al., 2021; **Figures 1**, **2**). Interestingly, OXT was previously shown to interact with the orexigenic hormone

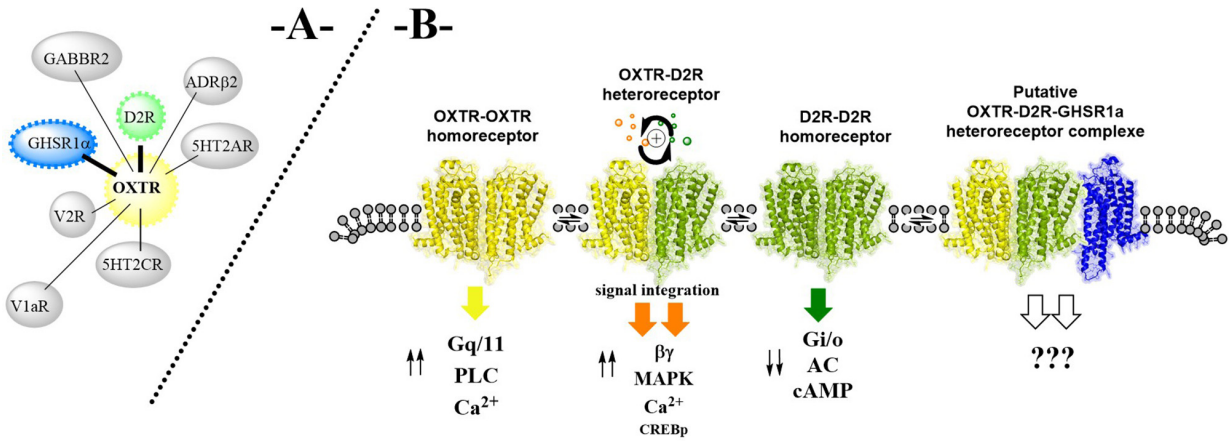

FIGURE 1
(A) On the existence of oxytocin (OXTR) heteroreceptor complexes (e.g., D2R-OXTR, GHS-R1a-OXTR, OXTR-5HT2AR, and OXTR-5HT2C, for further details see www.gpcr-hetnet.com) in the plasma membrane of brain regions and their putative balance with higher order oxytocin heteroreceptor complexes through a more general participation of the ghrelin receptor protomers in the heterodimers shown. **(B)** As an example, the balance between an OXTR homodimer, a D2R homodimer, and an OXTR-D2R heterodimer is given in the plasma membrane together with the potential formation of an OXTR-D2R-GHSR1a heterocomplex. OXTR homodimer signaling involves an increase in phospho lipase C (PLC) activity and calcium levels (Ca^{2+}) over Gq/11 activation while the D2R homodimer signaling takes place *via* activation of Gi/o producing inhibition of adenylate cyclase (AC) bringing down cyclic adenosine monophosphate (cAMP) formation. The ingration of these signals develops in the OXTR-D2R heterodimer and results in an enhanced activity over both the cAMP response element-binding protein (CREB), the mitogen-activated protein kinase (MAPK), and PLC-Ca^{2+} signaling pathways, mediated over the beta/gamma components of the G proteins.

ghrelin, where intravenous OXT administration reduced the circulating levels of ghrelin (Vila et al., 2009). In contrast, *in vitro* exposure of neurohypophyseal cells to ghrelin resulted in enhanced oxytocin secretion from the cells (Galfi et al., 2016). Previous data have also demonstrated that oxytocin administration modulates serotonin (5-HT) synthesis and 5-HT receptor binding potential, resulting in an overall modulation of the serotonergic system (Mottolese et al., 2014). The OXTR, GHSR, D2R, 5-HT2AR, 5-HT2CR, are known to play critical roles in a variety of physiological processes such as metabolism, and central appetite regulation, mood, and social behavior (Wardman et al., 2016; Grammatopoulos, 2017). Thus, OXTR crosstalk or dimerization will impact downstream signaling, conferring functional significance in several metabolic and stress-related disorders, including obesity and depression. Both, GHSR, 5HT2AR and 5HT2CR dimerization with the OXTR have been shown to result in attenuation of oxytocin-mediated downstream signaling (**Figure 2**; Chruścicka et al., 2019, 2021; Wallace Fitzsimons et al., 2019; Borroto-Escuela et al., 2021). However, the scale and functional outcome of OXTR, and other types of GPCR dimerization in the centrally regulated mechanisms are not yet fully appreciated and are only beginning to emerge.

D2R-OXTR heterocomplexes

In 2013, evidence was obtained for the existence of D2R-OXTR heterocomplexes in the nucleus accumbens and the caudate putamen (Romero-Fernandez et al., 2013) using *in situ* proximity ligation assay (Borroto-Escuela et al., 2013). These results were validated by using the BRET technique in HEK293 cells after co-transfection with $D2R^{Rluc}$ and $OXTR^{GFP2}$ (de la Mora et al., 2016). In D2R binding saturation experiments in accumbal membranes using 3H-raclopride (D2R antagonist), oxytocin at 3 nM increased the maximal binding capacity (Bmax) values for the D2R antagonist, indicating that through allosteric receptor-receptor interactions, oxytocin can increase the availability of the D2R to bind the D2R antagonist due, e.g., to reduced internalization of the D2R protomer (Romero-Fernandez et al., 2013).

In 3H-raclopride competition experiments with dopamine (DA), oxytocin (3 nM) highly significantly increased the affinity of the high-affinity D2R agonist binding sites, giving indications that oxytocin can increase the D2R recognition and signaling in accumbal membranes (Romero-Fernandez et al., 2013). It was found that oxytocin increased D2R Gi/o coupling in accumbal membranes, using the GTP gamma S accumulation assay (Romero-Fernandez et al., 2013). Based on the outstanding work of Young and colleagues on the interactions between DA and OXT systems (Young and Wang, 2004) and in line with the results of Romero-Fernandez (Romero-Fernandez et al., 2013), it seems likely that the D2R-OXTR heterocomplexes play a significant role in social behavior. Based on the impressive study of Striepens et al. (2014), it becomes important to determine in future work if it is also possible to observe changes or not in 11C-raclopride binding assays in rodents. It is certainly of high interest to establish if there are differences

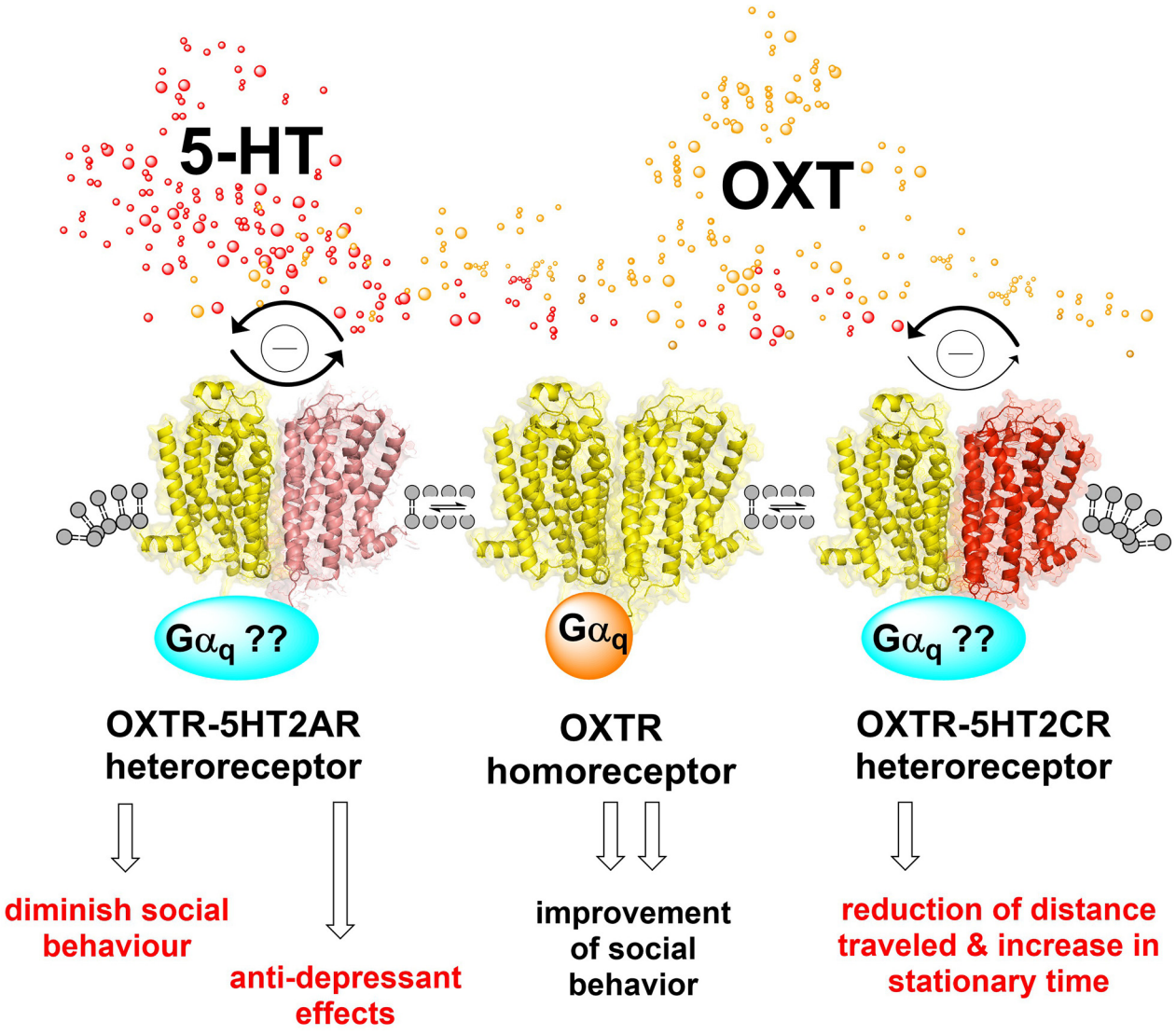

FIGURE 2
Oxytocin and serotonin heteroreceptor complexes in the brain. The OXTR-5-HT2AR heteroreceptor complex, shown as a heteroreceptor dimer in the plasma membrane, is found in the left region. The bidirectional antagonistic allosteric receptor-receptor interaction is outlined leading to attenuation of the oxytocin receptor protomer and 5-HT2AR protomer signaling as indicated by the connected two arrows in strong black color. A possible modulation in the G alpha q coupling of this heteroreceptor complex is indicated by the question mark. The 5HT2AR agonist-induced allosteric inhibition of the oxytocin receptor protomer can diminish its increase in social behavior (Froemke and Young, 2021). The Oxytocin receptor protomer (OXTR) can upon activation allosterically inhibit 5-HT2AR protomer signaling and diminish the 5-HT2AR signaling with possible antidepressant effects since 5-HT2AR mediates depressive effects (Borroto-Escuela et al., 2021; Perez de la Mora et al., 2022). The oxytocin homo-receptor complex, shown as a homo dimer, is found in the center of the illustration, coupled to G alpha q. It improves upon the activation of social behavior (Froemke and Young, 2021). The OXTR-5-HT2CR heteroreceptor complex, shown as a heteroreceptor dimer in the plasma membrane, is illustrated on the right side of the figure. The ability of the 5-HT2CR protomer (red) activation to allosterically attenuate the oxytocin receptor protomer G alpha q mediated signaling is substantially stronger (thick arrow) than the ability of the OXTR receptor agonist to allosterically diminish the 5-HT2CR G alpha q signaling (narrow arrow). It may involve differential changes in the degree of alterations in G alpha q coupling and of coupling also to other G proteins. In line with the biochemical results, the 5-HT2CR antagonist strongly enhanced the oxytocin receptor agonist-induced reduction of distance traveled and increase in stationary time (Chruścicka et al., 2021). These findings underline the functional relevance of the OXTR-5-HT2 complexes and their receptor-receptor interactions. Thus, the findings give indications that blockade of 5-HT2CR signaling can enhance oxytocin receptor signaling and produce improvement of social disease.

in the ability of OXT to modulate D2Rs in, e.g., rodent vs. human.

It is of substantial interest that the enhanced bidirectional allosteric D2R-OXTR interactions (Figure 1) with improved signaling over the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), mitogen-activated protein kinase (MAPK) and phospholipase C (PLC) signaling pathways, can have relevance for the anxiolytic effects observed

upon microinjections of the D2R agonist quinpirole and oxytocin into the central amygdala (de la Mora et al., 2016). The Shock-probe burying test was used which represents an unconditioned model of anxiety/fear. The anxiolytic effects were blocked by co-infusion with a D2R-like antagonist raclopride in the central amygdala (de la Mora et al., 2016). Thus, restoring the faciliatory D2R-OXTR interactions can represent a new type of treatment for excessive anxiety. The receptor interface can involve transmembrane segment 5 (TM5) and the N-terminal region in view of the two triplet amino acid homologies observed in these regions that is hypothesized to favor the appearance of hot spots which increases the strength of the receptor interface formed (Tarakanov and Fuxe, 2010; Borroto-Escuela et al., 2018a).

It will be of interest to test if also putative D3R-OXTR complexes can be involved in social behavior in view of the existence of D2R-D3R heterocomplexes (Scarselli et al., 2001). D1R-D3R and A2AR-D3R heterocomplexes have also been demonstrated (Torvinen et al., 2005; Fiorentini et al., 2008) as well as D3R-nAChR heterocomplexes (Bono et al., 2020).

Oxytocin receptor-ghrelin receptor (GHS-R1a) heterocomplexes

Over the last years, the ghrelin receptor (GHS-R1a) has been shown to heterodimerize with several other GPCRs, including the neurotensin receptor 1 (NTS1R; Takahashi et al., 2006), the dopamine D1R (Jiang et al., 2006; Schellekens et al., 2013a) and D2R (Kern et al., 2012); the melanocortin receptor 3 (MCR3; Rediger et al., 2011; Muller et al., 2013; Schellekens et al., 2013a) and the 5HT2CR (Schellekens et al., 2013a; Kern et al., 2015). For reviews on ghrelin and its receptor forming the mentioned heterocomplexes, see Schellekens et al. (2013b), Borroto-Escuela et al. (2014), Wellman and Abizaid (2015), and Ringuet et al. (2021). Similarly, the OXTR has also been shown to heterodimerize with the D2R (Romero-Fernandez et al., 2013; de la Mora et al., 2016). In addition, recent evidence from the Schellekens group has shown that the OXTRs can form functional heteroreceptor complexes with the GHS-R1a (**Figure 1**; Schellekens et al., 2013a,b) and also with the 5-HT2AR (Chruścicka et al., 2019) and 5-HT2CR (Schellekens et al., 2015), the latter two being discussed in later paragraphs. Notably, co-expression of the GHS-R1a and the OXTR was shown to significantly impair oxytocin-mediated Gαq signaling (Wallace Fitzsimons et al., 2019). Ghrelin is a gut hormone (28-amino acid peptide) that can cross the blood-brain barrier and reach the CNS, where it activates the GHS-R1a, resulting in a significant enhancement of appetite, food intake, and modulation of food reward signaling (Schellekens et al., 2013a,b,c). However, the role of the GHS-R1a in the brain as a target for ghrelin is not clear, since penetration into the brain by ghrelin mainly may take place *via* rapid sensing of circulating ghrelin by hypothalamic appetite-modifying neurons (Schaeffer et al., 2013) and over the median eminence open to the portal blood (Rodriguez et al., 2010). Moreover, the GHS-R1a possesses a high constitutive activity that reaches 50% of its maximal activity that can be modulated by dynamic expression and allosteric mechanisms in GPCR-GHS-R1a complexes (Holst et al., 2003; Petersen et al., 2009; Schellekens et al., 2013a,b; Perez de la Mora et al., 2022). The novel GHS-R1a/OXTR pair was revealed by the Schellekens group using *in vitro* approaches and a novel flow cytometry-based fluorescence resonance energy transfer (fc-FRET) technique (Wallace Fitzsimons et al., 2019). Furthermore, co-location of the two receptor protomers was observed in primary hippocampal and hypothalamic cultures of postnatal day 1 (P1) Sprague Dawley rats. Wallace Fitzsimons et al. (2019) showed increased trafficking of the OXTR/GHS-R1a pair following co-expression (Chruścicka et al., 2018). Notably, the most significant finding was that the formation of the GHS-R1a-OXTR heterocomplex led to an attenuation of oxytocin-induced calcium mobilization mediated *via* G alpha q signaling. This reduction was diminished upon administration of a GHS-R1a antagonist (Wallace Fitzsimons et al., 2019). The mechanism was proposed to involve a slower recycling of the OXTR protomer in this heterocomplex and/or a partial switch in the OXTR signaling from G alpha q towards G alpha i signaling with inhibition of adenylyl cyclase (AC), cAMP, and protein kinase A (PKA) signaling pathway (Wallace Fitzsimons et al., 2019).

The latter mechanism is attractive and is in line with evidence that allosteric transmembrane receptor-receptor interactions have a significant role in altering the signaling of the participating receptor protomers (Fuxe and Borroto-Escuela, 2018; Borroto-Escuela et al., 2021). However, it remains to be determined if the GHS-R1a modulates the OXTR protomer recognition *via* allosteric receptor-receptor interactions and what the functional consequences are of this intricate interaction *in vivo*. As mentioned above, the GHS-R1a also forms heterocomplexes with other GPCRs like dopamine and serotonin receptor subtypes (Schellekens et al., 2013a,b). This raises the possibility of trimeric OXTR-GHS-R1a-D2R heterocomplexes, in addition to heteromeric complexes of GHS-R1a-OXTR, D2R-OXTR, and D2R-GHS-R1a, which may be independent of ghrelin for its signaling (**Figure 1**; Holst et al., 2003; Petersen et al., 2009). Therefore, It seems possible that the GHS-R1a can act as a dynamic adapter GPCR to modulate and fine-tune higher order OXTR heteroreceptor complexes across a wide range of functionalities, from social behavior, food intake to mood and reward functions (Schellekens et al., 2013b,c). Further mechanistic understanding as well as translation of heteromeric significance *in vivo* will be key for the full understanding of how the GHS-R1a operates in the OXTR heteroreceptor complexes of the brain.

Hypothesis on the integrative operation of the D2R, OXTR, and GHS-R1a protomers forming multiple heterodimers and higher order heterocomplexes modulating food intake considering their molecular integration in the different circuits of food intake

A highly significant review has been written by Onaka and Takayanagi (2019) on the role of the oxytocin-OXTR system in food intake. Food intake activates vagal afferents which reach the nucleus tractus solitarius where A2 noradrenergic neurons (Dahlstroem and Fuxe, 1964) project to the hypothalamus, especially those expressing prolactin-releasing peptide (Okuno et al., 2012), where the hypothalamic oxytocin neurons become stimulated (Okuno et al., 2012). The result was an OXTR-mediated reduction of food intake with the termination of the meal. Under special conditions, an increased food intake was found (Onaka and Takayanagi, 2019). However, the oxytocin neurons may not be the major direct target. Instead, primary targets may involve the Agouti-related peptide (AgRP)/neuropeptide Y (NPY) positive neurons in the arcuate nucleus with orexigenic effects and the proopiomelanocortin (POMC) positive arcuate neurons with anorexic effects which play an important role in food intake (Sohn, 2015). These two neuronal populations project to neurons in the paraventricular hypothalamic nucleus expressing melanocortin 4 (MC4), almost lacking the OXTRs (Onaka and Takayanagi, 2019). There also exists a neuronal D2R positive population in the arcuate nucleus of the hypothalamus (Romero-Fernandez et al., 2014) that can contribute to the ability of the ergot D2R agonist cabergoline to inhibit food intake (Kern et al., 2015).

To understand how all these transmitter signals can be integrated in their modulation of hedonic food intake, the existence of a GABAergic neuronal cell population is proposed in the hypothalamus forming a nucleus in which all these transmitter signals can be integrated to obtain a proper regulation of food reward (**Figure 3**). The GABA axons can then project to GABA interneurons inhibiting the meso-limbic DA reward neurons with origin in the ventral tegmental area (VTA) where several DA nerve cell subgroups exist (**Figure 3**; Dahlstroem and Fuxe, 1964; Fuxe, 1965a; Anden et al., 1966; Arbuthnott et al., 1970; Fuxe et al., 2010b). The GABA projection neurons will upon activation reduce the activity of the GABAergic interneurons and set free the activity of certain populations of VTA DA reward neurons, since their inhibitory synaptic GABA A receptor-mediated transmission becomes reduced (**Figure 3**; Suyama and Yada, 2018). As an example, we will focus on the relevance of the integrative allosteric D2R, OXTR, and GHS-R1a interactions in heteroreceptor complexes (**Figure 4**) altering the firing of the postulated hypothalamic GABA projections to the GABA interneurons reducing their inhibitory activity setting free activity in many meso-limbic DA reward neurons. Upon their activation DA can be released in the nucleus accumbens and activate D2R on the ventral striatal-pallidal GABA neurons producing inhibition of the activity of these GABA anti-reward neurons (Borroto-Escuela et al., 2018b). In this way, the palatable food intake can cause rewards to develop in the cortical networks (Schellekens et al., 2013a,b,c; Onaka and Takayanagi, 2019).

Coming back to the postulated hypothalamic GABA neurons potentially located within the lateral part of the medial forebrain bundle and projecting to certain GABA interneurons of the ventral tegmental area, it is proposed that they are enriched in D2 receptors like the ventral striatal-pallidal GABA anti-reward neurons (Borroto-Escuela et al., 2018b). It may be that these D2Rs are the major targets for the ability of the D2R agonist cabergoline to reduce food intake (Kern et al., 2015). In view of the demonstration of D2R-OXTR heterocomplexes with enhancing allosteric receptor-receptor interactions in the brain (Romero-Fernandez et al., 2013), it is suggested that they also exist in these postulated hypothalamic GABA neurons. Oxytocin has also been reported to preferentially bring down carbohydrate intake and leave fat intake unaffected (Onaka and Takayanagi, 2019). It can involve an allosteric enhancement of D2R protomer signaling in the D2R-OXTR heterocomplex. The major action of these events may be a hyperpolarization of these GABA neurons due to the D2R protomer-induced opening of the G protein inwardly rectifying potassium channels (GIRK channels; **Figure 4**), causing a reduction in the firing of these postulated GABA hypothalamic-VTA projection neurons setting to a substantial degree the GABA inter-neurons free from inhibition. Thus, due to an enhancement of the GABA interneuron-mediated inhibition of some VTA DA cell groups, some meso-limbic DA reward neurons can become inhibited and mediate the inhibition of food reward.

It should also be considered that the OXTR can form heterocomplexes with both the GHS-R1a and the D2R. Thus, a formation of the putative D2R-GHS-R1a-OXTR heterocomplex may exist and modulate the activity of the postulated hypothalamic GABA projection neurons to the GABA interneurons of the VTA (**Figures 3**, **4**; Kern et al., 2012, 2015). When the ghrelin receptor is pharmacologically antagonized or knocked out, the D2R agonist cabergoline can no longer inhibit food intake. It is likely that it leads the allosteric modulation by the ghrelin receptor protomer of the D2R and OXTR protomers in the complexes is lost. It can lead to failure to reduce the firing of the hypothalamic GABA neurons and maintain inhibition of GABA interneurons. As a result, increased activity can develop in some meso-limbic DA reward neurons (Kern et al., 2012; Wellman and Abizaid, 2015). Going back to the key hypothalamic GABA neurons postulated to exist (see above), it seems clear that the D2R protomer-mediated inhibition of food intake depends also on

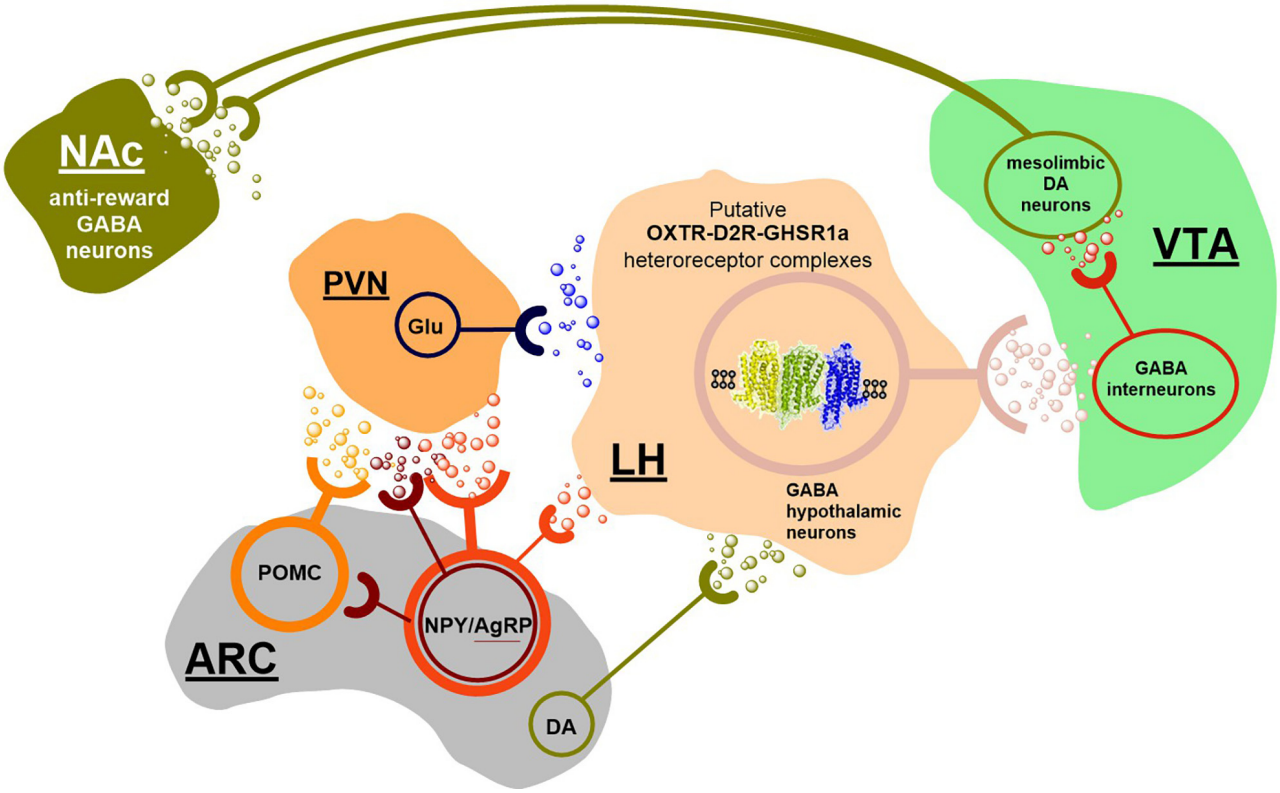

FIGURE 3
Hypothesis on the brain circuitry of food reward. Food intake activates vagal afferents which reach the nucleus tractus solitarius where A2-noradrenergic positive neurons project to the hypothalamus, where the hypothalamic oxytocin neurons become stimulated with reduction of food intake and termination of the meal (not shown). However, under certain conditions the oxytocin neurons may not be the major direct target. Instead, primary targets may involve the Agouti related peptide (AgRP)/neuropeptide Y (NPY) neurons in the arcuate nucleus with orexigenic effects and the arcuate proopiomelanocortin (POMC) neurons with anorexic effects which play an important role in food intake. These two neuronal populations project to neurons in the paraventricular hypothalamic nucleus expressing melanocortin 4 receptor, almost lacking the OXTRs. There also exists a neuronal D2R in the arcuate nucleus of the hypothalamus that can contribute to the ability of the ergot D2R agonist cabergoline to inhibit food intake. To understand how the various orexigenic and anorexigenic signals in the hypothalamus, including the gastric peptide ghrelin, can be integrated into their modulation of reward circuits involving the hedonic aspects of food intake, it is proposed the existence of a GABAergic neuronal population in the lateral hypothalamus. This population can form a nucleus that can receive these signals directly or indirectly. and integrate them mainly through two types of heteroreceptor complexes, OXTR-D2R-GHS-R1a high order heterocomplexes and NMDAR-D2R heterocomplexes. This Integration process can have a major role in determining the activity of these inhibitory GABA hypothalamic neurons. These key integrative GABA neurons send projections to the GABA interneurons inhibiting DA cell groups in the ventral tegmental area belonging to the meso-limbic DA reward neurons projecting to the nucleus accumbens. The major integrative mechanism in the key hypothalamic GABA neurons shown can be the postulated OXTR-D2R-GHSRIa high-order heteroreceptor complexes in the plasma membrane of extrasynaptic and synaptic membranes of these GABA neuron populations forming a GABA nucleus. This integrative mechanism can have a major role in controlling and modulating the glutamate drive on these GABA neurons by the ability of the activated D2R protomer to open the G protein-coupled inwardly rectifying potassium (GIRK) channels leading to hyperpolarization and reduction of the glutamate drive. The modulation of the glutamate drive can also involve NMDAR-D2R heterocomplexes. A dynamic balance between glutamate drive and D2R protomer mediated inhibition of these key GABA neurons can in this way be obtained with an appropriate firing of these inhibitory GABA neurons projecting onto the GABA interneurons in the VTA area. In this way, a suitable GABA release and correct inhibition of the meso-limbic DA reward neurons can be obtained. As a result, the GABA anti-reward neurons in the nucleus accumbens involved in food reward regulation can be properly regulated. This hypothesis will be tested in future work.

the Ghrelin receptor protomer. The postulated key hypothalamic GABA neurons discussed, can thus contain D2R-GHS-R1a-OXTR heterocomplexes in which dynamic allosteric receptor-receptor interactions can develop to modulate the D2R signaling and enable dynamic changes in food reward. As mentioned, GHS-R1a-OXTR heterocomplexes have been demonstrated with the ability to modulate oxytocin signaling (Wallace Fitzsimons et al., 2019) and can exist in the GABA neurons postulated above.

However, as proposed also other hypothalamic orexigenic and anorexigenic transmitter signals may reach including these postulated key hypothalamic integrative GABA neurons indirectly or directly. It can involve the AgRP and NPY released from axons originating in the arcuate nucleus with orexigenic effects and POMC also from the arcuate nucleus with anorexigenic effects. They are regarded to mainly project to hypothalamic paraventricular neurons expressing

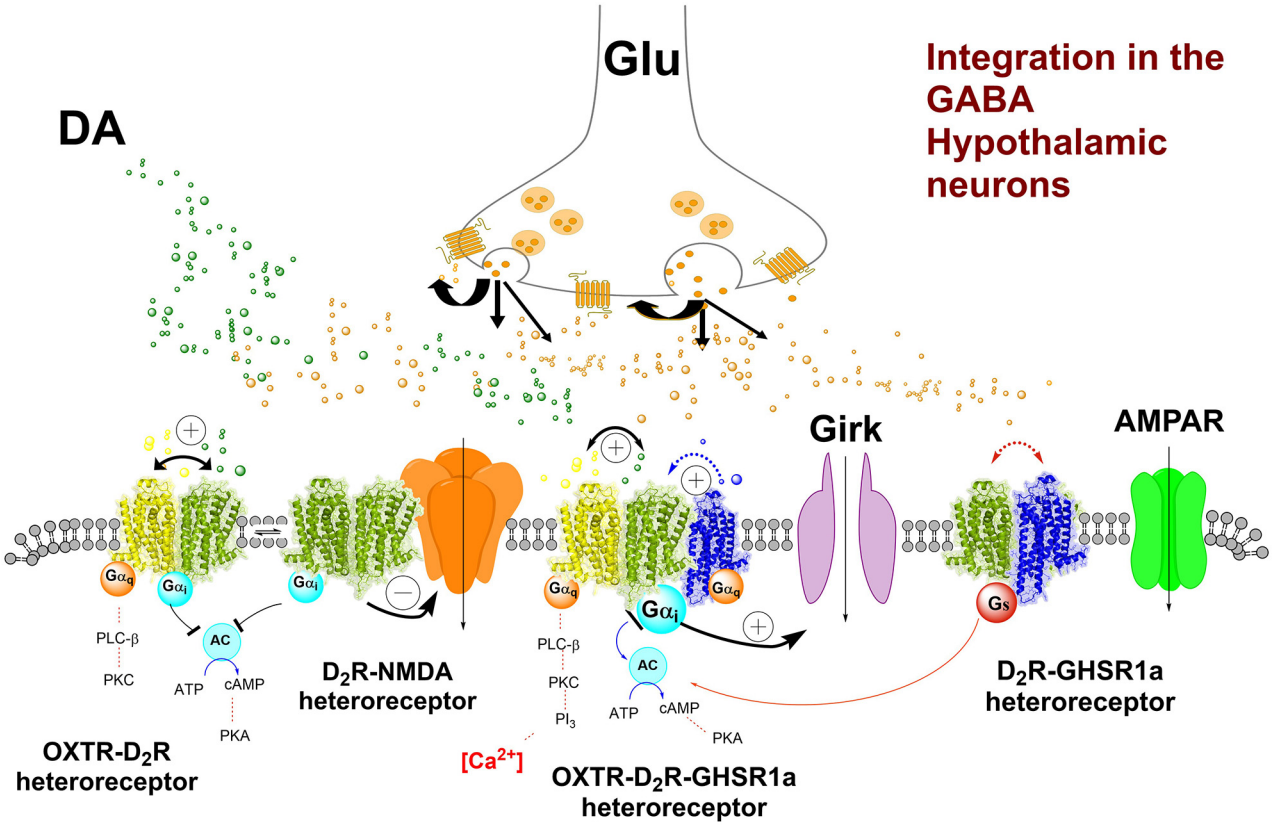

FIGURE 4
Hypothesis on the key heteroreceptor complexes in the proposed inhibitory GABA nerve cell population (nucleus) in the lateral hypothalamus projecting to the inhibitory GABA interneurons in the ventral tegmental area (VTA) controlling meso-limbic DA reward neurons in the VTA. The key higher order heterocomplexes OXTR-D2R-GHS-R1a and the NMDAR-D2R are shown in the plasma membrane of the GABA neurons. The trimeric complex is indicated to be in balance with the OXTR-D2R, OXTR-GHS-R1a, and D2R-GHS-R1a in the plasma membrane. The pharmacology indicates that D2R activation results in the inhibition of food intake related to the inhibition of food reward. The mechanism existing in the trimeric complex may be the D2R-induced opening of the GIRK channels leading to inhibition of the firing of the hypothalamic GABA neurons. Through positive allosteric receptor-receptor interactions the OXTR protomer can enhance the inhibitory D2R signaling. Also, GHS-R1a likely plays a role in this trimeric complex since the removal of the Ghrelin receptor blocks the inhibitions of food intake by the D2R protomer (see text). Thus, it seems likely that the existence of the Ghrelin receptor protomer is necessary for the correct allosteric receptor-receptor interactions to develop by allowing the appropriate conformational changes to develop in this trimericheteroreceptor complex. Thus, the D2R protomer activation can allow the inhibition of the hypothalamic GABA neurons projecting to the VTA GABA interneurons. Also, the potential existence of the NMDAR-D2R hetero complexes in the hypothalamic GABA neurons may help reduce the glutamate drive through D2R protomer-mediated inhibition of the NMDA receptors Thus, this mechanism may also contribute to lowering food-reward. There can exist other types of glutamate receptors located on the hypothalamic GABA neurons that can play an important role like the AMPA receptor and kainate receptors. They can contribute to strong glutamate activation of the hypothalamic. GABA neurons lead to considerable increase of glutamate drive and increased activity in the meso-limbic DA reward neurons by the inhibition of the GABA interneurons and increased food reward can develop also in this way.

MC4Rs (Onaka and Takayanagi, 2019). These neurons may project directly to the postulated key hypothalamic integrative GABA neurons and are glutamatergic (Onaka and Takayanagi, 2019). Their detailed connections have not been established.

The hypothesis introduced proposes that food reward regulation can be accomplished through the existence of key integrative GABA neurons in the lateral hypothalamus sending projections to GABA interneurons inhibiting DA subgroups in the VTA being part of the meso-limbic DA reward neurons to the nucleus accumbens and limbic cortex. Major integrative mechanisms in these key hypothalamic GABA neurons can be the high-order D2R-GHS-R1a-OXTR heterocomplexes in the plasma membrane of extra-synaptic and synaptic membranes and the integration of the synaptic glutamate receptors (Suyama and Yada, 2018) with the D2R, especially through NMDAR-D2R heterocomplexes (Liu et al., 2006). In such ways a dynamic balance between glutamate drive and D2R-mediated inhibition of these GABA neurons can be obtained, leading to an appropriate firing of the inhibitory GABA signaling onto GABA

VTA interneurons obtaining a suitable GABA release and correct inhibition or lack of inhibition of the component of the mesolimbic DA neurons involved in food reward.

A novel OXTR-5HT2AR-heterocomplex and its potential function for brain and behavior

The 5HT2AR-OXTR heteroreceptor complex was recently discovered in the laboratory of Dr. Schellekens (Chruścicka et al., 2019). Initial considerations for a potential dimer between 5-HT2AR and OXTRs were based on the fact that both GPCRs are located in 5-HT neurons and 5HT2ARs stimulate oxytocin release from the paraventricular hypothalamic neurons (Zhang et al., 2002; Yoshida et al., 2009). Therefore, a specific crosstalk between the OXTR and the 5-HT2AR receptors exists and the OXTR had also already been demonstrated in another heterocomplex of D2R-OXTR (Romero-Fernandez et al., 2013; **Figures 1**, **2**). In the Schellekens lab, the first evidence for a physiological interaction came again from fc-FRET-based experiments using HEK293 cells (Chruścicka et al., 2019). A robust fc-FRET, depicted as a percentage of cells and median fluorescence was shown. It should be noted that the fc-FRET signal was not caused by overexpression, random collision, or dimerization of fluorescent proteins. Next, cellular colocalization of the OXTR and the 5-HT2AR was found not only in the plasma membrane but also intracellularly which is in line with a co-trafficking of both receptors together. Final evidence was delivered using *in situ* proximity ligation assay (PLA), which demonstrated the relevance of the 5-HT2AR-OXTR heterocomplexes *in vivo* in rodent brains.

High densities of PLA puncta were observed in the pyramidal cell layer of CA2 and CA3 in the rat dorsal hippocampus using confocal microscopy. Substantial densities of PLA puncta were also observed in the cingulate cortex around pyramidal nerve cell bodies and along apical dendrites. In the nucleus accumbens shell also accumulations of PLA puncta with high and low densities were found indicating that the 5-HT2AR-OXTR heterocomplex was found in certain types of nerve cell populations (Chruścicka et al., 2019). While no other brain regions have been investigated to date, these results are promising for the potential relevance of the 5HT2AR/OXTR pair in other regions of the brain as well.

Functionally, an attenuation of the Gαq-mediated OXTR and 5-HT2AR receptor protomer signaling was observed, upon the formation of this heteroreceptor complex (Chruścicka et al., 2019). The results indicate that this attenuation is dependent on the specific bidirectional antagonistic receptor-receptor interaction in this complex and not on their expression level, nor on the fluorescent tags or gene delivery mode. It should be underlined that none of the receptor antagonists for the two receptor protomers of the 5-HT2AR-OXTR heterocomplex blocked their signaling. Thus, the mechanism involved is not yet fully clear, but it may be that the orthosteric binding sites for the endogenous transmitter 5-HT and oxytocin remain in the heteroreceptor complex but not for the orthosteric antagonist binding site for the OXTR and 5HT2AR protomers in the 5-HT2AR-OXTR heterocomplex. This complex may offer new strategies for the treatment of mental diseases, especially depression (Perez de la Mora et al., 2022), and social behavior (**Figure 2**). It will be interesting to investigate if the GHS-R1a is also a potential heteromeric partner in this novel complex, forming a higher-order GHS-R1a/OXTR/5-HT1AR complex.

A novel OXTR-5-HT2CR heterocomplex and its potential function for brain and behavior

The Schellekens group also recently demonstrated the formation of a 5-HT2CR-OXTR heterocomplex, using *in vitro* heterologous cell expression systems and fc-FRET combined with *ex vivo* proximity ligation assay (Chruścicka et al., 2021).

Noteworthy, co-expression of the 5-HT2CR protomer was able to markedly diminish the oxytocin-induced increases in Gαq-mediated calcium mobilization of the OXTR. The mechanism is the production of a constitutive allosteric brake on the G alpha q signaling in the OXTR protomer made possible through the formation of the 5-HT2CR-OXTR heterocomplex. Interestingly, the inhibition on OXTR mediated signaling was restored following a pharmacological targeting of the 5-HT2CR using RS102221 a specific 5-HT2CR antagonist. This suggests that the receptor interface mediating the allosteric wave requires an intact 5-HT2CR agonist binding site for the allosteric wave to pass into the OXTR protomer from the 5-HT2CR protomer. A similar but weaker antagonist allosteric event developed when 5-HT activated the 5-HT2CR protomer in the presence of the OXTR protomer forming the heteroreceptor complex (**Figure 2**). Thus, also a constitutive allosteric wave-induced by the OXTR, although reduced compared to the wave induced by 5-HT2AR, exists to bring down the 5-HT2CR G alpha q signaling upon activation by 5-HT. In line with these results, it was found in cells co-expressing the two receptor protomers that the basal internalization and trafficking of the OXTR protomer was enhanced, an action which was again diminished by the 5-HT2CR antagonist (Chruścicka et al., 2021).

Using a proximity ligation assay, the 5-HT2CR-OXTR heterocomplexes were clearly present in brain slices in the dorsal hippocampus and the retro-splenial granular and agranular cortex. They were mainly found in the pyramidal cell layer of the CA1, CA2, and CA3 regions with the highest density in the CA3 region. These regions are mainly built up of glutamate neurons. PLA signals were also found over some GABA interneurons mainly scattered in the cell layers of oriens

and radiatum, especially of the CA1 region. It will be of high interest to study in detail many other relevant regions like the forebrain, the caudate putamen and nucleus accumbens, the hypothalamus, and the serotonin, dopamine, and noradrenaline nerve cell groups of the lower brain stem. It also will be of high interest to compare the PLA positive distribution pattern of the 5-HT2AR-OXTR and the 5-HT2CR-OXTR heterocomplexes in adjacent sections, e.g., dorsal hippocampus and nucleus accumbens *ex vivo*.

It was previously demonstrated that OXTR and 5-HT2CR have the ability to participate in locomotor activity (Nebuka et al., 2020). It, therefore, became of interest to test if also the 5-HT2CR-OXTR heterocomplexes have a role in locomotor activity (Chruścicka et al., 2021). It was of substantial interest that a 5-HT2CR antagonist enhanced the hypoactivity induced in mice by oxytocin (**Figure 2**). The 5-HT2CR antagonist used was SB242084 and the specificity of the effect observed was indicated by the observation that this 5-HT2CR antagonist alone increased locomotor activity (Chruścicka et al., 2021). It will be of interest to determine the cellular location and functions of the 5-HT2CR-OXTR heterocomplex involved, once the 5-HT2CR-OXTR heterocomplexes have been mapped out using the PLA method. However, the basal ganglia is also a putative target (Chruścicka et al., 2021).

In relation to functional relevance, both the OXTR and 5-HT2CR are expressed in dorsal raphe neurons with their interactions leading to diminished anxiety (Yoshida et al., 2009). It will therefore be interesting to demonstrate if targeting the OXTR/5HT2C dimer has a potential anxiolytic effect.

Understanding tuning (modulation) and fine-tuning (metamodulation) neurotransmission in the brain in a novel way. The role of the heteroreceptor complexes

These concepts have been discussed over many years and especially by the Ribeiro and Sebastiao group (Ribeiro and Sebastiao, 2010) in relation to adenosine and its adenosine receptors. Based on the current work on OXT and OXTR heterocomplexes and other types of heteroreceptor complexes, it is proposed that the GPCR heterocomplexes are important mediators of meta-modulation. The activation, e.g., of the OXTR by OXT leads to modulation of OXTR protomer signaling, and through the allosteric receptor-receptor interactions induced by the activated OXTR protomer, other protomers of distinct OXTR heteroreceptor complexes undergo meta-modulation (fine-tuning), including D2R, 5-HT1AR, and 5-HT2CR protomers (Romero-Fernandez et al., 2013; Chruścicka et al., 2019, 2021). This molecular integrative mechanism is hypothesized to play a major role in metamodulation both at the postsynaptic and presynaptic level and in extrasynaptic membrane regions where heteroreceptor complexes have a major integrative role (Fuxe et al., 2010a; Borroto-Escuela et al., 2017).

Limitations and future studies

While GPCRs are mainly described as functioning monomers, the formation of GPCR heterocomplexes is increasingly being recognized and has important consequences for the discovery and development of GPCR-based pharmaceutical targets as heteromerization is associated with altered GPCR signaling (Borroto-Escuela et al., 2017, 2018b; Fuxe and Borroto-Escuela, 2018).

Several techniques have been successfully employed to demonstrate the OXTR-GPCR interactions, such as *in vitro* cellular overexpression systems, where colocalization has been measured with fluorescence microscopy, receptor dimerization with fc-FRET, BRET, as well as using *ex vivo* PLA and immunofluorescence (Schellekens et al., 2015; de la Mora et al., 2016; Chruścicka et al., 2019; Wallace Fitzsimons et al., 2019; Chruścicka et al., 2021). The pharmacological relevance of interactions has been equally studied using downstream analysis, including calcium mobilization assays and cAMP assays. In addition, single cell co-expression analysis using mouse and human cortical data from the Allen Brain Atlas has brought some translational validation of potential GPCR co-expression. Computational approaches for modeling and predicting GPCR dimerization have been provided by the GGIP web server (Nemoto et al., 2022) and online resources including the GPCR-HetNet (Borroto-Escuela et al., 2014). The relevance of GPCR heterodimerization *in vivo* has been discussed in the past. Furthermore, functional GPCR interactions have revealed physical heteroreceptor complexes with allosteric receptor-receptor interactions between receptor pairs, with each complex resulting in unique alterations to GPCR recognition, signaling, and trafficking (Fuxe and Borroto-Escuela, 2016, 2018). Nevertheless, a gap in the physiological relevance of many heteroreceptor complexes remains, with a limited number of *in vivo* heterodimerization studies published compared to the number of identified heteroreceptor complexes. Future studies should focus on the validation of heteroreceptor complex formation *in vivo* under healthy and pathophysiological conditions, as well as in depth analysis of the heterodimer's physiological role.

Future aspects

The OXTR has a high potential to form heteroreceptor complexes, the same is true for GHS-R1a including the GHS-R1a-OXTR heterocomplexes as demonstrated over the last two decades. In 2019 the GHS-R1a-OXTR heteromerization was

found for the first time (Wallace Fitzsimons et al., 2019). It will now be of highest importance to determine if in fact in general the OXTR and GHS-R1a come together in the brain forming high-order heteroreceptor complexes also including the DA, noradrenaline (NA), and 5-HT receptor subtypes, and other types of GPCRs. It seems possible that also, e.g., receptor tyrosine kinase (RTK) and ionotropic receptors can be involved in the complexes formed. Based on the role of the OXTR and GHS-R1a, especially in the central autonomic and neuroendocrine system, social behavior and food intake, these integrative complexes can have a special role in the limbic system, the hypothalamus, and the lower brain stem.

Evidence suggests that oxytocin can increase the density and length of 5-HT axons during development, which indicates the involvement of RTK in the 5-HT and oxytocin receptor-receptor interactions (Eaton et al., 2012). There are also signs of support for the view that 5-HT and oxytocin interplay in the nucleus accumbens significantly mediate the rewarding aspects of social behavior (Dolen et al., 2013).

It is also of interest that galanin-like peptides can be released by stress from neurons in the arcuate nucleus and intracerebroventricular injections of galanin-like peptides enhance the release of oxytocin (Onaka et al., 2005). Furthermore, galanin receptors have been found in the arcuate nucleus of the hypothalamus (Kinney et al., 1998; Leibowitz, 1998) and oxytocin receptors are widespread throughout the hypothalamus (Yoshimura et al., 1993). These observations open the possibility that galanin receptors may form complexes with oxytocin receptors, especially in the hypothalamus with a focus on the arcuate nucleus, which should be tested in future work.

The OXTR and GHS-R1a may usually come together as heterodimer complexes in which the high constitutional activity of the GHS-R1a may alter the conformation of the OXTR and facilitate its affinity and binding to other receptors like the various monoamine receptors. However, it should also be noted that the GHS-R1a also may form complexes with other receptors like monoamine GPCRs. Such interactions may also facilitate the formation of high-order heteroreceptor complexes. An alternative is also that GHS-R1a *via* its interaction with some surrounding receptors can reduce their affinity for the OXTR and block the formation of unsuitable high-order heteroreceptor complexes.

This can become an exciting new field for understanding integrative processes in the plasma membrane. However, increases in our understanding of the molecular hot spots in the receptor interface involving the postulated key role of the trimeric amino acid homologies in the receptor interface formed, especially in transmembrane domains (Tarakanov and Fuxe, 2010; Borroto-Escuela et al., 2018a) as well as electrostatic interactions, especially in intracellular domains, is warranted before the field will be able to fully interrogate the functional significance of, e.g., OXTR heteromerization (Woods et al., 2005).

Author contributions

We confirm and declare that all authors meet the criteria for authorship according to the ICMJE, including approval of the final manuscript, and they take public responsibility for the work and have full confidence in the accuracy and integrity of the work of other group authors. They have substantially contributed to the conception or design of the current *Review Article*. They have also participated in the acquisition, analysis, and interpretation of data for the current manuscript version. Furthermore, they have helped revising it critically for important intellectual content; and final approval of the version to be published. In addition, they have contributed to this last version of the manuscript in writing assistance, technical editing, and language editing. DB-E, HS, MP, and KF have a prominent role in the conception of the hypothesis introduced and their discussion. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neonatal oxytocin gives the tempo of social and feeding behaviors

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The nonapeptide oxytocin (OT) is a master regulator of the social brain in early infancy, adolescence, and adult life. Here, we review the postnatal dynamic development of OT-system as well as early-life OT functions that are essential for shaping social behaviors. We specifically address the role of OT in neonates, focusing on its role in modulating/adapting sensory input and feeding behavior; both processes are involved in the establishing mother-infant bond, a crucial event for structuring all future social interactions. In patients and rodent models of Prader-Willi and Schaaf-Yang syndromes, two neurodevelopmental diseases characterized by autism-related features, sensory impairments, and feeding difficulties in early infancy are linked to an alteration of OT-system. Successful preclinical studies in mice and a phase I/II clinical trial in Prader-Willi babies constitute a proof of concept that OT-treatment in early life not only improves suckling deficit but has also a positive long-term effect on learning and social behavior. We propose that in early postnatal life, OT plays a pivotal role in stimulating and coordinating the maturation of neuronal networks controlling feeding behavior and the first social interactions. Consequently, OT therapy might be considered to improve feeding behavior and, all over the life, social cognition, and learning capabilities.

KEYWORDS

oxytocin, neurodevelopment, suckling, social interaction, Prader-Willi syndrome, Schaaf-Yang syndrome, autism

Highlights

- Actors of oxytocin system are dynamically regulated during early postnatal development.
- Oxytocin is necessary to integrate early sensory experiences and shape neuronal circuits.
- In mothers and neonates, oxytocin is critical for suckling and to establish the infant-mother bond and first social interactions.
- Early oxytocin treatment improves suckling and has positive long-term effects on social interactions.
- Suckling alterations might be a physiological marker for early diagnostic of ASD and indication of OT-treatment.

Introduction

The perinatal period is critical for health and behavior later on life. The idea that the cause of a disease could be related to this critical period has been developed 30 years ago in the concept called "Primal Health research" (for review, Odent, 2001) that is now abandoned despite its relevance. The perinatal period is critical for pathologies related to feeding disorders or to sociability. An important factor to consider during this "primal period" is the neuroendocrine system (Lesage et al., 1996). The central oxytocin (OT) system, which projects to limbic and other central brain areas, appears to be a key regulator of the evolution and expression of different types of social systems in many species (for reviews: Choleris et al., 2009; Heinrichs et al., 2009; Insel, 2010). The current view is that OT modulates the coupling of central neuronal networks that process sensory cues activated during social interactions (Johnson and Young, 2017). More generally OT has been proposed as an allostatic hormone, acting in the brain and in peripheral organs, where it modulates both social and non-social vital behaviors by maintaining stability through changing environments (Quintana and Guastella, 2020). However, these assignments have been applied to the role of OT at adulthood.

During the last years, the scientific community studied the dynamic development of the neural OT circuitry. They have highlighted that how and when the neural circuit of the OT-system is organized in early development might have important consequences on behavior, a hypothesis indicates the "organizational effects of OT" (Eaton et al., 2012; Miller and Caldwell, 2015). More recently, studies revealed that an impact on OT-system ontogenesis during early-life period affects long-term behavioral expression (Onaka and Takayanagi, 2021). Furthermore, it is striking that the distribution of OT-receptor (OTR) in the brain undergoes dynamic changes in expression through the postnatal development with a peak of expression in the early infancy (in rodents and humans) and that this distribution correlates with brain regions controlling the sensory modalities primarily used to initiate social interactions (Hammock and Levitt, 2013; Tamborski et al., 2016).

Here, we discuss the early postnatal life role of OT shaping the sensory inputs and stimulating suckling, both contributing to the first social behaviors *via* the infant-mother bond. We also report the positive effects, in particular the long-term effects, of an early-life OT-treatment in neurodevelopmental diseases (NDD) such as Schaaf-Yang and Prader-Willi syndromes.

Oxytocin neurons and oxytocin receptors are dynamically regulated through development

OT-system is defined by OT-producing cells and OT-target cells that together determine the qualitative and quantitative characteristics of OT responses. The action of OT is then controlled by the release of OT, the quantity and spatio-temporal expression of OT-binding sites on the target cells (OT-receptors and vasopressin receptors), and the intra-cellular signaling pathways triggered by OT. Many reviews have described the source of OT production (Althammer and Grinevich, 2017), the mechanisms of release (Johnson and Young, 2017; Brown et al., 2020), and the cellular signaling pathways *via* the OT-binding sites (Busnelli and Chini, 2018; Jurek and Neumann, 2018). Here, we will focus on developmental setup of the OT-system.

OT is produced by hypothalamic neurons of several regions: the Supraoptic Nucleus (SON), the Periventricular preoptic nucleus (PvPO) the Paraventricular Nucleus (PVN), the Accessory Nuclei (AN), the Bed Nucleus of the Stria Terminalis (BNST) and in a recently identified region named Antero-Lateral Preopticarea (ALPO; Soumier et al., 2022). Recently, a comprehensive map of OT/AVP neurons and projections has been generated in the mouse brain during development (Madrigal and Jurado, 2021) and at adulthood.[1] OT and AVP expression show distinct developmental dynamics in the mouse brain, with developmental maturation of AVP preceding that of OT (Madrigal and Jurado, 2021). The number of OT cells selectively increases during a critical window of postnatal development in several hypothalamic regions: in the PvPO and PVN, as well as in ALPO (Soumier et al., 2022). Noticeably, AVP-expressing cells in the different hypothalamic nuclei (PVN, SON, Medial Preoptic Nucleus, Tuberal Nucleus), as well as in the extra-hypothalamic regions, such as the Medial Amygdala (MEA) and BNST, remain stable over time, from birth to adulthood (Soumier et al., 2022). Interestingly, in most of hypothalamic nuclei, there is a high percentage of neurons coexpressing OT and AVP that decreases at adulthood (Madrigal and Jurado, 2021).

OTR is a seven-transmembrane segment G protein-coupled receptor (GPCR). To date only one subtype of OTR has been described which is closely related to the three vasopressin (AVP) receptors, OT binds also AVPR-1a with a lower affinity. OTR mapping at the protein level is hampered by the lack of specific anti-OTR-antibody. Consequently, the distribution of OTR expression has been analyzed using different experimental approaches, such as receptor binding of radiolabeled OT analogs on tissue sections, *in situ* hybridization and transcriptomic analysis, and the use of transgenic mice expressing a fluorescent reporter under the control of the OTR promoter. In adult rodents, a comprehensive list of brain areas expressing OTR has been reported in the rat and mouse brain (Jurek and Neumann, 2018). The four main and best-studied OTR-expressing brain regions are the hypothalamus, prefrontal cortex, hippocampus, and amygdala (Jurek and Neumann, 2018; Carter et al., 2020). Son et al. (2022) have shown that there is no significant correlation comparing the quantity of OT projections and OTR expression across the whole brain, suggesting important indirect OT-signaling in OTR-expressing areas.

1 https://kimlab.io/brain-map/ot_wiring

Comparative analysis of OTR distribution in brain rodents (i.e., prairie voles, rats, and mice) revealed species, sex, experiences, and developmental differences in OTR expression (Vaidyanathan and Hammock, 2017). In rats, using radiolabeled OT, it was shown that OTRs progressively appear in several brain regions throughout the development, being first detected in the presumptive embryonic region of the vagal motor nucleus from the embryonic day 14.5 (E14.5), and reaching a well-defined "infant" pattern of distribution after the Postnatal day 10 (PND10). OTR expression then follows a differential time course depending on the brain structure considered. Interestingly, during the early postnatal period some transient expressions are detected in several brain areas (Tribollet et al., 1989, 1991; Yoshimura et al., 1996). After PND13, the density of OTR drops sharply in several brain regions, and expression in new brain areas appears; this is referred to as the first transition to the adult pattern, which is almost reached at PND18. Around weaning and beyond, a second transition takes place that is characterized by a new remodeling of OTR expression, disappearing from some areas and increasing in others. Finally, the adult pattern of OTR expression is established at PND60-90 (Vaidyanathan and Hammock, 2017; Muscatelli et al., 2018).

A similar radioligand binding approach was performed in the mouse brain and reported an early detection of OT-binding sites atE16 (Tamborski et al., 2016), with a peak around 2 weeks after birth followed by a decrease in OT-binding sites in all brain regions thereafter (Hammock and Levitt, 2013); such a strong a transient expression of OTR around PND14 is particularly detected in different cortical regions (Hammock and Levitt, 2013). Yongsoo Kim's lab used a fluorescent reporter mouse model (i.e., OTR Venus mice) and established a publicly available brain-wide map of the OTR in mice during postnatal development[2] (Newmaster et al., 2020). The drawback of this map is that it does not allow to visualize transitory expression. Studies in prairie voles also showed a dynamical expression profile of OTR over time (Prounis et al., 2018).

In conclusion, in all rodents examined (i.e., mice, rats, and prairie voles), *Otr* mRNA and OT-binding sites are present in embryos, even though the mature form of OT is not detected before birth, and the peak of OTR expression is observed around 2 weeks after birth. The distribution of OTRs during brain development is different from that of adult brains and can be classified into three expression profiles: 1) clusters of neurons with constant expression, where OTR expression begins to be detected during development and is maintained throughout life, 2) sites with transient expression where OTR is only observed during a developmental time window and its expression is no longer detectable after that, and 3) neurons where OTR expression begins to be detected during puberty and is maintained throughout life (Vaidyanathan and Hammock, 2017). OTR expression is sexually dimorphic, with *Otr* mRNA expression generally higher in female than in male brains (Tamborski et al., 2016).

In the human brain, similarly to rodents, OTR expression begins to accelerate just before birth, with a peak level expression occurring during infancy (Rokicki et al., 2022). There is, however, a sexual dimorphism of OTR expression. In girls, a peak of expression is observed around birth, with a decrease in expression during childhood, and a dip during adolescence. In boys, compared with girls, the peak of OTR expression is delayed in early childhood and the difference in expression between brain regions is more pronounced (Rokicki et al., 2022). This study used genome-wide exon-level transcriptome approach to define OXTR transcript density in 16 brain regions through different ages (pre-natal to 82 years old) and using males and females. The study is robust but there is a lack of quantification of the active transmembrane OT-receptors.

OTR are also strongly detected in the peripheral tissues of neonatal mice and prairie voles. In particular, OTR is transiently and highly expressed in the oro-facial region of mouse with marked sex and species differences (Greenwood and Hammock, 2017).

Noticeably, the distribution of OT and vasopressin (VP) receptors shows overlapping expression in many regions and specific non-overlapping expression in some brain structures as shown in the lemurs (Grebe et al., 2021). These two neural systems play a role in the same signaling pathway, and have either complementary or opposing functions depending on the species, sex, age, and social experiences.

The dynamic of OT release in postnatal development is poorly studied and, paradoxically, although there is a huge number of OTR in the infant brain, the synaptogenesis of OT neurons is not fully completed. Interestingly, Hoffiz et al. (2021) showed that birth triggers specifically c-Fos activation of VP and OT neurons from the suprachiasmatic (VP only), supraoptic, and paraventricular nuclei of the hypothalamus. These activations are high at 3 h postnatal and returned to baseline levels at P1.

In conclusion, the pattern of OT-system is highly dynamic throughout development, particularly from birth with transition phases at weaning time, puberty, and young adulthood (Figure 1).

OT-system integrates sensory experiences in early life and shapes developmental neuronal circuits

At adulthood, the role of OT as a modulator of sensory processing in relation with the social behavior has been clearly shown for olfaction (Oettl et al., 2016; Oettl and Kelsch, 2018) and touch (Tang et al., 2020; Yu et al., 2022). OT has been shown to modulate pain perception (Poisbeau et al., 2018). In dams, OT modulates audition allowing them to recognize the vocalizations of their pups and to adapt maternal behavior accordingly (Schiavo et al., 2020).

2 https://kimlab.io/brain-map/OTR/

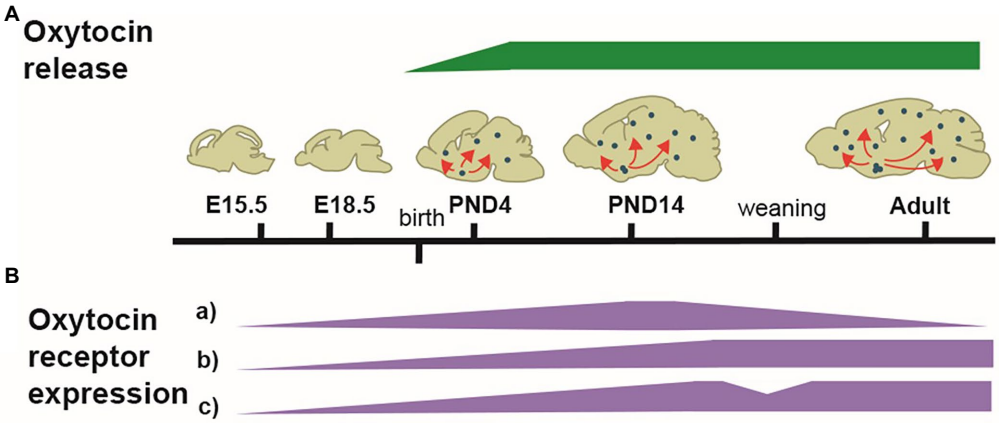

FIGURE 1
Illustration of the developmental dynamic of the OT-system. **(A)** Schematized patterns of OT produced in the hypothalamus and released in the forebrain (green). OT is first released at birth. **(B)** Schematized patterns of OTR expression (purple). From E14.5, OTRs progressively appear in several brain regions, with different dynamic patterns of expression. In many areas, OTRs pick between PND14-PND21, followed by either a decline (a) or a stabilization (b); in some areas, a reshaping of OTRs expression occurs at weaning, with a disappearance from some areas and an increase in others (c). The adult pattern of OTR expression is achieved at PND60-90.

During postnatal development, numerous studies show a role of OT-system as an integrator and modulator of sensory inputs, allowing to shape brain circuits and connectivity (Grinevich and Stoop, 2018). Interestingly, VP and OT neurons of the supraoptic and paraventricular nuclei of the hypothalamus were specifically activated in the 30 min following birth in mice and rats (Hoffiz et al., 2021).

Some of the pioneer studies showed that in rat (Nelson and Alberts, 1997; Lenz and Sengelaub, 2010), rabbit (Caba et al., 2003), or prairie voles pups (Barrett et al., 2015), mimicking parental licking stimulates the activity of hypothalamic OT neurons. In the rat, this stimulation also induced an increase in OT concentration in the spinal cord, suggesting that maternal licking may affect the maturation of sensory and autonomic centers (Lenz and Sengelaub, 2010). Affiliative stimuli, defined by gentle tactile stimuli of the pups during developmental period, activate also OT neurons (Walker et al., 2017). Maternal care (skin to skin contacts) stimulates the central OT in pups creating the conditions for inducing a preference for maternal odor (Kojima and Alberts, 2011a; Kojima et al., 2012) and for establishing a social affiliation in rat pup's filial huddling preference (Kojima and Alberts, 2011a; Kojima et al., 2012). The increase in OT induced in pups by contact with the mother also facilitates the development of thermal-seeking huddling behavior (Kojima and Alberts, 2011b).

One of the most convincing demonstration of the sensory cues-dependent release of OT in the pups' brain comes from experiments based on blocking early sensory stimulation (Zheng et al., 2014). Deprivation of sensory inputs, such as whisker deprivation, right after birth (ending at PND 14) results to reductions of the firing rates of OT PVN neurons and lower released of OT in the brain of juvenile mice (Zheng et al., 2014). This deprivation also affects other sensory cortices in the brain and caused a reduction in excitatory synaptic transmission across the other sensory cortices, demonstrating that OT promotes cross-modal, experience-dependent cortical development. Similar results were obtained in dark rearing. Injection of OT into the brains of sensory-deprived animals enabled them to recover this deficiency and improved the brain's response to other sensory inputs. Conversely, increased sensory stimulation from birth through environmental enrichment increases at PND14 the level of OT, excitatory synaptic transmission in several sensory cortices, and corrects the effects of sensory deprivation. This study thus demonstrates that during the period of synaptogenesis, OT promotes excitatory synaptic transmission and, in sensory cortices, mediates early experience-dependent multimodal plasticity. Noticeably, this action of OT, which regulates excitatory synaptic transmission in pyramidal neurons of sensory cortices, is maximal around PND14 and ceases after PND18, revealing a sensitive/critical period (Zheng et al., 2014). Similarly, sensory experience regulates the expression of OTRs with a similar time course, an elevation at PND14, and essentially no change at PND18 (Maldonado et al., 2021). More generally, OTR expression in the pyramidal glutamatergic neurons of sensory cortex peaks around PND14 and drops significantly at PND21 (Hammock and Levitt, 2013; Newmaster et al., 2020; Maldonado et al., 2021). Then, at PND28, *OTR* expression is more important in GABAergic neurons, especially somatostatin interneurons (Zheng et al., 2014). Thus, a reduction in OTRs expression may promote the closure of the sensitive/critical period (Zheng et al., 2014).

In a similar manner, it has been shown that OT affects spontaneous activity patterns in the mouse developing visual cortex, recruiting Somatostatin interneurons and allowing to refine the synaptic connections in the visual cortex prior to eye opening (Maldonado et al., 2021). OT is also required in early infancy to impose the positive quality of olfactory imprinted memory in the nursed neonates, in which imprinted memory is associated with a pleasant mental state. Importantly, there is a critical period (first week of life) during which OT, by imposing

positive quality on imprinted odor memory, contributes to smooth social interactions in the adult life (Inoue et al., 2021). Noticeably, during early infancy, the transient strong oro-facial expression of OTR (see above) suggests also an effect of OT-system in the peripheral control of sensory inputs. In our team, we have shown a role of OT in thermo-sensory reactivity of neonates. Indeed, in a cool environment, neonate mice emit ultrasonic vocalizations that trigger a "pup retrieval" behavior from their mothers. Inactivation of OT neurons prevents this thermo-sensory reactivity of neonates (Da Prato et al., 2022).

Altogether, these data reveal a stimulation of OT-system in response to all types of sensory inputs (tactile, visual, olfactive, thermal), in particular those linked to the oro-facial stimulation, triggered at birth and during a critical period of time of infancy (Figure 2). In this period, sensory experience influences the production of OT and OT shapes neuronal circuits by modulating spontaneous and evoked activity.

OT-system and sensory experiences in early life shape the first neonates-mother bond, the ground of social interactions

In all mammals, the mother-infant bond is the first social experience. Many studies report the role of OT in mother-infant bonding induced by lactation and maternal behavior in the mother (Nagasawa et al., 2012; Okabe et al., 2012). In addition, an important effect of maternally produced OT at the time of birth could protect the neonatal brain of rodents from birth stress by decreasing perinatal neuronal activity (Tyzio et al., 2014). On the other side, the role of OT produced by the newborn in stimulating bonding with its mother has been much less studied. The newborn's OT-system is activated by parental care which is responsible for all of the sensory inputs described above (Paragraph 2); deficiencies in parental care, as it happens in maternal separation, impact the OT-system and alter social and emotional behaviors later on in adulthood (Onaka and Takayanagi, 2021).

OT in the mother is required for lactation and shapes maternal behaviors

OT has gained considerable attention for its role in modulating bond formation on the mother side (Uvnas-Moberg and Eriksson, 1996). OT is a key component in the transition to motherhood, affecting molecular pathways that dampen stress reactivity, promote positive disposition, and regulate healthy maternal behaviors (Bell et al., 2014). Maternal breastfeeding behavior is vital for newborn's access to food and survival, and to establish a solid bond between the mother and neonates. OT is well known for its crucial role in lactation and suckling (Uvnas-Moberg and Eriksson, 1996). Indeed, OT knockout mice, although able to deliver pups, have a complete failure of milk letdown (Nishimori et al., 1996) During lactation, milk synthesis is promoted by prolactin and oxytocin stimulates milk ejection. A study in lactating rats showed a switch of prolactin inhibition into excitation on OT neuron activity (Augustine et al., 2017). In addition, suckling activity by the pups stimulates central release of OT in the mother (Neumann et al., 1993), therefore providing a mean for stimulating milk production, and also reinforcing mother-infant bonding. Furthermore, mothers provide olfactory cues and signals that direct their unexperienced newborns to the nipple and optimize initial sucking success and, therefore, viability (Al Ain et al., 2013). In addition to control maternal behavior and milk letdown, dam's OT contributes to the olfactory signals attracting pups toward the nipple. Indeed, the administration of OT in a mother whose nipples have been washed reinstates the attachment of the pups to the

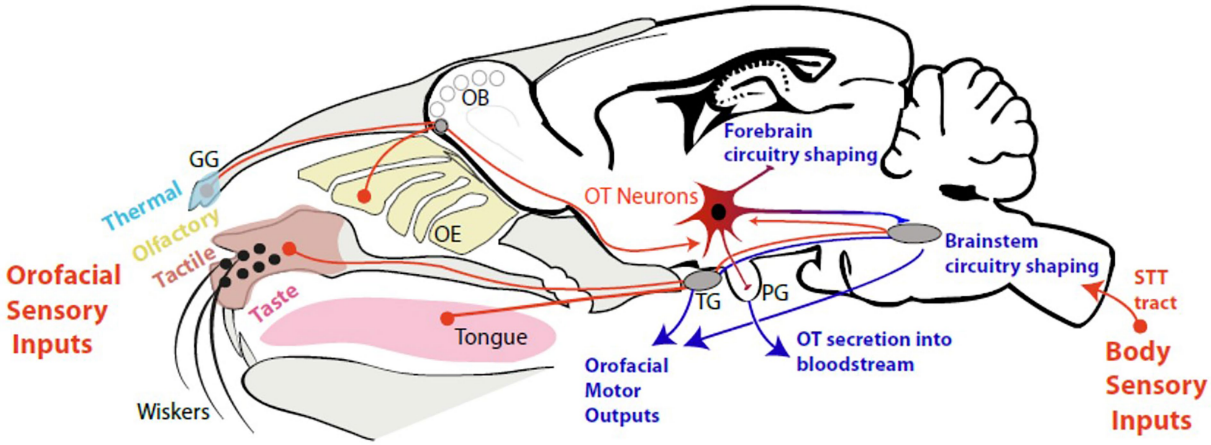

FIGURE 2
The oro-facial sensory inputs in neonates stimulate OT neurons. OB: Olfactory Bulb; OE: Olfactory Epithelium; OT: Oxytocin Neurons; GG: Grueneberg Ganglion; PG: Pituitary Gland; TG: Trigeminal Ganglion; STT: Spino-Thalamic tract.

nipples; this suggests that a substance, which acts as an olfactory cue for the pups, may be excreted from the nipple area in response to circulating OT (Singh and Hofer, 1978). Newborn rats are strongly attracted to the odor of amniotic fluid when exposed to the nipple for the first feeding (Arias and Chotro, 2007). Similarly, in mouse, olfactory cues present in amniotic fluid and milk induce nipple grasping before the first suckling experience (Al Ain et al., 2013). During the following suckling, milk or maternal saliva can trigger sucking (Al Ain et al., 2013). In rabbits, a specific pheromone in milk is responsible for nipple grasping (Schaal et al., 2003).

The mother develops cross-modal sensory perception of olfactory, auditory, and tactile stimuli from the pups, which allows her to recognize her own pups and induces stereotyped maternal behavior (Nagasawa et al., 2012; Okabe et al., 2012). Although it has been known for decades that OT can trigger maternal behavior such as pup retrieval, nursing, or grooming a newborn (Pedersen and Prange Jr., 1979; Pedersen and Boccia, 2003; Rilling and Young, 2014), the neuronal encoding of this behavior has started to be deciphered only recently. First, given the important role of pup calls, Marlin et al. (2015) revealed that OT increases the sensitivity of auditory cortex neurons of the dam to mouse pup calls. A hypothalamo-cortical circuit involving a sub-population of OT neurons projecting from the PVN to large population of OTR-expressing interneurons located in the bilateral auditory cortex of female allows the dams or an OT-treated virgin female to disinhibit the auditory cortex firing after pup call stimulation and to facilitate pup retrieval (Marlin et al., 2015). Remarkably, it has also recently been shown that mouse alloparenting behavior might be acquired by social transmission and involves OT (Carcea et al., 2021). In the mother's brain, OT is thought to amplify the neural circuits activated by signals from the pups, such as distress calls. This amplification would occur in brain regions important for learned aspects of maternal care, including the left auditory cortex. These precious alloparenting experiences acquired during co-housing (mother with virgin female) are likely to improve the quality of early maternal care when the virgins themselves have litters (Carcea et al., 2021).

OT in neonates shapes the first social behaviors *via* the infant-mother bonds

Mother-infant bonding is not only a positive factor of newborn survival (Nowak et al., 2000), but also serves the newborn's formation of functional neural circuits through sensory stimulation experiences (Sur and Rubenstein, 2005). From birth, mammalian neonates must efficiently interact with their mother to obtain care and food (Schaal et al., 2009). Olfactory, tactile, and thermal cues coming from the environment or the mother's body promote sensory stimulations that elicit the neonates to undertake active, often stereotyped, behaviors such as nipple-searching, sucking, ultrasonic vocalization, wriggling calls for successful feeding and warming (Nowak et al., 2000; Grimsley et al., 2011). As described above, OT-system is active from birth and responds to social/sensory stimulation produced by the mother. The production and release of OT in the newborn is required for shaping these first sensory-motor functions and to establish a strong relationship with the mother.

OT in neonates and the early feeding behavior/suckling

Mouse neonates suck milk after finding their mother's nipples on their own. The olfactory function is essential for nipple-finding behavior and milk sucking. The stimulation of the tactile system (defined as the "trigeminal-whisker system") cannot replace the absence of olfactory input in mouse neonates. (Hongo et al., 2000). However, it might participate since the olfactory and trigeminal systems interact; indeed, odorants stimulate the olfactory bulb but also the trigeminal nerve (Frasnelli et al., 2007). Alberts and Ronca (2012) proposed that, in rat neonates, mechanical and thermal sensory stimulations just before and during birth established the sufficient conditions for the maternal odor learning that guides newborn's sucking responses. Thus, the hypothesis is that odors learned prenatally in association with perinatal stimuli around birth, become conditioned stimuli for nipple attachment (Pedersen et al., 1982; Alberts and Ronca, 2012). Thus, a sensitive period to learn odor-preference (of the mother) has been proposed, the neural circuit involved the olfactory bulb, the piriform cortex, the amygdala, and the locus coeruleus, that produces norepinephrine (NE) which is required to enhance odor-preference in this sensitive period (Sullivan, 2003). Today, studies have to be conducted to assess a role of OT in mother odor learning guiding newborn's sucking responses. OT neurons are activated just after birth (Hoffiz et al., 2021) and there is a transient but strong expression of OTR around birth in several feeding-relevant peripheral regions of the face (Greenwood and Hammock, 2017), suggesting a role of OT in the integration of sensory inputs associated with suckling. Interestingly, rabbit pups are nursed and fed once every 24 h (unusual among mammals) and the OT neurons of the SON and PVN are differentially activated by sucking of milk and anogenital stroking, a sensory input from the mother to enhance suckling in pups (Caba et al., 2003). It should be noted that OT is present in milk and colostrum and thus regulates the intestinal development of newborns and protects their gut from inflammation (Klein et al., 2017).

Several publications suggest that OT is involved in motor outputs involved in sucking. Hypoglossal (XII) motoneurons innervate extrinsic and intrinsic muscles of the tongue and are necessary for sucking. Using brainstem slices of 5–9-day-old rats and whole-cell patch clamp recordings from XII motoneurons, Wrobel et al. (2010) proposed that VP and OT function as neuromodulators of the hypoglossal (XII) nucleus and may be part of neuronal networks underlying rhythmic tongue movements. These effects were mediated by vasopressin 1A (V1A) and OT-receptors present in XII motoneurons as well as in interneurons and premotor neurons, making synaptic contact with them.

Perhaps the strongest demonstration for a role of OT in the newborn's feeding behavior comes from studies in our laboratory initially devoted to characterize the phenotype of *Magel2* deficient mice. Deficiencies in the OT-system are implicated in

neuropsychiatric diseases presenting an autism syndrome disorder, including Prader-Willi (PW) and Schaaf-Yang (SY) syndromes, characterized by impaired suckling at birth, requiring intubation feeding (Fountain and Schaaf, 2016; Figure 3). Both syndromes are associated with mutations in *MAGEL2* gene: either point mutations in SYS or a large chromosomal region including *MAGEL2* in PWS (Figure 3). Our team studied the *Magel2* KO mice, we observed the death of approximately 50% of the mutant mice within the first postnatal day due to deficiency in suckling activity and associated with low OT levels in the neonate hypothalamus (Schaller et al., 2010). This suggested that OT deficiency participate in the altered feeding behavior of *Magel2* knockouts, which was confirmed in further experiments. Indeed, injection of a specific potent OTR antagonist to wild-type pups 1–1.5 h after birth prevented suckling in approximately 50% of mouse neonates, which were found dead the day of the injection (Schaller et al., 2010). Interestingly, the same injection performed 12–24 h after birth had no effect on the pups. In addition, the feeding deficiency of *Magel2* knockouts was rescued by a single subcutaneous OT injection 3–5 h after birth (Schaller et al., 2010). In a phase 2 clinical study following on from the preclinical work, we have shown that intranasal administration of OT (during 1 week) in 18 Prader-Willi infants (4 weeks to 5 months old) improved and normalized sucking in 88% of babies. Sucking was assessed by the Neonatal Oro-Motor Scale and videofluoroscopy showing a great improvement of the motor outputs (Tauber et al., 2017). Therefore, these results indicate that manipulating the OT-system very early after birth could greatly impact on the initiation of suckling activity (including sucking) in *Magel2* KO newborn mice and Prader-Willi babies (Figure 4).

It is noteworthy that the role of OT in feeding behavior changes during development, as it stimulates milk production in the mother, stimulates feeding behavior in the neonate, and inhibits food intake in the adult. The underlying mechanisms that might support this developmental shift in role are currently unknown, but it is clear that the respective roles of maternally secreted OT and OT produced by infant brain will allow for a gradual tiling during the lactation period.

Long-term effects of oxytocin produced in early life

OT-system is disturbed in rodent and human NDD associated with autism spectrum disorders

OT-system is disrupted in several animal models of neurodevelopmental disorders characterized with autism-like phenotypes (Muscatelli et al., 2018; Wagner and Harony-Nicolas, 2018; Althammer et al., 2022). Indeed, mouse models, which are deficient for genes such as *Or* (Winslow et al., 2000; Ferguson et al.,

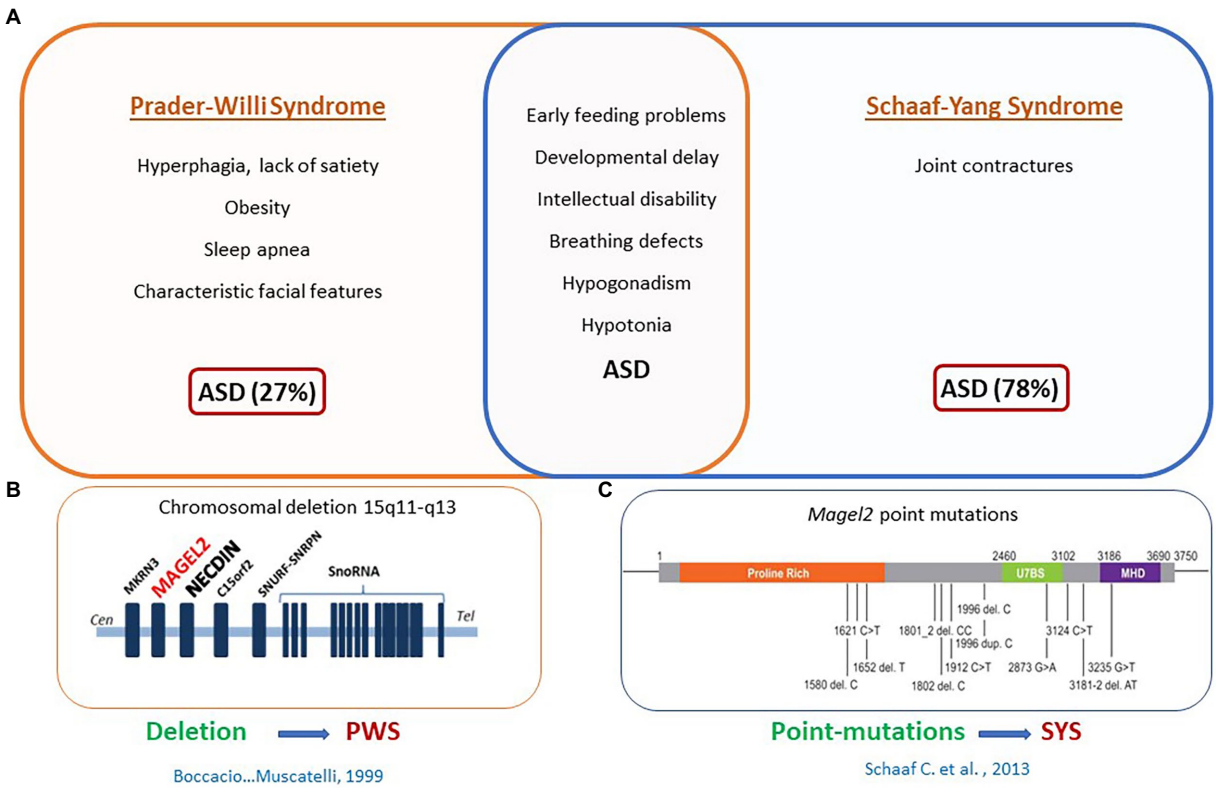

FIGURE 3
MAGEL2 is involved in Prader-Willi syndrome (PWS) and Schaaf-yang syndrome (SYS). **(A)** Clinical symptoms specific to PWS or SYS or common to both syndromes. **(B)** Common chromosomal deletion observed in PWS. **(C)** Point mutations found in MAGEL2 gene of patients with SYS.

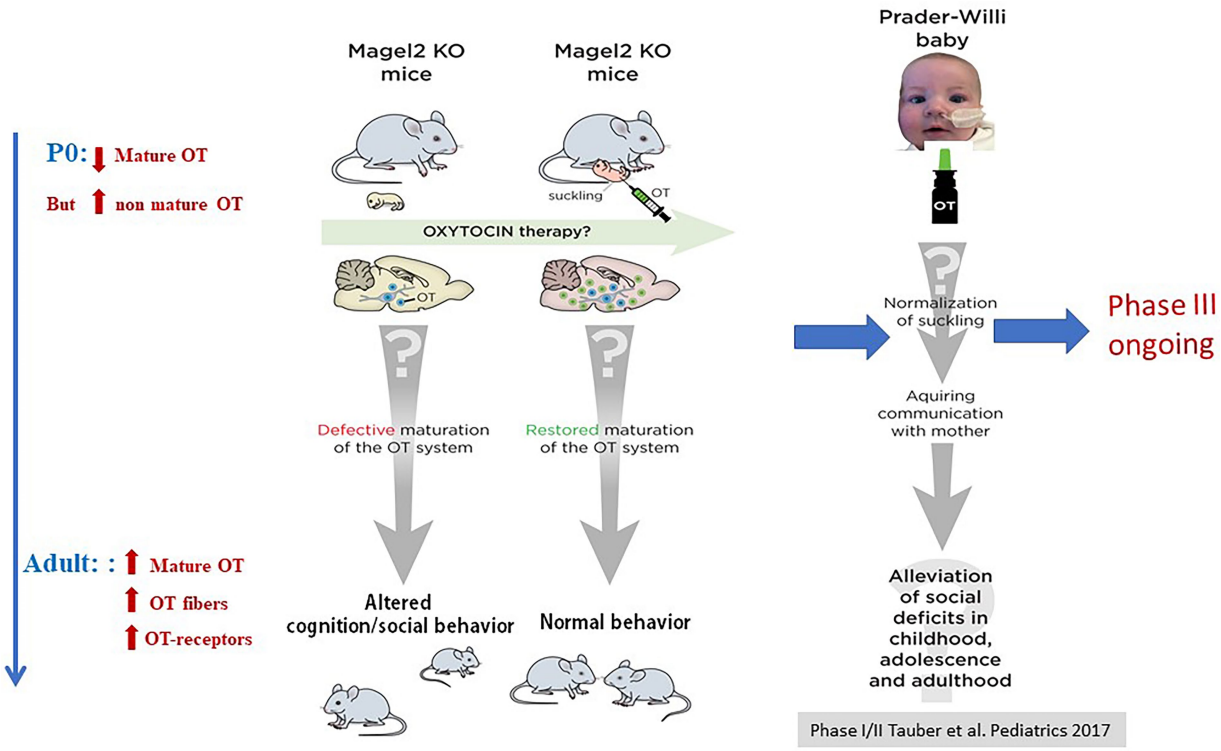

FIGURE 4
Alterations of OT-system and OT-rescue in *Magel2* KO mice and effects of OT intranasal administration in babies with PWS. Adapted from Muscatelli et al. (2018).

2001), *Otr* (Takayanagi et al., 2005; Sala et al., 2011, 2013), or *ADP-ribosyl cyclase* (CD38) (Jin et al., 2007; Liu et al., 2008), show changes in social behavior that are indicative of autism spectrum disorders (ASD). On the other hand, several rodent models known to be models of ASD, indirectly show a deficit of the OT brain system (Wagner and Harony-Nicolas, 2018). These models result from the inactivation of genes such as *Fmr1, Cntnap2, Magel2, Oprm1, Shank3* (Bosch and Neumann, 2008), *Nlgn-3* (Lefevre and Sirigu, 2016), or from environmental exposure to valproic acid. Although most studies of OT-dependent social behaviors have been conducted in adulthood, there is compelling evidence for a key role of OT, in infancy, in shaping various social behaviors and traits (Bosch and Neumann, 2008; Eaton et al., 2012; Miller and Caldwell, 2015; Lefevre and Sirigu, 2016; Muscatelli et al., 2017). Lukas et al. (2010) have shown that if pups are exposed to early-life stress, such as maternal separation, the normal development of V1A-R and OTR binding in specific forebrain regions is altered. Such alterations could contribute to aggression (Lopatina et al., 2018; Reichova et al., 2021) and other altered social behaviors, such as sexual behavior or social cognition in adulthood. In humans, recent studies suggest a link between child abuse (Smearman et al., 2016) and ratings of parental care (Unternaehrer et al., 2015) with the methylation status of the OTR promoter, conditioning the levels of OTR expression.

An unbalanced excitation/inhibition ratio and an altered synaptic plasticity have been associated with most of these pathologies and OT, *via* the OTRs, controls GABA-mediated Excitatory/Inhibitory (E/I) ratio (Lopatina et al., 2018) and synaptic plasticity *via* synaptic molecules (Reichova et al., 2021). Along this line, evidence for a unifying role of OT in pathogenic mechanisms responsible for social impairments across a broad range of autism etiologies has been provided (Hornberg et al., 2020; Lewis et al., 2020).

In addition, early-life adverse experience impairs social behaviors and has long-term, sex-dependent effects on the OT-system, in particular the expression of OTR (Bales and Perkeybile, 2012; Veenema, 2012; Perkeybile et al., 2019; Lapp et al., 2020). It has also been demonstrated that, in mouse pups, sensory experience influences OT production and that OT shapes neuronal circuits by modulating spontaneous and evoked activity. For instance, transection of the infraorbital nerve at P3, a well-known model of whisker deprivation leading to loss of barrel structures and callosal connection in the somatosensory cortex, compromises social memory and spatial memory in adult mice (Zhang et al., 2016). In this context, the adult social memory deficit is associated with a reduced quantity of OT in the hypothalamus and could be partially restored by intranasal administration of OT (Zhang et al., 2016).

Together, these studies support a role for the OT-system in the early postnatal development of various brain regions, especially in cortex and hippocampus. The OT-system resulted to be at the same time a target and a mediator of early sensory functions; it is

stimulated by sensory inputs and it mediates adaptative sensory and motor responses, *via* neuromodulation. The release of OT in infancy controls the quantity of OTR in the developing and adult brain and the E/I ratio *via*, partly, the GABAergic activity and the synaptic plasticity.

Long-term effects of oxytocin treatment in infancy

A highly informative approach to investigate the early effects of the OT-system is to administrate OT in neonates after birth. In wild-type prairie voles, such administration has lasting effects on both, the OT-system and the social behavior (Bales and Carter, 2003a,b; Cushing and Kramer, 2005; Bales et al., 2007). Similarly, the effects of maternal OT administration on prairie vole offspring development have also been characterized (Bales and Carter, 2003b; Kenkel et al., 2019). All pups showed at adulthood an increased alloparental caregiving toward pups and an increased close social contact with other adults; at adulthood, males showed an increased OTR density in the brain (Bales and Carter, 2003b; Kenkel et al., 2019). Of note, intranasal administration of OT to rhesus macaque neonates enhanced infants' affiliative communicative gestures and reduced salivary cortisol; and higher levels of OT were correlated with more social interest. Infants with better imitative skills were most sensitive to the positive action of OT; it suggests that sensitivity to OT may underlie early social motivation (Simpson et al., 2014).

Among the genetic cases of ASD, SYS and PWS are relevant neurodevelopmental diseases that manifest feeding difficulties from birth, developmental delay/intellectual disability, and ASD (Figure 3). This is an interesting example showing a deficit in suckling activity at birth (see above), and alterations in cognition and social behavior in juvenile and adult stages (Meziane et al., 2015; Bertoni et al., 2021). *Magel2* KO mice show a decrease in mature OT release at birth, which is correlated with alterations of the onset of feeding behavior; the administration of OT just after birth restores a normal suckling (see above) (Schaller et al., 2010). In adult mutants, an alteration of OT-innervation and OTR expression was also reported (Meziane et al., 2015) and OT-treatment during the first week of life (one subcutaneous administration every day, starting just after birth) restores both, a normal behavior at adulthood and normalizes the OT-system. To further study the long-term effects of OT on adult behavior, our team focused on social memory that is impaired in male *Magel2*-KO mice. We showed that *Magel2* and *Otr* transcripts are co-expressed in the dentate gyrus and CA2/CA3 hippocampal regions involved in the circuitry underlying social memory. In *Magel2* mutants, we revealed: an increase of the GABAergic activity of CA3-pyramidal cells associated with an increase in the quantity of OTR-expressing cells, mainly somatostatin interneurons, in specific hippocampal regions and developmental timings. In *Magel2*-deficient pups, we also observed a delay in the GABAergic development sequence. Most importantly, we have demonstrated the therapeutical effects of subcutaneous administration of OT in the mutant neonates, restoring all hippocampal alterations and social memory at adulthood (Bertoni et al., 2021).

In conclusion, although the molecular mechanisms and neuronal circuits involved remain largely to be explored, evidence have clearly emerged to demonstrate that OT-treatment in neonates or during infancy, plays a determinant role in shaping the social behavior of the infants by controlling the activity-dependent development of brain structures, with consequences on the adult behavior.

Conclusion and questions to address

The first sensorimotor and social behavior of a newborn mammal is to identify its mother, find the nipple, and suckle the milk. It is therefore not surprising that OT, by integrating sensory inputs in newborns, plays an important role in these processes. The OT-system is involved, from birth, in the first social interactions associated with feeding behavior on the mother's side (lactation, suckling) and on the baby's side (suckling) allowing the creation of a strong mother-infant bond. Thus, in addition to promoting the development of the sensory-motor system, OT has a concerted action in the mother and the baby, promoting the initiation of feeding behavior (Figure 5). How these two roles are related and dependent on OT circuits is illuminated by the pathologies in which both behaviors are affected.

Presumably, eating disorders in early childhood may lead to alterations in social behavior later in life. Early eating disorders could be an early marker of neurodevelopmental disorders such as ASD and could be an indication for early OT-treatment of these patients.

Considering the topic of this article, the main general questions to address in rodent models now are:

1. What sensory inputs affect OT-signaling in the first 2 weeks of life?
2. How does an identified sensory input affect the OT-system? In particular the expression of OTR (short and long term)?
3. What are the consequences, for an identified sensory input, of stimulation of the OT signal on sensory or motor responses?
4. What are the neural networks (functional connectivity) associated with a specific sensory stimulation involving the OT signal??
5. Does this OT signal play a role in the maturation of the OT-system?

These questions can be specifically applied to the role of OT in the initiation of sucking in rodents. To answer these questions, it would be necessary to develop efficient tools to study, around birth and in the first days of life, the connectivity of OT neurons and to manipulate OT neurons by optogenetics and chemogenetics.

In addition, studies to further analyze the alterations in early feeding and sucking behavior in ASD patients would be needed.

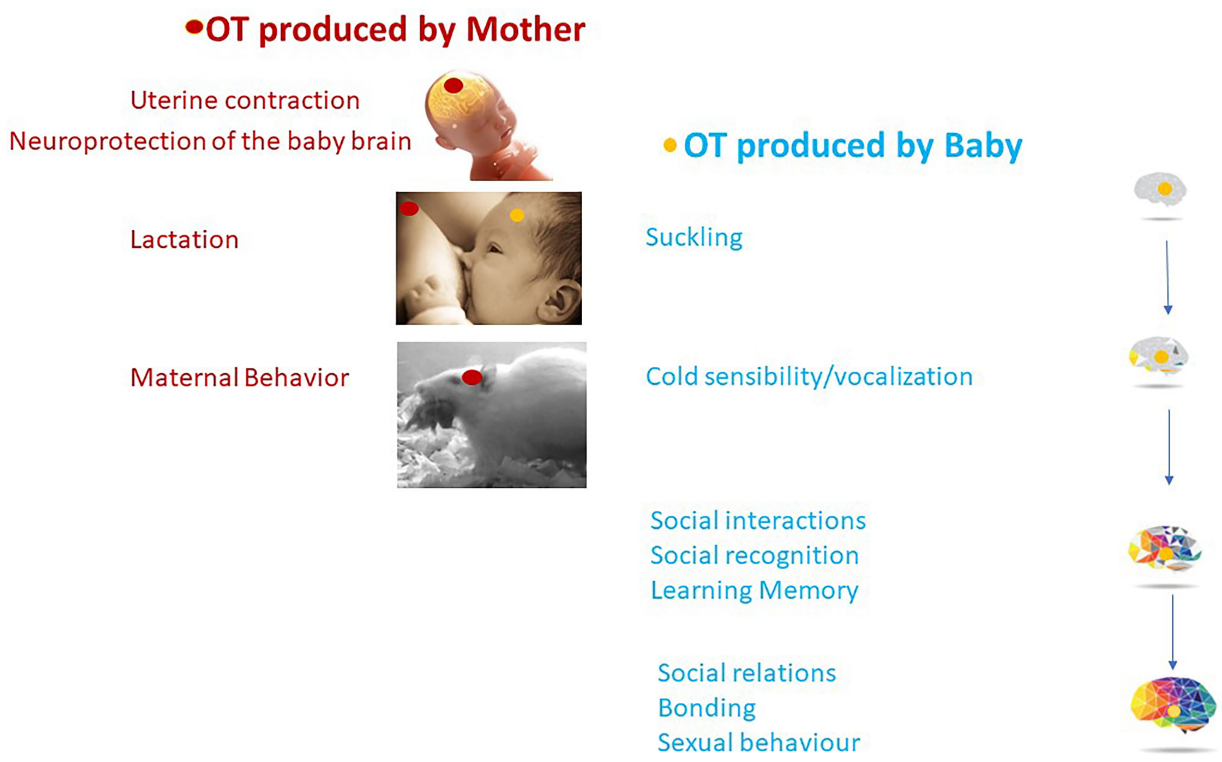

FIGURE 5
OT plays a concerted action between OT produced by the mother (in red) and OT produced by the baby (in blue) with long-lasting effects on social behavior and brain maturation.

Author contributions

FM designed and wrote the manuscript. VM and BC participated in the writing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Dissecting social decision-making: A spotlight on oxytocinergic transmission

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Social decision-making requires the ability to balance both the interests of the self and the interests of others to survive in social environments. Empathy is essential to the regulation of this type of interaction, and it often sustains relevant prosocial behaviors such as altruism and helping behavior. In the last decade, our capacity to assess affective and empathy-like behaviors in rodents has expanded our understanding of the neurobiological substrates that underly social decision-making processes such as prosocial behaviors. Within this context, oxytocinergic transmission is profoundly implicated in modulating some of the major components of social decision-making. Thus, this review will present evidence of the association between oxytocin and empathy-like and prosocial behaviors in nonhuman animals. Then, we will dissect the involvement of oxytocinergic transmission—across different brain regions and pathways—in some of the key elements of social decision-making such as emotional discrimination, social recognition, emotional contagion, social dominance, and social memory. Evidence of the modulatory role of oxytocin on social decision-making has raised considerable interest in its clinical relevance, therefore we will also discuss the controversial findings on intranasal oxytocin administration.

KEYWORDS

social decision-making, oxytocin, brain circuit, empathy, prosocial

Introduction

Survival in social environments is often complex and requires an intact functioning of the social decision-making ability that demands the right balance between the interests of the self and the interests of others. Surrounded by their conspecifics, individuals immersed in a society constantly relate to the social dimension and make decisions according to their mental states and intentions. Therefore, the equilibrium between self- and other-oriented aspects is fundamental for the ability to make appropriate social decisions and generate relevant prosocial behaviors such as helping behavior and altruism (Pfattheicher et al., 2022).

Empathy is described as an individual's ability to understand and feel the emotions of others. It is often considered to be one of the main factors driving prosocial behaviors like altruism (Bartal et al., 2011; Decety et al., 2016; Scheggia and Papaleo, 2020), a behavior

sometimes essential for survival in social environments (Rilling et al., 2008). Many non-human species have shown capabilities of empathy-driven prosocial behaviors towards their conspecifics (Decety et al., 2016; Scheggia and Papaleo, 2020), making them viable models for studying the neurobiological substrates of social decision-making processes (Scheggia et al., 2022). Along with empathy, social decision-making processes involving prosocial behaviors are affected by contextual information, such as familiarity (Scheggia et al., 2022), previous experiences (De Waal, 2008), stressors (Mudra Rakshasa and Tong, 2020), goals of interactions (Brucks and von Bayern, 2020), and individual differences (Bales and Perkeybile, 2012; Alonso et al., 2020).

Oxytocin is an evolutionarily conserved neuropeptide that modulates a large cluster of prosocial behaviors (Burkett et al., 2016; Yamagishi et al., 2020) and empathy-related processes (Pisansky et al., 2017). In a mammal's brain, oxytocin is released by the paraventricular nucleus (PVN) and supraoptic nucleus (SON; Sofroniew, 1983; Landgraf and Neumann, 2004). The oxytocin receptor (OTR) is widely expressed in several brain regions and peripheral organs (Gimpl and Fahrenholz, 2001), modulating different functions and complex behaviors. The OTR is a member of the rhodopsin-type (class I) GPCR family, influencing gene expression, neuronal excitability, synaptic adaptation, and neurotransmission. OTR has been found in various types of neurons such as glutamatergic pyramidal cells, GABAergic interneurons, and neuroendocrine cells (Huber et al., 2005; Jurek et al., 2015; Lin et al., 2018). This neuropeptide modulates social abilities and social behaviors such as social recognition (Oettl et al., 2016), social preference (Dölen et al., 2013), social fear (Pisansky et al., 2017), emotional discrimination (Ferretti et al., 2019), and empathy-like (Burkett et al., 2016; Scheggia and Papaleo, 2020) and prosocial behaviors (Heinrichs and Gaab, 2007).

Given the role of oxytocin in empathy-like and prosocial behaviors, our review offers an overview of the involvement of oxytocinergic transmission in the key components of social decision-making across different brain regions and pathways, such as emotional discrimination, emotional contagion, social dominance, and social memory (Figure 1). Finally, we will discuss the contrasting studies on the impact of oxytocin-based treatments in the clinical population.

Oxytocin in social decision-making processes motivated by empathy-like behaviors

Some decisions and behaviors involving other individuals can be driven by empathy (Bartal et al., 2011; Burkett et al., 2016), while other kinds of prosocial behaviors, such as cooperation, are not necessarily related to empathy (Decety et al., 2016). The role of oxytocin in modulating empathy-driven behaviors—such as parental care and prosocial behaviors—has been largely explored in humans (Hurlemann et al., 2010; Guastella and Hickie, 2016) and rodents (Gur et al., 2014; Nakajima et al., 2014; Burkett et al., 2016). Marlin and colleagues found that, in mice, the oxytocinergic signaling in the left auditory cortex processes the behavioral response to a mouse pup's distress calls and is also necessary for the maternal retrieval of isolated pups, enhancing the salience of vocal stimuli (Marlin et al., 2015).

Empathy can also motivate prosocial behaviors that are different from parental care. In a modified version of the human dictator game, in which one subject can choose between sharing or keeping the rewards from another participant, the infusion of oxytocin in the basolateral amygdala (BLA) of non-human primates favored the selection of prosocial tendencies (Chang et al., 2015). Oxytocin transmission in the insular cortex also mediates social decision-making in rats, modulating both approach and avoidance behaviors in a model of social affective preference (Rogers-Carter et al., 2018). Microinjections of an OTR antagonist in the insular cortex inhibited affective social behavior, with rats specifically avoiding juvenile stressed rats rather than stressed adults (Rogers-Carter et al., 2018). The oxytocin system is also involved in partner choice within groups of prairie voles. The intracerebroventricular infusion of a selective OTR antagonist prevented partner preference acquisition in mated male prairie voles, demonstrating the key role of oxytocin in pair bonding, which involves social decision-making processes (Johnson et al., 2016).

Several behavioral paradigms have been developed in the last decade aimed at investigating prosocial behaviors in rodents. It was found that rodents tend to approach and help stressed or trapped conspecifics (Bartal et al., 2011), avoid painful stimuli for the benefit of others (Hernandez-Lallement et al., 2020), and share food rewards with them (Scheggia et al., 2022), similarly to primates (Tan et al., 2017; Dal Monte et al., 2020). Yamagishi and colleagues found that the pharmacological block of the OTR in the anterior cingulate cortex (ACC) provoked a delay in learning helping behavior in rats, while the full acquisition of this behavior increased the activation of the immediate early gene c-Fos in ACC OTR-expressing neurons (Yamagishi et al., 2020). Another work from the same group revealed that OTR-knock-out prairie voles demonstrated impaired learning of the door-opening task and less interest in the soaked conspecific, suggesting that oxytocin modulates these helping and empathy-like behaviors in rodents (Kitano et al., 2022).

Oxytocinergic transmission regulates key components of social decision-making

Social decisions require continuous interpretation of the surrounding context that also includes other social agents and their mental states and actions (Bartz et al., 2011). These decisions are multidimensional in nature, and involve cognitive and emotional facets related to both the self and others. These include emotional discrimination, emotional contagion, previous experiences, and other social factors such as group dynamics, where oxytocin transmission is profoundly implicated.

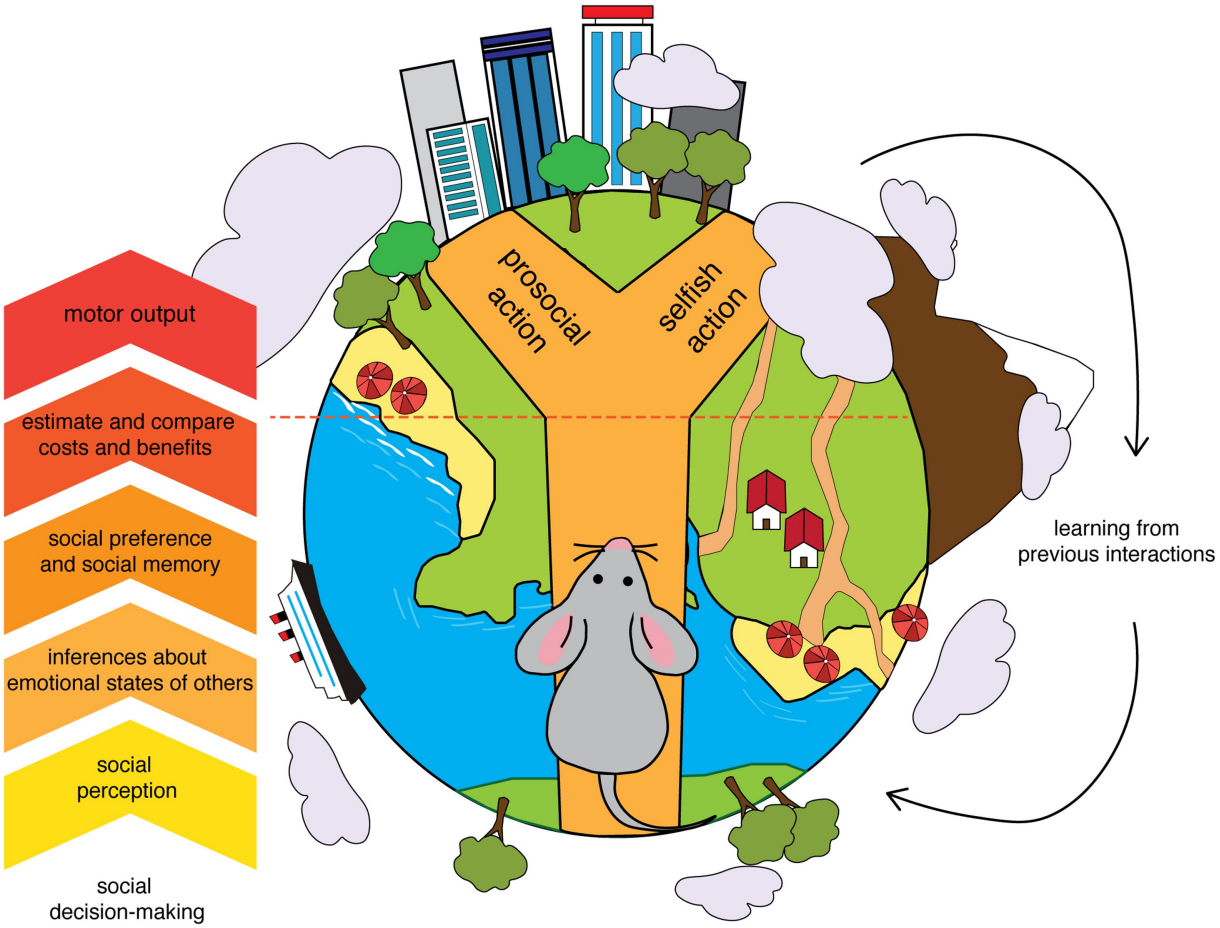

FIGURE 1
Core components of social decision-making. A simplified diagram showing some of the core components of the process of decision-making in a social environment. An anthropomorph mouse in the process of making a choice that could benefit others highlights how specific facets of this process are shared between rodents and humans. The diagram emphasizes the transformation from sensory information (social perception) to the motor output, that is a prosocial versus a selfish action. The interactions between the decision-making process and the consequences of the actions help to consolidate memories able to modulate future decisions.

Identifying and recognizing a conspecific is crucial in making appropriate social decisions. This ability is influenced by intra- and inter-species differences, in which the perception of the conspecific varies widely. For example, while in primates the use of vision and gaze plays a critical role in social perception and cognition, rodents largely rely on olfactive information (Gangopadhyay et al., 2021). Oxytocin is involved from the beginning of the processes of decision-making, during which sensory information is extracted from the social context. In the olfactory system, oxytocin is required for social cue processing (Oettl et al., 2016). Perception of social cues is the basis of understanding others' mental and emotional states. It has been reported that the PVN neurons projecting to the central amygdala (CeA) in mouse brains are selectively involved in emotional discrimination, likely through the interplay between oxytocin signaling and corticotropin-releasing factor, highly expressed in the CeA and involved in fear encoding (Ferretti et al., 2019). In addition, cortical areas are involved in the discrimination of conspecifics based on emotional states. Indeed, optogenetic inhibition of somatostatin-positive cells in the prelimbic region of the PFC (PL), which are highly enriched in OTR (Nakajima et al., 2014), impairs this ability (Scheggia et al., 2020).

Oxytocinergic signaling is also associated with mouse models of emotional contagion, a cognitive process by which observation of a conspecific in distress induces a similar affective experience in the observer. For example, both intranasal oxytocin administration (Pisansky et al., 2017; Zoratto et al., 2018) and chemogenetic stimulation of OTR-containing neurons (Pisansky et al., 2017) in mice increased the socially transmitted adoption of others' emotional states, with a subsequent downregulation of OTR in the amygdala when oxytocin was chronically given (Pisansky et al., 2017). State matching with a familiar conspecific under stress can also motivate consolation behavior (Burkett et al.,

2016), providing social buffering. This behavior was abolished by infusing an oxytocin receptor antagonist into the ACC. These reports highlight the relevance of oxytocinergic transmission in recognizing, understanding, and eventually sharing others' emotions, which is often crucial for successfully navigating the social environment.

Social groups involve dominant and subordinate members, forming a hierarchy that can affect multiple behaviors (Qu et al., 2017). Therefore, hierarchies represent an important variable in social interactions and prosocial behaviors (Cronin, 2012). In both mice and rats, social dominance consistently promotes prosocial actions (Gachomba et al., 2022; Scheggia et al., 2022) similarly to non-human primates, showing that prosocial behaviors are more often directed towards downward ranks (Cronin, 2012). In this context, oxytocin reduces the differences in social behavior between dominant and subordinate members, thereby flattening the status hierarchy (Jiang and Platt, 2018). In line with this evidence, the oxytocinergic system underlying the establishment and maintenance of social hierarchies in rats (Timmer et al., 2011) and dominant mice shows increased OTR levels when compared with subordinate individuals (Lee et al., 2019).

The oxytocinergic network is sensitive to early-life stressors that can provoke long-term social impairments. He and colleagues showed that when mandarin voles— socially monogamous rodents with biparental attachment in their pups—were raised under paternal deprivation, they manifested anxiety-like behavior and lower social preference during adulthood (He et al., 2019). Importantly, the authors found that voles deprived of paternal influence had significantly fewer oxytocin neurons in the PVN and a decreased OTR in the medial PFC (mPFC) in both females and males, and optogenetic stimulation of PVN-to-PL projecting neurons restored this impairment (He et al., 2019).

The PVN oxytocin neurons also project to the anterior olfactory bulb, where OTR is largely expressed (Knobloch et al., 2012). Stimulating this pathway increased social recognition memory in female rats, while its inhibition prevented the ability (Oettl et al., 2016). Social memory is another important aspect with an influence on social decision-making processes. The role of the hippocampus in social behaviors has recently gained attention (Okuyama et al., 2016; for review, see Okuyama, 2018). In particular, the identification of the so-called "social place cells" in the dorsal hippocampus of bats (Omer et al., 2018) and rats (Danjo et al., 2018) points to this area as fundamental for processing self- and other-related information in the spatial dimension. The OTR is largely expressed across different subfields of the hippocampus (for review, see Cilz et al., 2019) and has an influence on social behaviors. It has been reported that the OTR conditional silencing selectively in CA2/CA3 or forebrain pyramidal neurons reduced the persistence of long-term social memory without affecting sociability or social novelty. In agreement with these findings, pharmacological stimulation of OTR on hippocampal slices provoked long-term potentiation (Lin et al., 2018). Intriguingly, Raam and colleagues showed that optogenetic inhibition of intrahippocampal connections between OTR-containing cells in dorsal CA2/CA3, projecting to the ventral CA1, impaired social but not non-social discrimination in mice (Raam et al., 2017). In a Magel$^{2tm1.1Mus}$-deficient mouse, a model of autism-like disorders, an enhanced GABAergic activity of CA3 glutamatergic cells was found to be associated with an increased expression of OTR and somatostatin interneurons in both the dentate gyrus and CA2/CA3 regions. This effect might be responsible for their deficits in social memory, assessed using the social three-chamber task (Bertoni et al., 2021). Importantly, systemic administration of oxytocin in Magel$^{2tm1.1Mus}$-deficient pups restored both hippocampal dysfunction and behavioral deficits during adulthood (Bertoni et al., 2021), highlighting the clinical relevance of oxytocin in the sphere of social cognition and behavior.

This evidence strongly supports the crucial role of oxytocin in modulating neural activity across several brain areas, recruited at different levels of the decision-making process, with significant effects on social and prosocial behaviors.

Translating animal models: From endogenous system to oxytocin-based treatments

Fluctuations in endogenous oxytocin levels have been connected to both positive and negative modulations of social and prosocial behaviors (Crockford et al., 2014; Marsh et al., 2021; Tabak et al., 2022). This can be attributed to the influence of the oxytocin system on neural areas or circuitries related to reward (Scheele et al., 2013) and emotional processing, such as fear processing (Meyer-Lindenberg et al., 2011), attentional resources, and salience attribution to social stimuli (Dölen et al., 2013; Wei et al., 2022). Moreover, the anxiolytic effects driven by oxytocin changes can further contribute to the expression of social behaviors mainly due to the influence on the hypothalamic–pituitary–adrenal axis and the amygdala activity (Eckstein et al., 2015; Mitre et al., 2016; Neumann and Slattery, 2016). Furthermore, endogenous oxytocin levels are highly susceptible to sex, age, personality traits and predisposition, previous history, and context (Marsh et al., 2021). Genetics, epigenetics, and neurobiological factors have an impact on endogenous oxytocin, such as OTR variances (Rodrigues et al., 2009; Saphire-Bernstein et al., 2011; Spencer et al., 2022) and fluctuations across the lifespan (Audunsdottir and Quintana, 2022; Zak et al., 2022). These factors could modify the modulatory effects of oxytocin on social behaviors (Van IJzendoorn et al., 2011; Declerck et al., 2020; Marsh et al., 2021). For instance, contextual information associated with danger or social threat can stimulate oxytocin release that can be associated with aggressive-defensive or antisocial behaviors (Hurlemann and Marsh, 2019).

Dysregulation or malfunctioning of the oxytocin system has been reported in neuropsychiatric (Green et al., 2001; Yamasue and Domes, 2017; Goh et al., 2021) and neurodegenerative disorders (Gabery et al., 2015; Unti et al., 2018), mostly in the form of reduced endogenous oxytocin levels. In this case, the downregulation of the oxytocinergic transmission might be associated with anomalies in attention, evaluation, and response to external socio-emotional stimuli (Crockford et al., 2014; Gulliver et al., 2019). This could affect the cognitive and socio-emotional components necessary for expressing effective social decisions and behaviors regarding others (Marsh et al., 2021). Therefore, the assessment of endogenous oxytocin levels becomes crucial for the evaluation of the real effects of oxytocin-based treatments in the clinical setting (Marsh et al., 2021; Tabak et al., 2022).

Targeting oxytocinergic signaling has been considered to be an effective strategy to contrast social deficits in clinical populations. Intranasal application has been perhaps the principal route of oxytocin administration when compared with others, such as oral or intravenous, in the clinical and non-clinical setting (Quintana et al., 2021), due to the direct link with the central nervous system and the neglectable side-effects reported (Born et al., 2002; MacDonald et al., 2011; Bakermans-Kranenburg and van IJzendoorn, 2013). A good body of evidence revealed that the administration of intranasal oxytocin (IN-OXT) has beneficial properties on empathy and prosocial behaviors both in human (MacDonald and MacDonald, 2010; Geng et al., 2018; Leng and Leng, 2021) and nonhuman animals (Neumann et al., 2013; Huang et al., 2014; Chang et al., 2015; Pisansky et al., 2017; Zoratto et al., 2018). Specifically, studies on healthy human participants performing behavioral tasks readapted from the economic field (Sanfey, 2007) revealed that IN-OXT promotes and likely enhances relevant prosocial manifestations such as trust (Kosfeld et al., 2005), generosity (Domes et al., 2007), cooperation (De Dreu, 2012), altruism (Marsh et al., 2015), and social bonding (Lim and Young, 2006). However, subsequent efforts for replicating these initial results have failed, forcing researchers to downsize or review the claims around IN-OXT and its social properties (Nave et al., 2015; Declerck et al., 2020; Macchia et al., 2022).

Clinical studies reported beneficial effects on social dysfunctions following IN-OXT, including social decision-making deficits. Andari and colleagues reported increased trust and social preference within a virtual social interaction game involving 13 adult subjects with autistic spectrum disorder (ASD; Andari et al., 2010). More recently, clinical trials involving ASD participants revealed that long-term oxytocin-based treatments rescued neural activity or led to functional readaptations of areas such as the amygdala and the PFC, which are considered essential for establishing social interactions and making social decisions (Alaerts et al., 2020; Bernaerts et al., 2020). Nonetheless, Sikich et al. recently reported no effects after IN-OXT in measures of social functioning in a large-scale placebo-controlled study involving children and adolescents affected by ASD (Sikich et al., 2021). This was in line with a previous meta-analysis of 12 randomized clinical trials regarding the use of IN-OXT in ASD (Ooi et al., 2017).

In a meta-analysis by Bürkner and colleagues evaluating 12 randomized controlled trials in patients with schizophrenia, small but considerable effects of IN-OXT treatment on high-level social cognition were reported, including metallization and social inference abilities regarding others' intentions and actions (Bürkner et al., 2017). Further, Wigton and colleagues observed a higher prosocial tendency after a single-dose oxytocin inhalation in 20 adult patients with schizophrenia during a rewarded decision-making task, likely due to better emotional and metallization capacities driving their decisions (Wigton et al., 2022). This improvement was linked to significant changes in the level of neural activity in key regions within the social decision-making system such as the amygdala, the ACC, and the insula (Wigton et al., 2022). The literature reports contrasting results, showing no significant benefits for social functioning in patients with schizophrenia following IN-OXT when compared with other treatments (Williams and Bürkner, 2017).

Administration of IN-OXT has also been applied in patients with neurodegenerative disorders that are characterized by social dysfunction, including social decision-making deficits (Manuel et al., 2020; Mason et al., 2021). Patients with frontotemporal dementia (FTD) who were administered a single dose of IN-OXT improved their abilities to recognize facial expressions (Jesso et al., 2011). Particularly, the authors indicated a reduced emotional response from FTD patients to negative faces. They also found a trend for better recognition of positive faces, which might lead to augmented trust and cooperative behavior within the social context (Jesso et al., 2011). Accordingly, Finger et al. used IN-OXT in a randomized clinical trial including 23 FTD patients and reported, indirectly, increased levels of empathy and social exchange in their relationships with their caregivers (Finger et al., 2015). Further, an ongoing trial is considering the long-term beneficial effects of IN-OXT for FTD patients (Finger et al., 2018). Finally, Labuschagne and colleagues described a significant recovery in Huntington's disease patients' ability to discriminate between emotions after oxytocin inhalation, a skill associated with restored neural activity in the areas involving emotion processing (Labuschagne et al., 2018). Despite this evidence, negative results have been reported on the effects of IN-OXT in neurodegenerative disorders. For instance, a recent meta-analysis did not find any improvement in emotion recognition or expression for the FTD population after IN-OXT treatment (Leppanen et al., 2017).

Perspectives on future directions in clinical research

Although in many studies and clinical trials IN-OXT reduced social impairments, there is debate within the field about its effectiveness. As described, negative evidence exists for studies on neuropsychiatric (Dagani et al., 2016; Ooi et al., 2017; Williams and Bürkner, 2017; Sikich et al., 2021) and neurodegenerative (Leppanen et al., 2017) populations. Therefore, why is oxytocin

in its current form not helpful for many patients? Preclinical studies should reduce the drift between basic and clinical research and translate knowledge into human applications. This process should not exist exclusively to create novel treatments, but also to adjust procedures of drug administration in patients. For instance, it has been shown that oxytocin increases the salience of social stimuli (Jurek and Meyer, 2020). This could suggest a pairing of oxytocin treatment with some type of behavioral training. Another crucial aspect of oxytocin administration is that it is still not clear how much of the dose is getting to the brain. A recent study developed a fluorescent sensor for real-time measurement of extracellular oxytocin. This could aid in the understanding of oxytocin destination administered by the intranasal route (Ino et al., 2022).

An important aspect to consider is that some of the oxytocinergic actions might also be mediated by vasopressin, which is structurally similar to oxytocin and comes from the same ancestral gene (Gwee et al., 2009; Theofanopoulou, 2021), with relevant effects on a large cluster of social behaviors and physiological functions (for review, see Song and Albers, 2018). Although oxytocin and vasopressin receptors are distributed differently across the brain, their interaction has several consequences (Xiao et al., 2017). Oxytocin can also bind to vasopressin receptors (V1aR), with antagonist effects on OTR (Anacker et al., 2016; Tan et al., 2019).

Finally, possible reasons for oxytocin failure could involve the way we measure its effects as well as problems in study design. The most relevant limitations include sample size (Gulliver et al., 2019; Marsh et al., 2021), individual (Declerck et al., 2020; Macchia et al., 2022) and contextual differences (Bartz et al., 2011), statistical inference and power (Calin-Jageman and Cumming, 2019; Mierop et al., 2020), and dosage characteristics (Kosaka et al., 2016). Furthermore, many studies lack the use of effective control groups or the comparison between oxytocin and other drug treatments (Erdozain and Penagarikano, 2020; Mierop et al., 2020). Likewise, the development of standardized procedures for measuring social abilities, including the components involved in social decision-making processes, might benefit oxytocin research in the clinical setting (Marsh et al., 2021; Tabak et al., 2022).

Thus, a more holistic and interactive approach regarding IN-OXT use in the clinical and nonclinical setting appears necessary (Audunsdottir and Quintana, 2022; Putnam and Chang, 2022). This would require an acknowledgment of the relationship between the exogenous ways of administration and the endogenous oxytocin (Mierop et al., 2020; Quintana and Guastella, 2020; Tabak et al., 2022). This expanded perspective also highlights the opportunity for an evaluation of the joint action between endogenous oxytocin and other neuropeptides like vasopressin (Rilling et al., 2012) or other neurotransmitters (Dölen et al., 2013). In addition, combinatorial treatments with other drugs (Fan et al., 2020) or additional behavioral and psychological techniques, which can exploit individual-contextual information (Marsh et al., 2021; Wei et al., 2022), should be considered.

Concluding remarks

In recent years, considerable advances have been made in our ability to assess social decision-making processes in animal models. These advances had an impact on our understanding of the neurobiology underlying social decision-making processes, including when they take the form of prosocial behaviors that benefit others. Although not comprehensive, we reported increasing evidence of the modulatory role of oxytocin across the major elements in the process of making decisions in a social environment, from the perception of social stimuli to motor output. We highlighted a selection of studies and clinical trials that have reported the beneficial effects of oxytocin administration in neuropsychiatric conditions associated with dysfunctional social decision-making. However, given the heterogeneity of the responses to oxytocin-based treatments, we must address how we can best exploit our understanding of the oxytocin system through preclinical studies to target specific interventions for social dysfunctions in the clinical setting.

Author contributions

GC is the main writer of the review and completed the collection and analysis of relevant literature. FG contributed to analysis of literature. DS contributed to conception of the study, edited the manuscript, and created the figure. GC and FG wrote the manuscript. ML reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Modulation of the thermosensory system by oxytocin

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Oxytocin (OT) is a neurohormone involved early in neurodevelopment and is implicated in multiple functions, including sensory modulation. Evidence of such modulation has been observed for different sensory modalities in both healthy and pathological conditions. This review summarizes the pleiotropic modulation that OT can exercise on an often overlooked sensory system: thermosensation. This system allows us to sense temperature variations and compensate for the variation to maintain a stable core body temperature. Oxytocin modulates autonomic and behavioral mechanisms underlying thermoregulation at both central and peripheral levels. Hyposensitivity or hypersensitivity for different sensory modalities, including thermosensitivity, is a common feature in autism spectrum disorder (ASD), recapitulated in several ASD mouse models. These sensory dysregulations occur early in post-natal development and are correlated with dysregulation of the oxytocinergic system. In this study, we discussed the potential link between thermosensory atypia and the dysregulation of the oxytocinergic system in ASD.

KEYWORDS

autism spectrum disorder (ASD), oxytocin, thermo-sensory response, neurodevelopment, atypical sensory response

1. Introduction

Oxytocin (OT) is a nonapeptide mainly secreted by neurons located in both the parvocellular division and the magnocellular division of the paraventricular nucleus (PVN), as well as in the magnocellular division of the supraoptic nucleus (SON) and the accessory nuclei of the hypothalamus in mammals (Lawson et al., 2020). It is involved in many functions such as induction of parturition or lactation, social or reproductive behavior tuning, and modulation of energy balance (Yuan et al., 2020). It acts not only as a neurohypophysial hormone through secretion into circulation to conduct its peripheral effects but also as a neuromodulator in the central nervous system (CNS) through either synaptic or dendritic release as well as volume transmission release for which OT diffuses in the extracellular space to act on structures expressing its receptor (OTR) (Grinevich and Ludwig, 2021).

OT/OTR signaling emerges very early in the course of mammalian development and it is associated with a dynamic spatiotemporal OTR expression (Mitre et al., 2018). In rodents, OTR is detected in the brain during embryonic neurogenesis and peaks in the second week of life. Analyses of the human brain revealed that OTR expression begins to accelerate right before birth, with a peak level of expression occurring during early childhood (Rokicki et al., 2022). Moreover, in mice, OT-expressing neurons are settled at embryonic day E14.5 (Madrigal and Jurado, 2021). The immature form of OT is detected as early as E16.5 and the mature form is after birth (Sannino et al., 2017).

OT/OTR signaling dysregulation can have a drastic effect on neurodevelopment, suggesting that the oxytocinergic system during this critical window could be implicated in some neurodevelopmental disorders such as autism spectrum disorder (ASD) (Sannino et al., 2017). Such dysregulation of the oxytocinergic system has been demonstrated in different genetic models of ASD, and a recent meta-analysis of 31 studies suggests that children (but not adults) with ASD have lower blood oxytocin levels compared to neurotypical individuals (John and Jaeggi, 2021).

During early life, sensory systems are very important for the construction of future socio-cognitive and emotional behaviors (Grinevich and Stoop, 2018). The effects of OT on the development, maturation, and regulation of the sensory systems (Grinevich and Stoop, 2018; Wang et al., 2022) are mediated by experience-dependent plastic changes which are known to occur during the early childhood-adolescence window (Onaka and Takayanagi, 2021).

The implication of the oxytocinergic system to set up sensory functionalities during the early period and its downregulation in children with ASD could account for sensory processing atypicalities (i.e., hyposensitivity or hypersensitivity) (Robertson and Baron-Cohen, 2017). Atypia is experienced by 90% of patients with ASD and is experienced as early as a few months from the diagnosis, which makes it one of the earliest diagnostic criterion for this disorder (Grzadzinski et al., 2020). Moreover, knowing the impact of the sensory systems on socio-cognitive and emotional behaviors and the fact that patients with autism have an atypical sensory understanding of the surrounding environment could lead to altered socio-cognitive behaviors (Park et al., 2021). OT treatment might be beneficial for sensory processing (Hubble et al., 2017) and therefore could have a beneficial impact on some cognitive deficits (Kanat et al., 2017).

This modulation of sensory processing by the oxytocinergic system has been largely reviewed. In this study, we emphasize the pleiotropic effects of the oxytocinergic system on one overlooked specific sensory modality: thermosensory processing.

The thermosensory system allows us to sense external temperature variations and induce physiological and behavioral thermoregulation to maintain a stable core temperature. Sensing any drop in external temperature might become vital for mammalian newborns since, unlike their homeothermic adult counterparts, neonates are poikilothermic: their adaptation to external temperature is not yet fully established. This system also implies the ability to have the consciousness of the environmental temperature, namely temperature perception, which participates in our comprehension of the surrounding environment.

In addition, we summarize the different studies demonstrating the role of OT to modulate both physiological and behavioral thermoregulation. Atypical temperature perception as well as thermoregulation issues have been observed in ASD. Considering that both the oxytocinergic and the thermosensory systems have been found dysregulated in ASD, we hypothesize that OT dysregulation in ASD is a potential physiopathological mechanism of thermosensory dysfunction.

2. Part 1: OT effects on temperature sensing and regulation

The thermosensory system is essential for the survival of individuals. It enables us to not only have a conscious perception of external temperature but also induce a physiological response of thermoregulation, leading to heat production and retention under cold exposure, namely thermogenesis, as well as appropriate behavioral strategies to maintain a stable body temperature. The neural pathways that support this ability have been intensively investigated in the last decade in adult rodents, but it has received much less attention in newborns. The thermosensitivity to external temperature starts at the skin level where different types of thermoreceptors are expressed (Patapoutian et al., 2003) and activated by different ranges of temperature (Dhaka et al., 2006; Palkar et al., 2015; Lamas et al., 2019; Buijs and McNaughton, 2020), allowing humans to differentiate between cool, warm, cold, and hot. The skin on the body and the face is innervated by first-order thermosensory neurons, located, respectively, in the dorsal root ganglia (DRG) or the trigeminal ganglia (TG) (Xiao and Xu, 2021) and projecting to the medulla. The sensory information is then transmitted through two different neural pathways leading to thermosensation and thermoregulation responses (Morrison and Nakamura, 2011). The thermosensation pathways which correspond to the conscious perception of external temperature variations are provided by the spinothalamic tract projecting to the somatosensory cortex (Milenkovic et al., 2014; Bokiniec et al., 2018) and also to the insular cortex (mainly for humans) (Craig, 2002; Filingeri, 2016). In parallel, another part of the projections from the medullary neurons reaches the lateral parabrachial nucleus (LPB) (Morrison et al., 2014) to coordinate the thermoregulation in response to environmental temperature variations (Nakamura and Morrison, 2011). Two types of thermoregulation responses are commonly defined. First, an autonomic involuntary thermoregulation response is mediated by descending projections from the preoptic area (POA), leading

to activation through sympathetic pathways (Romanovsky et al., 2009) of different thermo-effectors. These effectors include the brown adipose tissue (BAT), the skeletal muscles, the heart, and the blood vessels that fight against temperature variations (Tan and Knight, 2018; Nakamura et al., 2022). Mammalian newborns are poikilotherms, and during this period only the BAT is recruitable for thermogenesis (Cannon and Nedergaard, 2004). The second thermoregulatory response implies a behavioral voluntary thermoregulation response using various behavioral strategies to allow mammals to stay as much as possible in a thermoneutral environment (Almeida et al., 2015; Jung et al., 2022). It has been shown recently that such behavior involves the lateral hypothalamus (LH) (Jung et al., 2022). These neural pathways are represented in Figure 1. Different studies investigating the action of OT on this thermosensory modality found that OT has a pleiotropic mode of action by tuning both central circuitry and peripheral thermos-effectors.

2.1. OT participates in maintaining stable core temperature through activation of non-shivering thermogenesis

Hypothalamic OT neurons are polysynaptically connected to the BAT (Oldfield et al., 2002), which produces heat in response to cold temperatures (Cannon et al., 1998). The descending projections arising from OT neurons of the paraventricular nucleus (OT PVN neurons) (Oldfield et al., 2002) innervate sympathetic preganglionic neurons of the intermediolateral (IML) nucleus of the spinal cord (De Luca et al., 1989; Bamshad et al., 1999; Foster et al., 2010), which express OTR (Reiter et al., 1994) and trigger BAT to produce heat through the sympathetic nervous system and β-adrenergic activation (Takayanagi et al., 2008). Besides this OT-regulated sympathetic action, endocrine regulation of the BAT by OT exists since BAT adipocytes express the OTR (Lawson, 2017) and it is known that OT can activate BAT's lipolysis pathway (Deblon et al., 2011). Additionally, different brain structures involved in thermoregulation, such as the POA (Shi and Bartness, 2000), the dorsomedial hypothalamic nucleus (DMH) (Shi and Bartness, 2000), and the ventromedial hypothalamic nucleus (VMH) (Whitman and Albers, 1998), express the OTR (Gimpl and Fahrenholz, 2001; Yoshida et al., 2009) and are innervated by OT PVN neurons.

Different approaches have been undertaken to study how OT modulates the capacity of the BAT to generate heat through lipid oxidation. First, pharmacological treatments with OT or analogous applied through different routes of administration have been performed to study their effects on BAT thermogenesis. In rats, OT injection in the anterior POA causes hyperthermia (Lin et al., 1983), and OT intracerebroventricular (ICV) administration in the third ventricle (3V) or fourth ventricle (4V) elevates interscapular BAT (IBAT) temperature (Roberts et al., 2017) and increases core body temperature (Ong et al., 2017). In mice, central OT injection produces a transient elevation of the colonic temperature (Mason et al., 1986), local application of OT into the median raphe nucleus (MnR) increases the body temperature (Yoshida et al., 2009), and ICV OT administration in mice 3V or 4V is reported to elevate IBAT temperature (Roberts et al., 2017). In rabbits, OT ICV injection produces dose-related hyperthermia and increases the body temperature (Lipton and Glyn, 1980). Roberts et al. (2017) demonstrated that the effect of OT on BAT thermogenesis is OTR-dependent since a lack of effect of the OT ICV injection in mice and rats was observed when the animals were pretreated with OTR antagonist. Thus, in different species, exogenous OT in the central nervous system has been shown to produce hyperthermia through a non-shivering thermogenesis response and without the elevation of locomotor activity for the rodent models (Deblon et al., 2011; Maejima et al., 2011; Blevins et al., 2016; Iwasa et al., 2019). Especially, peripheral OT administration in rats showed a reduced core body temperature (Ring et al., 2006; Hicks et al., 2014; Ong et al., 2017) as well as an absence of a thermogenesis response (Iwasa et al., 2019). Kohli et al. (2019) explained this contradiction by the fact that peripheral OT mediates its effects through the activation of arginine vasopressin (AVP) receptor V1A rather than OTR since pretreatment with V1A antagonist can reduce the OT-mediated hypothermia, while pretreatment with OTR antagonist does not.

Second, the development of OT knockout (KO) and OTR KO mice has been very useful for studying the impacts of a lack of OT/OTR signaling on thermoregulation. Hence, OT KO mice have difficulties maintaining their body temperature when they are exposed to cold temperatures (Kasahara et al., 2007; Harshaw et al., 2018). Moreover, exposure to cold results in c-Fos expression within OT PVN neurons, highlighting the implication of those neurons in thermogenesis induced by cold exposure (Kasahara et al., 2007). These results are in line with previous examinations of induced cold stress activation of the PVN (Baffi and Palkovits, 2000; Bratincsák and Palkovits, 2004). In the same line, the author demonstrated that OTR KO mice also failed to maintain their body temperature when exposed to cold (Kasahara et al., 2013; Harshaw et al., 2018). These results correspond with those of OTR KO mice harboring impaired thermoregulation (Takayanagi et al., 2008; Camerino, 2009). To directly link the deficit in thermogenesis with OTR signaling, the author rescued the expression of the OTR by injecting an AAV-Oxtr-IRES-Venus virus into the DMH and the VMH of OTR KO mice. This rescue compensated for some of the previous deficits in thermoregulation when the injected mice were exposed to a cold environment (Kasahara et al., 2013). Additionally, the authors proved the importance

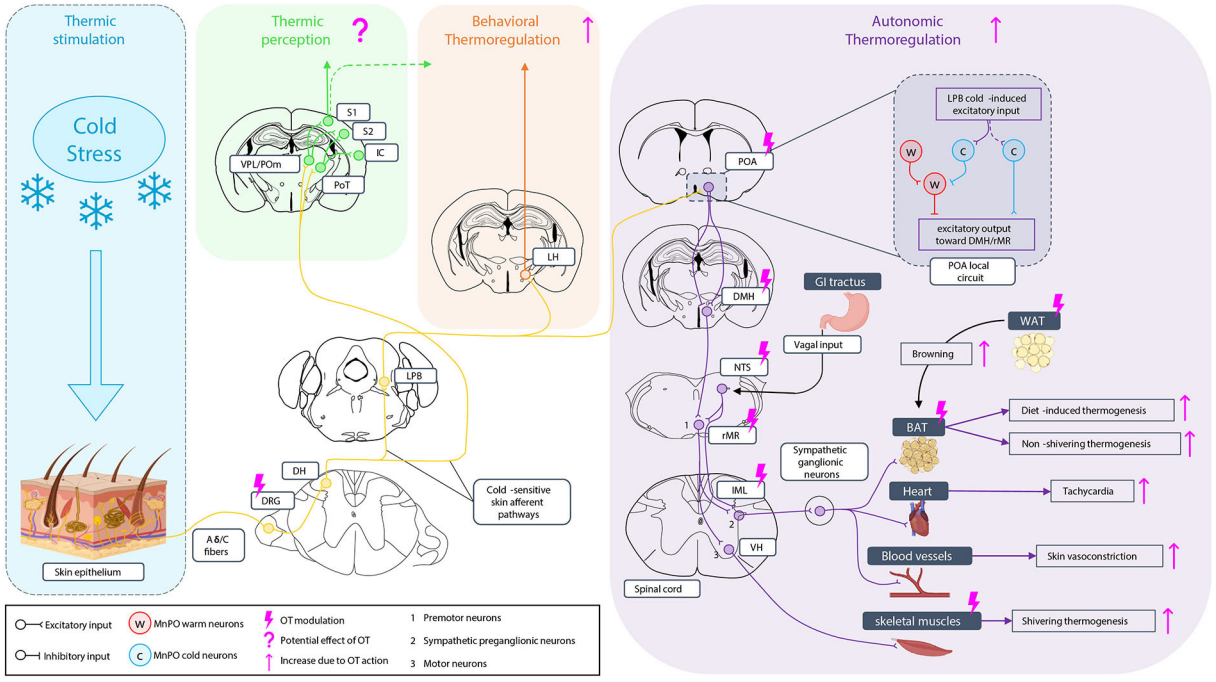

FIGURE 1
Oxytocinergic modulation of the thermosensory system under cold stimulation. Under cold exposure, skin thermoreceptors expressed at dorsal root ganglia (DRG) neurons ending are activated and the sensitive information is conducted to medullar neurons of the dorsal horn (DH). The information is sent through two types of cold-sensitive skin afferent pathways: i) in one case, to the posteromedial (POm), the ventral posterior lateral nucleus (VPL), and the posterior triangular nucleus (PoT) of the thalamus. The PoT project to the insular cortex (IC), the VPL, and the PoT project to the accessory somatosensory cortex (S2), and the VPL and the POm project to the primary somatosensory cortex (S1) giving the perception of temperature; ii) in the second case, the cold-sensitive skin afferents contact the lateral parabrachial nucleus (LPB) where the information is once more separated in two pathways. The first goes to the lateral hypothalamus (LH) to engage the behavioral thermoregulation. A potential implication of the somatosensory cortex in behavioral thermoregulation is not excluded. The other one is related to autonomic thermoregulation. LPB projection goes to the preoptic area (POA), an integrating center of temperature information with a local circuit in which the inputs from the LPB excite excitatory cold-sensitive neurons but also lead to the activation of cold-sensitive neurons of the median preoptic nucleus (MnPO) that inhibit warm-sensitive neurons, leading to an excitatory output of the POA toward the dorsomedial hypothalamus (DMH). Neurons of the DMH then project to the rostral medullary raphe region (rMR) which is also contacted by neurons of the nucleus tractus solitarius (NTS) receiving visceral vagal input, for the induction of the diet-induced thermogenesis. Premotoneurons of the rMR project then to sympathetic preganglionic neurons of the IML, activating the sympathetic ganglionic neurons to induce the non-shivering thermogenesis of the brown adipose tissue (BAT), the diet-induced thermogenesis on the BAT (related to NTS input), heart tachycardia, and vasoconstriction of skin blood vessels. Premotoneurons of the rMR project also to motoneurons of the ventral horn (VH) of the medulla to induce skeletal muscle shivering thermogenesis. Oxytocin (OT) can modulate behavioral thermoregulation without knowing yet whether it can act on LH. It can modulate the autonomic thermoregulation at different levels increasing BAT and muscle thermogenesis, tachycardia, and vasoconstriction but also by stimulating white adipose tissue (WAT) browning toward BAT to increase the thermogenesis capacity.

of the OT/OTR system in the rostral medullary raphe (rMR) for thermoregulatory function under cold exposure (Kasahara et al., 2015). The role of OT neurons in thermoregulation has also been studied in the diphtheria-induced ablation of these neurons. Upon cold exposure, OT-neuron–ablated mice showed a lower core body temperature, lower BAT response to cold, and a decrease in vasoconstriction in the skin, indicating once more the importance of the oxytocinergic system in thermoregulation (Xi et al., 2017). Pharmacogenetic stimulation of mice OT PVN neurons performed using DREADDs technology resulted in increased energy expenditure and IBAT temperature (Sutton et al., 2014). Similarly, a recent study in mice showed that the optogenetic activation of OT PVN neurons stimulates the sympathetic premotor neurons of the rMR through a direct connection, leading to an increase of the sympathetic outflow increasing both the BAT thermogenesis and the cardiac tachycardia (Fukushima et al., 2022). This increases the supply of oxygen and nutrients to the BAT, enhancing its thermogenic function and facilitating the systemic distribution of the heat generated by the BAT (Nakamura, 2011). To complement these data, a study of OTR gene expression after cold stress has been undertaken, showing upregulation of this gene in the brain, reinforcing the role of the oxytocinergic system in response to cold stress challenge (Camerino et al., 2018).

Thus, disruption of OT/OTR signaling results in thermogenesis deficits and the incapacity of

mammals to maintain a stable temperature under cold environment exposure.

2.2. OT increases energy expenditure through BAT thermogenesis activation

Another approach to studying the effect of OT on BAT thermogenesis is to look at the effect of OT on energy expenditure, an indirect indicator of BAT thermogenesis activation. Energy homeostasis resides in the balance between energy intake that mainly comes from food consumption and energy expenditure which represents the basic metabolic processes and exercises. The process of BAT non-shivering thermogenesis is an important component of energy expenditure (Seale and Lazar, 2009; Saito, 2013). In addition to its thermoregulatory function in cold environments, the BAT can turn excess energy into heat to maintain the energy balance in rodents and humans (Nakamura and Nakamura, 2018). This process is called diet-induced thermogenesis (DIT) (Hibi et al., 2016). In the same manner, the assessment of OT's effects on energy expenditure has been addressed with the exogenous administration of OT. Oxytocin infusion in the third ventricle of mice (Zhang and Cai, 2011; Zhang et al., 2011) or OT injection in the VMH of rats (Noble et al., 2014) promote energy expenditure. Similarly, subcutaneous OT injection in DIO (Diet-induced obese) mice (Maejima et al., 2011) or chronic subcutaneous OT injection in DIO rhesus monkeys (Blevins et al., 2015) promotes energy expenditure. Moreover, the chemogenetic activation of OT PVN neurons that project to ChAT-positive neurons of the IML increases energy expenditure (Sutton et al., 2014). Conversely, mice harboring a viral-induced (synaptotagmin-4 overexpression) diminution of OT exocytosis (Zhang et al., 2011), or a diphtheria toxin-elicited reduction in OT PVN neurons (Wu et al., 2012; Xi et al., 2012), or mice treated with an OTR antagonist by ICV injection (Zhang and Cai, 2011), or mice harboring a deletion of OTR (Nishimori et al., 2008) or OT (Camerino, 2009) gene display a reduction in energy expenditure. The shRNA silencing of OTR expression in the nucleus tractus solitarius (NTS) has highlighted its role in diet-induced thermogenesis in a rodent model (Ong et al., 2017).

Collectively, these data indicate that OT/OTR signaling is a very important modulator of the thermogenic response to cold exposure by controlling BAT thermogenesis and energy expenditure. As Lawson et al. (2020) mentioned, the question remains what is the correlation between increasing energy expenditure and increasing BAT thermogenesis and the OT subpopulations that generate these activations.

2.3. OT browning induction of white adipose tissue

Another mode of action for OT to promote energy expenditure by increasing the thermogenesis capacity is through the "browning" of white adipose tissue (WAT). Nedergaard and Cannon (2014) define browning as the increase in the production of the uncoupling protein 1 (UCP1) in the WAT depots converting it to beige adipose tissue (Ishibashi and Seale, 2010), brite adipose tissue (Petrovic et al., 2010), convertible adipose tissue (Loncar, 1991), ectopic adipose tissue (Lehr et al., 2009), inducible adipose tissue (Lee et al., 2011), or recruitable adipose tissue (Schulz et al., 2013). This UCP1 protein is a marker of BAT associated with thermogenesis function and energy expenditure (Plante et al., 2015). This phenomenon of WAT browning was observed for the first time by Young et al. (1984), where the adipose tissue acquired the specificity of BAT when mice were exposed to cold.

Peripheral injection of OT in mice has been reported to increase the number of UCP1-expressing cells in visceral and subcutaneous WAT (Plante et al., 2015). Moreover, repeated cold exposure of mice has been shown to increase hypothalamic OT secretion with a significant elevation of plasma OT. This elevation of plasma OT increases both the expression of OTR and UCP1 in BAT as well as in inguinal WAT (IWAT) (Yuan et al., 2020). It is essential to remember that the effect of OT on BAT or WAT could also be mediated indirectly through the activation of the sympathetic nervous system (Blevins et al., 2015).

Furthermore, OT can differentiate adipocyte precursors into brown adipocytes after cold exposure (Yuan et al., 2020). In line with these results, OT infusion in mice's fourth ventricle elevates UCP1 expression in IWAT (Edwards et al., 2021). In athletic women, a high OT level has been reported to be associated with a secretion of hormones (irisin and FGF-21), leading to WAT browning and an increase in energy expenditure (Lawson et al., 2014). Conversely, Ott et al. (2013) showed that a single intranasal (IN) OT administration in men does not affect energy expenditure. Lawson et al. (2014) argue that the induction of browning and subsequently increased energy expenditure might require chronic high OT levels instead of transient OT elevation.

In addition to fat tissues, mice skeletal muscles mediating the shivering thermogenesis and expressing OTR (Gajdosechova et al., 2015) are also activated by peripheral OT, which is also able to upregulate the expression of genes related to heat production such as the uncoupling protein 3 (UCP3) (Yuan et al., 2020). Moreover, a cold exposure at 4°C as short as 6h has been shown to increase the expression of OTR in the soleus and tibialis anterior muscles (Conte et al., 2021), which potentiates the action of OT on these thermoeffectors.

Thus, Camerino (2021) mentioned that OT influences both shivering and non-shivering thermogenesis by regulating the expression of heat production-related genes in BAT, skeletal muscles, and WAT.

2.4. OT modulation of thermoregulatory behaviors

When exposed to cold, thermogenesis response is of two types: (i) involuntary autonomic thermogenesis (as discussed above) where OT acts directly or indirectly on the thermoeffectors, and (ii) voluntary behavioral thermoregulation whose function is to implement strategies to limit exposure to cold or heat loss in the case of a cold environment condition. It appears that this second aspect is also regulated by OT.

As previously noted, since locomotion is not yet fully functional until 10 days of age in rodents, autonomic thermogenesis is restricted to BAT non-shivering thermogenesis in neonates (Asakura, 2004). Therefore, this behavioral thermoregulation is an important component of their survival.

One of the behavioral strategies, called thermotaxis, which consists of animals moving from a cold or hot uncomfortable temperature toward a neutral temperature is lacking in OT KO mouse pups (Harshaw et al., 2018). Another thermoregulatory behavior called huddling, used by rodents' pups and adults (Alberts, 1978) to fight against the cold (Harshaw and Alberts, 2012), is also affected in OT KO mouse pups showing less cohesivity (Harshaw et al., 2018). These authors found that a deficit of BAT thermogenesis in OT KO pups contributes to the observed phenotype (Harshaw et al., 2018), a result confirming to that of Sokoloff and Blumberg (2001), showing that inhibition of BAT thermogenesis compromises huddling in rat pups. Moreover, as Harshaw et al. (2021) mentioned in their review, OT manipulation has been shown to impact huddling in different models of rodents such as meadow voles (Beery and Zucker, 2010), rats (Kojima and Alberts, 2011), naked mole-rats (Mooney et al., 2014), and mice (Arakawa et al., 2015; Tan et al., 2019). It is also true for marmoset in which IN OT administration increases huddling (Smith et al., 2010) and OTR antagonist treatment reduces it (Smith et al., 2010; Cavanaugh et al., 2018).

Under cold exposure, since pups do not yet have the capacity for thermotaxis, another strategy is the use of ultra-sonic vocalization (USV) to alert their warmth-giving dam (Portfors, 2007). We have previously showed that this thermoregulatory behavior is also modulated by OT (Da Prato et al., 2022). Indeed, we showed that IN administration of an OT agonist rescues the deficit of reactivity to vocalize under cold stress in an autistic mouse model presenting OT deficiency (Magel2$^{+/-P}$).

Thus, another way that the OT can participate in maintaining a stable body temperature for the survival of the animal in addition to its modulation of autonomic thermoregulation is to enhance behaviors promoting heat retention. This is even more important for the poikilotherms newborns which are more vulnerable to cold exposure and subsequent lethal hypothermia.

2.5. OT effects on temperature perception

In comparison to adults, little information exists in newborns on the neural pathways supporting this thermal perception. Furthermore, from our knowledge, nothing has been published on the effect of OT on thermal perception except studies on pain induced by extreme temperatures. In the context of neuropathic pain caused by thermal hyperalgesia, OT has been shown to alleviate nociception by activating OTR-expressing GABAergic interneurons of the spinal cord (Sun et al., 2018). Furthermore, OT could have a direct effect on the DRG neurons to induce the analgesia of thermal pain. Such action is produced by activation of the vasopressin-1a receptor (V1a) rather than OTR, even if OTR is expressed in the DRG (Han et al., 2018). However, while OTR is known to be expressed in the somatosensory cortex (Son et al., 2022), the action of OT with thermoception in this cortical region has never been explored so far.

Thus, by signaling either through OTR or VIA receptors, OT can target every actor of the thermoregulatory system at both peripheral and central levels. These sites of action are summarized in Figure 1.

3. Part 2: Importance of the oxytocinergic system in the sensory processing in the case of ASD, a focus on atypical thermosensory response

3.1. The interconnection between the oxytocinergic system and ASD

ASD is characterized by two types of manifestations that could be combined: deficits in communication and social interaction as well as stereotyped behaviors and restricted interests (Diagnostic Statistical Manual of Mental Disorders: *D. S. M.*, 2013). Many publications reported a potential dysfunction of the oxytocinergic system as a pathophysiological mechanism of ASD (Insel et al., 1999; Hammock and Young, 2006; Green and Hollander, 2010; Meyer-Lindenberg et al., 2011; Zink and Meyer-Lindenberg, 2012; Lukas and Neumann, 2013; Preti et al., 2014; Lee et al., 2015; Romano et al., 2016) and particularly the importance of the oxytocinergic system during the critical window of the early life regarding the development of ASD (Muscatelli et al., 2018). In addition, dysregulation of

the oxytocinergic system has been demonstrated for different genetic mouse models of ASD (see Wagner and Harony-Nicolas, 2018 as a review) such as Fmr1-KO (Francis et al., 2014), Oprm1-KO (Gigliucci et al., 2014), Cntnap2-KO (Peñagarikano et al., 2015), Nlgn-3-KO (Hörnberg et al., 2020), Shank3-KO (Harony-Nicolas et al., 2017; Rajamani et al., 2018), and Magel2-KO (Schaller et al., 2010; Meziane et al., 2015; Fountain and Schaaf, 2016) and also the autism Valproic Acid-induced mouse models (Dai et al., 2018). Moreover, mice harboring alteration of the oxytocinergic system displayed an ASD phenotype (Zhang et al., 2017) that could be partly improved by OT administration. This is the case for the OTR-KO (Ferguson et al., 2000), the OT-KO (Sala et al., 2011), the CD38-KO (a protein of OT release regulation) (Jin et al., 2007), and the Magel2-KO mice (Meziane et al., 2015). In humans, a meta-analysis of 31 studies reported that, children with autism, but not adults, present a lower OT level that could be reliable for some of the social and cognitive deficits (John and Jaeggi, 2021). Many preclinical and clinical studies gave rise to clinical trials to assess whether acute IN administration of OT has beneficial effects on patients with autism. A systematic analysis of 28 studies on the effects of OT IN administration in the treatment of ASD showed beneficial effects on social functioning but nothing relevant for the resting part of the ASD symptoms (Huang et al., 2021). In the case of repeated IN OT administration on patients with ASD, the treatment did not show a really strong effect on improving ASD symptoms (Martins et al., 2022).

Another meta-analysis in which authors analyzed 12 fMRI studies to search for the neural effect of IN OT administration in ASD patients concluded that the treatment can modulate the activation of different brain regions depending on the type of paradigm stimulus but specified that the link between alleviation of the social deficits and the OT-induced activation of this brain network remains unclear (Fathabadipour et al., 2022).

While the results of OT treatment in the case of ASD are not very conclusive on its curative effect, it appears that OT may be beneficial for some ASD symptoms and could be considered a promising treatment. It should be noted that the beneficial effect of this kind of treatment seems to be more pronounced for newborns than for adults (Althammer et al., 2022). Thus, further studies are still needed to assess the value of using OT as a new therapy to treat social impairments in ASD.

3.2. Atypical sensory processing in ASD

Patients with ASD present atypical sensory processing with hyposensitivity or hypersensitivity to different sensory modalities which are considered by the diagnostic and statistical manual of mental disorder 5th edition (DSM-5) as an ASD diagnosis criterion (Diagnostic Statistical Manual of Mental Disorders: *D. S. M.*, 2013). These sensory perceptions of atypia could be partly explained by morphological changes in the brain, particularly in the thickness of the cortex (Habata et al., 2021). Moreover, sensory atypia occurs in 90% of patients with ASD (Robertson and Baron-Cohen, 2017), affects every sensory system (Marco et al., 2011; Baum et al., 2015; Balasco et al., 2020), is detected before the diagnosis is made (Baranek et al., 2013; Estes et al., 2015; Grzadzinski et al., 2020), is a predicting factor for the lack of high-order socio-cognitive behavior (Hong et al., 2019; Vlaeminck et al., 2020; Park et al., 2021), and is linked with the severity of the ASD phenotype (Baum et al., 2015).

For example, patients with ASD are unable to perceive their environment comprehensively and are more focused on the details of what they see, which deprives them of spontaneously forming an overall image from the elements which constitute it but also gives them a better visual acuity for visuospatial detection task (Shah and Frith, 1983; Plaisted et al., 1998; O'Riordan et al., 2001; Baldassi et al., 2009; Joseph et al., 2009; Kéïta et al., 2010). Related to this capacity that patients with ASD have to focus on the details, data from a meta-analysis of 26 studies highlighted the fact that patients with ASD have an increased activity in temporal and occipital regions important for perception and recognition of objects and a decreased activity in the prefrontal region involved in cognitive functions such as decision making, planification, and execution (Samson et al., 2012). Another characteristic of patients with ASD is their difficulty in eye contact (Senju and Johnson, 2009; Madipakkam et al., 2017), which is essential to emotion perception and the development of sociability (Tong et al., 2021). Some studies showed that hesitancies in eye contact can be improved with IN OT administration in adults with ASD (Guastella et al., 2008; Auyeung et al., 2015; Hubble et al., 2017) which then enhances both their ability to process faces as well as their social interaction and empathy ability (Domes et al., 2013; Kanat et al., 2017). This deficit could come from an unpleasant or even painful excessive arousal resulting from the overactivation of the subcortical system including regions of the superior colliculus, the pulvinar of the thalamus, and the amygdala (Hadjikhani et al., 2017).

The auditive perception is also altered in children with ASD who have difficulty discerning the relative order of two nearby tones and show a delay in the neural responses evoked by these auditory stimuli compared to healthy children. This prolonged latency in auditory responses is considered a criterion of autistic severity (Kwakye et al., 2011). In addition, adult patients do not perceive vocal information in the same way as healthy adults and show difficulties in processing the human voice with other sounds or noises (Gervais et al., 2004).

In the case of tactile perception, it has been shown that patients with ASD present a higher detection threshold for static stimuli (acute stimuli) and a lack of sensitivity to dynamic (which increases in amplitude over time to a detectable threshold) stimuli suggesting aberrant habituation, whereas healthy individuals show poorer detection of dynamic stimuli compared to static stimuli (Puts et al., 2014; Tavassoli et al., 2016). Additionally, the temporal discrimination of successive tactile stimulations seems also to be altered with an increased

threshold of detection (Buyuktaskin et al., 2021). Moreover, patients with ASD have an aversion to touch, suggesting that a tactile stimulus, albeit weak, is a source of discomfort indicating a potential hypersensitivity to this type of stimulus (Moore, 2015; Kaiser et al., 2016). This tactile atypia could be explained by an excitation/inhibition imbalance at the level of somatosensory neurons of the DRG (Lipina and Blundell, 2022), modification of somatosensation and somatotopic map (Espenhahn et al., 2021), or even direct alteration of the somatosensory circuit in patients with ASD (Orefice, 2020).

The olfactory system is also impaired in patients with ASD, with deficits in odor identification, odor sensitivity, and odor preference that vary in degree depending on the complexity of the disorder (Crow et al., 2020; Lyons-Warren et al., 2021; Yang et al., 2022). However, the detection seems to not be altered (Lyons-Warren et al., 2021).

Similarly, the taste perception is also atypical in patients with ASD with increased sensitivity to food texture as well as specific taste preferences for acidic tastes and greater sensitivity to aftertastes, leading to selective eating behaviors (Chen et al., 2022; Nimbley et al., 2022).

Furthermore, the integration of multisensory stimuli is atypical in patients with ASD with altered temporal processing of audiovisual multisensory information (Kawakami et al., 2020) that could be related to the atypical neural network (Matsuzaki et al., 2022). It is also the case for visuo-tactile information for which patients with ASD have a smaller peripersonal space that could be linked with some of the social impairment in ASD (Noel et al., 2020).

This sensory atypia is also found in ASD genetic mouse models. For example, mouse models with mutations in Mecp2, Gabrb3, Fmr1, or Shank3 exhibit tactile hypersensitivity (DeLorey et al., 2011; Orefice et al., 2016; Orefice, 2020), Grin2b–/– mice have a hypo reactivity to oral tactile stimulation, leading to reduced suckling response, causing the premature death of these mice (Kutsuwada et al., 1996). Syngap1+/– mice sensory cortex activation induced by whisker stimulation is reduced, showing an alteration of tactile information processing (Michaelson et al., 2018). Shank2–/– mice have hypo reactivity to tactile stimulation as well as reduced nociception to chronic pain (Ko et al., 2016), and Cntnap2–/– mice exhibit an increased pain sensitivity to tactile, thermic, and chemical stimuli (Dawes et al., 2018). The Mecp2 KO, a mouse model of Rett syndrome, displays a decreased amplitude in visually evoked responses in the visual cortex and a decrease in visual acuity (LeBlanc et al., 2015; Banerjee et al., 2016). The Grin1+/– model presents an impaired visual depth perception (Lipina et al., 2022). Electrophysiological recordings of the auditory cortex of Fmr1KO mice revealed an impaired response to auditory tones suggesting hypersensitivity of auditory neurons, a phenotype also present in patients with X-Fragile (Rotschafer and Razak, 2013). Tbr1+/– mice model of ASD displayed altered olfactory discrimination and ASD-related behavior (Huang et al., 2019). In genetic models of ASD, such as FMRP, MeCP2, CAPS2, uPAR, NL3, NPN2, and En-2 KO mice, the GABAergic signaling is impaired with excitation/inhibition balance disturbance, reducing the potential of the animals to make experience-dependent refinement of their sensory circuit (Gogolla et al., 2009).

Thus, patients with ASD are a heterogenous population in which a variety of atypical sensory processing occurs and that could be a determinant factor for the development of the disorder. As we reviewed here, OT is an essential component of the sensory system modulation and also a neuropeptide involved in many aspects of autism, showing thus the interplay between these three components.

3.3. The special case of the thermosensory system in ASD

We previously reported that OT has been used as a therapeutical treatment for the socio-cognitive part of the deficits present in ASD. Moreover, some studies tend to show that the sensory deficits in autism could also be rescued by OT treatment, notably for the visual system and the ability to maintain eye contact. Considering both the interaction between OT and the sensory system and the alteration of the oxytocinergic system in ASD, it seems logical that OT treatment could be beneficial to treat sensory atypia in ASD. However, to the best of our knowledge in the literature, not all sensory modalities have been explored to demonstrate a potential overall benefit of OT treatment in autism-related sensory atypia. Thus, in this last part of the review, we focus on the thermosensory system, a sensory system that has received less attention compared to others but is atypical in ASD and is known to be regulated by OT.

Initial studies reported hypersensitivity to thermal pain but normal detection of non-nociceptive temperatures in adults with ASD, whereas the opposite was found in adolescents with a hyposensitivity to non-painful temperatures and pain thresholds to normal temperatures (Cascio et al., 2008; Duerden et al., 2015). However, two recent studies showed that the response to temperature in individuals with autism is atypical with paradoxical heat sensations when a cold stimulus is perceived as hot or burning and an insensitivity to the outside temperature (Duerden et al., 2015; Fründt et al., 2017). In the case of Prader-Willi Syndrome (PWS), patients present a decreased detection threshold for cold temperatures and an increased detection threshold for warm temperatures. In addition, the sensations of pain related to cold and hot temperatures were altered (Priano et al., 2009). This abnormal sensory perception could be due to an impairment of small-fiber sensory nerves in patients with ASD (Chien et al., 2020).

Furthermore, impaired thermoregulation is a widely recognized symptom in PWS (Cassidy et al., 2012) and has been suggested to be linked with fewer OT PVN neurons (Swaab, 1997). Indeed, in PWS, there are many cases of children with high fevers and no infectious causes that in some cases lead to hyperpyrexia that can be fatal (Ince et al., 2005). Severe cases of sudden hypothermia also exist (Watanabe et al., 2003). This phenotype is observed from the first months of life and seems to persist since cases in adolescents have also been described (McVea et al., 2016). Additionally, in Schaaf-Yang Syndrome (SSY), 67% of patients also experience these temperature instabilities that may manifest as excessive sensitivity to cold or hypersudation (McCarthy et al., 2018).

Recently, using an autistic mouse model of SSY (Magel2 mouse), our team showed hyporesponsiveness to cold temperatures with cold-induced USV delay that could be partially restored with acute IN administration of an OT agonist (Da Prato et al., 2022).

Thus, the thermosensory system is another example of a sensory modality in which the perception is atypical for ASD patients and for which evidence seems to show that OT could be a promising therapeutical approach.

4. Conclusion

The action of OT/OTR signaling on sensory processing and more particularly on the sensitivity to external temperature in the healthy and ASD case has been reviewed.

This nonapeptide is strongly associated with the development of some ASD symptoms such as sensory atypia. It is an important modulator of all the parameters of the autonomic thermoregulation with action at every level of the circuit including the thermo-effectors. This modulation by OT also concerns the different components of behavioral thermoregulation. Animals receiving external OT administration undergo an upregulation of their thermoregulatory capacity, and animals presenting an alteration of the oxytocinergic system showed deficits of thermoregulation and then difficulties to keep a stable core body temperature. These findings have been extended to behavioral thermoregulation and have been mainly conducted on pups.

While thermosensation is under intensive investigation, there are remaining outstanding issues to be addressed. First, as the LH has been recently brought to light as a major structure for this behavioral thermoregulation, no study has yet investigated a direct effect of the OT on this structure in the case of behavioral thermoregulation. It would then be necessary to find out if the same perennialization of these behaviors is induced by an action of the OT on the LH.

Second, it should be noted that a gap exists between information provided by adult animals compared to pups. Recording physiological parameters are indeed more challenging in pups than in adults because miniaturized tools are not always available. This includes monitoring pups' temperature. In behavioral experiments, the monitoring of body temperature is important because it is a readout of the thermoregulatory response. Rectal probing is not adapted and other methods can be used to monitor temperatures. The implantation of temperature transponders under the skin or even in the peritoneal cavity is a good solution for chronic and accurate measurements. However, this kind of system is mostly applicable to adult mice. Other less invasive techniques such as the use of thermic cameras or infrared thermometers are recommended for both adults and pups and have the advantage to monitor local body change. Another point that has to be raised concerning the thermosensory system is the small number of studies that explore thermal perception and the fact that no study exists in the case of newborns. It would be interesting to see if the thermosensation is a cortical modality and if so which part of the cortex is concerned notably in the case of newborns. Then, it would be possible to confront data from newborns regarding thermosensation with the few published data in adults.

A third question that is still not addressed is the effect of OT on thermosensation. In the same manner, thermosensation is poorly explored in the autistic model. Knowing that deficits of thermic perception have been observed in patients with ASD and mainly during adolescence and that low levels of OT are present in children and adolescents with ASD, it seems appropriate to think that thermic perception deficits could be found in animal models. This could help to better understand the origin of these thermosensory deficits in patients with ASD. Concerning these deficits, many clinical trials using IN OT administration to treat atypical sensory perception in ASD present encouraging results. Therefore, such treatment could be tested for improvement of atypical thermic perception in patients with ASD.

Author contributions

UZ and VM defined the detailed plan of the review. UZ drafted the initial version. VM revised the article. FM and LC critically read the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neuromodulatory functions exerted by oxytocin on different populations of hippocampal neurons in rodents

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Oxytocin (OT) is a neuropeptide widely known for its peripheral hormonal effects (i.e., parturition and lactation) and central neuromodulatory functions, related especially to social behavior and social, spatial, and episodic memory. The hippocampus is a key structure for these functions, it is innervated by oxytocinergic fibers, and contains OT receptors (OTRs). The hippocampal OTR distribution is not homogeneous among its subregions and types of neuronal cells, reflecting the specificity of oxytocin's modulatory action. In this review, we describe the most recent discoveries in OT/OTR signaling in the hippocampus, focusing primarily on the electrophysiological oxytocinergic modulation of the OTR-expressing hippocampal neurons. We then look at the effect this modulation has on the balance of excitation/inhibition and synaptic plasticity in each hippocampal subregion. Additionally, we review OTR downstream signaling, which underlies the OT effects observed in different types of hippocampal neuron. Overall, this review comprehensively summarizes the advancements in unraveling the neuromodulatory functions exerted by OT on specific hippocampal networks.

KEYWORDS

hippocampus, oxytocin, oxytocin receptor (OTR), neuromodulation, oxytocinergic pathways, neural circuit

1. Introduction

Oxytocin (OT) is a cross species and conserved hypothalamic hormone widely known for its peripheral hormonal effects in inducing labor and lactation (Nickerson et al., 1954; Caldeyro-Barcia and Poseiro, 1959; Brown et al., 2020). However, OT also acts as a neuromodulator in the central nervous system controlling various social and emotional forms of behavior such as attachment, social exploration, social recognition, aggression, anxiety, fear conditioning, and fear extinction (Donaldson and Young, 2008; Heinrichs et al., 2009; Matsuzaki et al., 2012; Dumais and Veenema, 2016; Olivera-Pasilio and Dabrowska, 2020). In humans, OT is involved in stress reduction, in increasing trust and altruism, and in improving an individual's ability

to interpret the mental and emotional states of others (Kosfeld et al., 2005; Ruissen and de Bruijn, 2015; Declerck et al., 2020). Moreover, the oxytocinergic system is associated with cognitive functions by taking part in the learning processes and in the formation of social, spatial, and episodic memory (Abramova et al., 2020). Accordingly, a link between deficits in the oxytocinergic system and neuropsychiatric disorders such as autism, schizophrenia, depression, bipolar disorder, and borderline personality disorder has been proposed (Dumais and Veenema, 2016; Iovino et al., 2018).

The hippocampus is a key structure for most of these emotional, behavioral, and cognitive functions (Sweatt, 2004; Immordino-Yang and Singh, 2013; Rubin et al., 2014), it receives input from hypothalamic OT-expressing fibers, and subgroups of hippocampal cells expresses OT receptors. OT influences hippocampus at multiple levels by modulating processes of learning and memory (Chini et al., 2014; Rajamani et al., 2018; Pekarek et al., 2020) and social behavior (Raam et al., 2017; Bertoni et al., 2021), remodeling the intrinsic hippocampal circuit in newborn autism models (Raam et al., 2017; Bertoni et al., 2021), and stimulating adult hippocampal neurogenesis (Leuner et al., 2012; Lin et al., 2017). The action of OT in the hippocampus relies on a precise, finely tuned, and timely modulation of specific neurons in each hippocampal subregion. The expression of oxytocin receptors (OTRs) is indeed restricted to specific classes of hippocampal neurons that have been determined in multiple studies (Campbell et al., 2009; Mitre et al., 2016; Lin et al., 2017, 2018; Raam et al., 2017; Lin and Hsu, 2018; Tirko et al., 2018; Cilz et al., 2019; Meyer et al., 2020; Bertoni et al., 2021). Moreover, the effects of the OT on individual OTR-expressing neurons, as well as the intracellular signaling pathways that are activated, are highly heterogeneous due to a promiscuous G protein coupling of the OTR (Gravati et al., 2010). Previous studies have described in detail the functional modulation carried out by OT on the specific neuronal types in each hippocampal region (Mühlethaler and Dreifuss, 1983; Mühlethaler et al., 1984; Raggenbass et al., 1989; Zaninetti and Raggenbass, 2000; Raggenbass, 2001; Succu et al., 2011; Owen et al., 2013; Harden and Frazier, 2016; Tirko et al., 2018; Maniezzi et al., 2019; Hu et al., 2021), and the initial focus of this review is to summarize the main findings of these studies. Since excitatory and inhibitory hippocampal neurons of each subregion are differently modulated by OT, the release of OT in hippocampal networks could result in a transient reshaping of the excitation/inhibition (E/I) balance. These changes could in turn affect signal processing and the subsequent information transfer throughout the hippocampal network. A similar oxytocinergic neuromodulation of E/I balance has also been demonstrated at cortical level, where it enables maternal behavior (Marlin et al., 2015), suggesting that OT could act in multiple brain areas with an apparently common general mechanism (Lopatina et al., 2018).

In this review we look at how OT is able to exert specific actions in the different regions of the hippocampal formation. Specifically, we present and discuss recent advances in our understanding on how OT modulates OTR-expressing hippocampal neurons by causing a temporary E/I balance shift that could influence signal processing and transfer through the hippocampal tri-synaptic circuit. We focus on the description of (i) the OTR-expressing neuronal populations in each hippocampal subregion, (ii) the OT-dependent electrophysiological modulation of each hippocampal neuronal population, (iii) the OT-mediated synaptic plasticity at the hippocampal synapses, (iv) the OTR signaling pathways underlying the functional effects observed on each neuronal population in the hippocampus. In this review, the systematic description of the various neuromodulatory effects, and related mechanisms, induced by OT at the hippocampal level, will provide a comprehensive neurobiological interpretation of those behavioral responses that are known to be controlled and regulated by this neuropeptide.

2. Oxytocin receptor distribution in the hippocampus

Oxytocin is synthesized principally in magnocellular and parvocellular neurons of the paraventricular nucleus (PVN) and in magnocellular neurons of the supraoptic nucleus (SON) of the hypothalamus (Swanson and Sawchenko, 1983). A subset of oxytocinergic neurons has also been found in the extended amygdala, and in the accessory and tuberal nuclei of the hypothalamus in mice (Biag et al., 2012; Son et al., 2022). SON and PVN magnocellular neurons mainly project to the posterior lobe of the pituitary gland (neurohypophysis) from which OT is secreted into the bloodstream (Kiss and Mikkelsen, 2005), but they also have axonal collaterals innervating numerous forebrain structures (Ross and Young, 2009; Knobloch et al., 2012). Usually, SON and PVN magnocellular neurons discharge asynchronously. However, under specific conditions (i.e., during suckling and lactation), their firing patterns become synchronized, resulting in a coordinated release of large amount of oxytocin into the bloodstream. Such synchronization is made possible by the fact that oxytocinergic magnocellular neurons regulate their own firing by somato-dendritic release of OT (Pow and Morris, 1989; Leng et al., 2008; Rossoni et al., 2008; Numan and Young, 2016; Jurek and Neumann, 2018; Valtcheva and Froemke, 2019). PVN parvocellular neurons send their axons and release the hormone in various brain areas involved in cognition, brain homeostasis, and somatic visceral responses, such as thalamus, cortex, amygdala, striatum, hippocampus (Gimpl and Fahrenholz, 2001; Stoop, 2012; Mitre et al., 2018; Son et al., 2022).

The action of OT is implemented by its binding to specific and highly conserved G-protein coupled receptors. There is only a single type of oxytocin receptor (OTR), that is able to perform a range of functions by coupling to different G-proteins (G_q, G_o/G_i, or G_s) and activating a variety of intracellular pathways (Alberi et al., 1997; Chini et al., 2008; Gravati et al., 2010; Busnelli et al., 2012; Busnelli and Chini, 2018). Moreover, the expression of OTRs is not ubiquitous, but is restricted to specific classes of neurons that vary from region to region in the brain, which leads to the generation of highly specific responses (Campbell et al., 2009; Grinevich et al., 2016; Mitre et al., 2016; Newmaster et al., 2020; Froemke and Young, 2021; Grinevich and Ludwig, 2021). The distribution of OTRs in the brain and peripheral structures has been characterized using radioligand binding, RNA *in situ* hybridization, and more recently by specific antibodies for mouse OTR (Mitre et al., 2016) and fluorescent reporter mouse lines (Yoshida et al., 2009; Nakajima et al., 2014).

In the hippocampus, the OTRs are highly expressed (Mitre et al., 2016), but they are not evenly distributed. Differences in receptor expression are observed in relation both to the hippocampal subregions and to different neuronal subtypes (**Table 1**). In the dentate gyrus (DG), OTRs are present almost exclusively in the region of hilus, where they are expressed by the GABAergic interneurons (INs) and, to a lesser extent, by the excitatory mossy cells (Lin et al., 2017; Raam et al., 2017; Lin and Hsu, 2018;

TABLE 1 Oxytocin receptor expression in hippocampal areas and neuronal phenotypes.

Region	OTR-expressing neurons	References
DG	• Hilar GABAergic INs	Campbell et al., 2009
	• (SST+, PV+, CR+, nNOs+, PV- and CCK-)	Mitre et al., 2016
	• Hilar Mossy cells (few)	Harden and Frazier, 2016
		Lin et al., 2017
		Raam et al., 2017
		Lin and Hsu, 2018
		Meyer et al., 2020
		Bertoni et al., 2021
CA2-CA3	• PV+ (principally) and SST+ GABAergic INs	Campbell et al., 2009
	• PYRs	Mitre et al., 2016
		Lin et al., 2017
		Raam et al., 2017
		Lin et al., 2018
		Lin and Hsu, 2018
		Tirko et al., 2018
		Bertoni et al., 2021
CA1	• PV+ GABAergic INs	Raggenbass et al., 1989
		Zaninetti and Raggenbass, 2000
		Campbell et al., 2009
		Owen et al., 2013
		Mitre et al., 2016
		Raam et al., 2017
		Lin and Hsu, 2018
		Maniezzi et al., 2019
SUBICULUM	• PYRs	Raggenbass et al., 1989
		Hu et al., 2021

Bibliographical references for each area are reported.

Meyer et al., 2020; Bertoni et al., 2021). GABAergic INs of the hilus constitute a neurochemically (Lin et al., 2017; Raam et al., 2017; Meyer et al., 2020) and electrophysiologically (Meyer et al., 2020) heterogeneous population: immunohistochemical studies have shown OTR expression in somatostatin- (SST^+), parvalbumin- (PV^+), calretinin- (CR^+), neuronal nitric oxide synthase- ($nNOS^+$), and neuropeptide Y-positive (NPY^+) GABAergic INs (Lin et al., 2017; Raam et al., 2017; Meyer et al., 2020), but there is evidence for OTR expression even in parvalbumin- (PV^-) and cholecystokinin-negative (CCK^-) INs (Harden and Frazier, 2016). In CA2/CA3 regions of the hippocampus, OTRs have been identified in both glutamatergic pyramidal cells (PYRs) and INs (Lin et al., 2017, 2018; Raam et al., 2017; Lin and Hsu, 2018; Tirko et al., 2018; Bertoni et al., 2021). Among the GABAergic OTR- positive (OTR^+) INs of the CA2/CA3 areas those co-expressing PV are significantly more abundant than those expressing SST (Raam et al., 2017). Notably, as the CA2 subregion is related to maternal behavior, and oxytocinergic modulation and plasticity in CA2 are salient for the identification of pup vocalizations, scents and location, murine mothers show a higher percentage of OTR^+ cells in this region compared to males and virgin females (Mitre et al., 2016). OTRs have also been identified in the CA1 region of the hippocampus (Raggenbass et al., 1989; Campbell et al., 2009; Mitre et al., 2016; Raam et al., 2017; Lin and Hsu, 2018), where OTR expression has been reported principally in GABAergic INs (Raam et al., 2017) as confirmed by functional investigations (Zaninetti and Raggenbass, 2000; Owen et al., 2013; Maniezzi et al., 2019). Finally, autoradiography experiments found OT-binding sites in the subiculum (Raggenbass et al., 1989), while more recent electrophysiological studies demonstrated a direct OTR-dependent action on subicular PYRs (Hu et al., 2021).

Over the last 5 years, studies have reported the expression of OTRs also in glial cells (astrocytes and microglia) of the hippocampus (Havránek et al., 2017; Zhu and Tang, 2020; Althammer et al., 2022a,b; Maejima et al., 2022), as well as in other brain areas (Loth and Donaldson, 2021; Baudon et al., 2022; Gonzalez and Hammock, 2022; Knoop et al., 2022). However, the exact function of these glial OTRs remains elusive. One possibility is that they could facilitate neuromodulation *via* the release of specific gliotransmitters (Baudon et al., 2022). The presence of OTRs in astrocytes seems to be species-specific since a prominent subpopulation (40%) of astrocytes in the dorsal CA2 region of 5–7 week old rats expressed OTRs (Althammer et al., 2022a), whereas they were not present in mice (Althammer et al., 2022b). Data regarding OTR expression and function in glial cells is far from conclusive with more research being required in this area.

3. Oxytocinergic functional modulation of specific neurons of the hippocampus

As noted above, the expression of OTRs throughout the hippocampus is unique and heterogeneous and it is restricted to specific but different neuronal types in each region. Consequently, the oxytocinergic neuromodulation within this area is highly complex. In general, the release of oxytocin in the hippocampus reshapes the E/I balance of local circuits through two distinct but synergic mechanisms: (i) first-order direct modulation of neurons expressing OTRs; (ii) second-order indirect modulation of neurons not expressing OTRs, locally contacted by directly modulated neurons (Froemke and Young, 2021). Here, we focus on reviewing the known direct and indirect modulatory effects exerted by OT on neuronal function within each hippocampal region.

3.1. Dentate gyrus (DG)

The dentate gyrus (DG) represents the main entry point of information into the hippocampus *via* perforant pathway as it is the first station of the hippocampal tri-synaptic circuit. The OTRs are mainly expressed in the GABAergic INs and the excitatory mossy cells in the hilum of the DG, whereas there has been no reported expression in the granular layer (Lin et al., 2017, 2018; Raam et al., 2017; Lin and Hsu, 2018; Meyer et al., 2020). Nevertheless, the electrophysiological effects of the OT on the neurons of this area remain poorly understood.

Harden and Frazier (2016) identified a subpopulation of GABAergic INs in the deep hilum of the DG of juvenile rats

(**Figure 1A**) on which TGOT (Thr4,Gly7-oxytocin, a selective agonist of OTRs) had a direct OTR-dependent excitatory effect. The activation of the OTR in these neurons depolarized their membrane potential (probably due to an IP3-mediated increase in the intracellular Ca^{2+} and/or in the Na^{+} permeability) and increased their firing rate (**Figure 1B**). In turn, the activating action of TGOT on the hilar GABAergic INs was reflected in an indirect effect on the mossy cells that receive *en passant* somatodendritic synapses from the former: these cells responded to TGOT administration with an increase in the frequency and amplitude of GABAergic spontaneous inhibitory post-synaptic currents (sIPSCs) (**Figures 1A, C**). It is worth noting that a small subpopulation of OTR-expressing mossy cells exists (Raam et al., 2017; Meyer et al., 2020), but the direct action of OT on this neuronal type is still unknown.

The effect of OT on the local circuitry of the DG consists of an initial first-level direct activation of the hilar GABAergic INs, resulting in an increased GABA release in the hilum of the DG. This is followed by a second-level indirect inhibition of the glutamatergic mossy cells (**Figure 1C**). However, the final effect on the granular cells of the DG, the projective neurons of this area, remains to be investigated. Although granular cells do not express OTRs (Lin et al., 2017, 2018; Raam et al., 2017; Lin and Hsu, 2018; Meyer et al., 2020), it is reasonable to postulate that they could also be indirectly inhibited by OT, since they receive synaptic contacts from both hilar GABAergic INs (Meyer et al., 2020) and mossy cells (Scharfman, 1995; **Figure 1A**). The importance of the oxytocinergic modulation of the DG for the general functionality of the hippocampal circuit is highlighted in mice lacking OTRs showing an overall aberrant activation of the DG in response to a social stimulus (Raam et al., 2017). Although the exact mechanisms still needed to be addressed, it is possible to hypothesize that OT in the DG could control the progression or restriction of information flow within the hippocampal circuit (Harden and Frazier, 2016).

3.2. CA3/CA2 regions of the hippocampus

The involvement of CA3/CA2 regions in social recognition (Lu et al., 2015; Alexander et al., 2016; Raam et al., 2017; Lin et al., 2018) supports a role for oxytocinergic modulation of cellular and synaptic responses in these areas. Accordingly, CA2 and CA3 PYRs and parvalbumin positive GABAergic INs (PV^{+} INs) express OTRs in mice (Mitre et al., 2016; **Figure 2A**) and receive input from oxytocinergic fibers (Tirko et al., 2018). Electrophysiological characterization of the oxytocinergic modulation of CA2 has been performed by Tirko et al. (2018). They found that application of TGOT leads to increased excitability of CA2 PYRs by causing depolarization, inducing burst firing (**Figure 2B**), and changing the shape of the action potentials (reducing both the peak amplitude and the after-hyperpolarization). TGOT-mediated depolarization of PYRs has also been observed in the presence of glutamatergic and GABAergic blockade, indicating a first-order direct effect. Furthermore, the OTR agonist depolarizes PV^{+} INs located in the pyramidal layer causing an increase in their firing rate (**Figure 2B**). Since the excitability is enhanced also during synaptic blockade, the TGOT-mediated effect on PV^{+} INs is direct too. The ionic mechanism underlying these depolarizations has been proven to rely on a reduction of the M-current (Tirko et al., 2018).

During oxytocinergic modulation, PYRs and PV^{+} INs influence each other (**Figure 2C**). Indeed, recordings from PV^{+} INs reveal an increase in the frequency and amplitude of the excitatory post-synaptic potentials (EPSPs), while recordings from PYRs uncover an increase in the frequency and amplitude of the inhibitory post-synaptic potentials (IPSPs). The role of GABAergic input is essential during the TGOT-mediated bursts generated by PYRs: indeed, it significantly elevates the intra-burst frequency and restricts burst duration. This firing pattern is able to increase the reliability of synaptic communication (Lisman, 1997).

The TGOT-induced bursts in CA2 PYRs firing has a profound effect on the downstream CA1 area, determining the depression of both the mono-synaptic excitatory outputs and the di-synaptic inhibitory outputs toward CA1 PYRs (Tirko et al., 2018). However, the depression of inhibitory output is consistently greater than that of the excitatory output. As a result, the IPSC:EPSC ratio shifts toward a net excitatory drive, thus favoring the transmission transfer from CA2 to the downstream CA1 area (Tirko et al., 2018).

Although experimental data are still missing, authors postulated a similar mechanism also for the oxytocinergic modulation of the CA3 hippocampal region, due to the common features of these two subregions (Tirko et al., 2018).

3.3. CA1 region of the hippocampus

In CA1 only PV^{+} GABAergic INs express OTRs (Mitre et al., 2016; Raam et al., 2017). Accordingly, extracellular recordings performed on rats suggested that OT exerts a direct excitation on a specific population of GABAergic INs exerted by OT (Mühlethaler and Dreifuss, 1983; Mühlethaler et al., 1984; Raggenbass et al., 1989; Zaninetti and Raggenbass, 2000; Raggenbass, 2001). Consistently with these findings, OT has been found to modulate the neuronal network in the hippocampal CA1 field of the mouse by acting directly on the PV^{+} fast-spiking GABAergic INs and indirectly on the other neurons in this area, including the projecting PYRs (**Figure 3A**). The administration of TGOT induces a sustained depolarization of the membrane potential of the fast-spiking GABAergic INs that determines a significant increase in their firing rate when it occurs at their spike threshold (**Figure 3B**), as verified by two independent studies (Owen et al., 2013; Maniezzi et al., 2019). The intracellular pathways and the biophysical mechanisms at the basis of this effect are still controversial, even if the persistence of the depolarizing response in presence of synaptic blockers confirms the first-order direct nature of this effect (Maniezzi et al., 2019).

In contrast, at spike threshold PYRs are hyperpolarized by TGOT administration, and their firing rate is significantly decreased (**Figure 3B**) as well as their overall excitability (i.e., reduced spontaneous action potentials and decreased firing frequency in response to depolarizing injected current in TGOT vs. CTRL) (Owen et al., 2013; Maniezzi et al., 2019). Blockade of $GABA_A$ receptors completely abolishes these effects, confirming their second-order indirect nature and their dependence on the primary direct excitation of fast-spiking GABAergic INs (Maniezzi et al., 2019). Supporting this conclusion, TGOT has been found to induce a significant increase in phasic and tonic inhibition of CA1 PYRs (**Figure 3C**): the increase in phasic inhibition is demonstrated by a reversible increase in sIPSCs frequency and amplitude due to enhanced release of GABA vesicles in the synaptic cleft from fast-spiking INs following TGOT administration (Owen et al., 2013; Maniezzi et al., 2019); the increase in tonic inhibition is demonstrated by the reversible slowdown in spontaneous IPSC kinetics and the outward shift in the holding

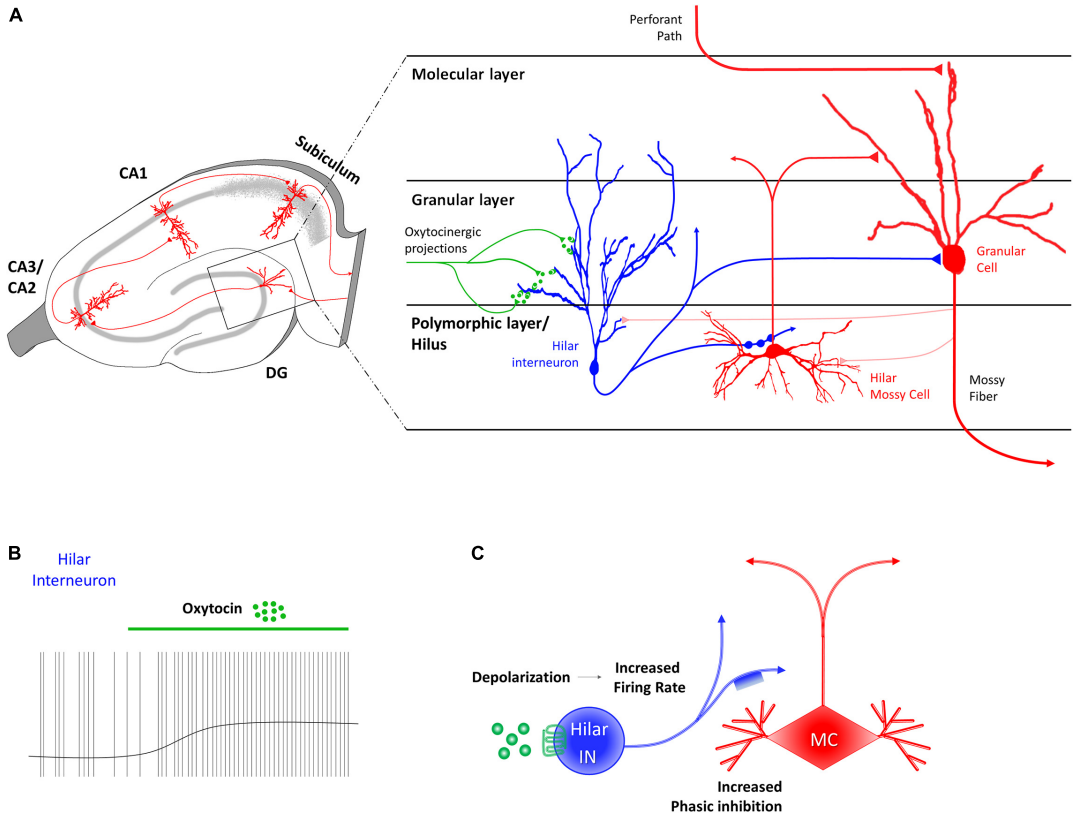

FIGURE 1
Receptor distribution, oxytocinergic projections and main effects exerted by oxytocin (OT) at dentate gyrus (DG) region of the rodent's hippocampus. **(A)** At the DG region, OT receptors (OTRs) are found in granular layer, on the dendrites of hilar GABAergic fast-spiking interneurons (blue). Hilar GABAergic fast-spiking interneurons, whose cell body is located in the polymorphic layer, extend axonal projects both to hilar mossy cells (red) and to granular cells (red) of the granular layer. **(B)** OT induces a direct and sustained depolarization of the hilar fast spiking interneurons membrane potential and a consequent increase of their firing rate. **(C)** The OT-dependent increased firing rate of hilar fast spiking interneurons (FS IN–blue) through the binding to OTR (green) causes indirect phasic inhibition on the glutamatergic mossy cells (MC–red).

current due to GABA escape from the synaptic cleft by spillover and activation of perisynaptic and extrasynaptic $GABA_A$ receptors (Maniezzi et al., 2019).

Looking at the general impact on integration of information, signal transfer, and signal processing within the CA1 region, OT–by increasing phasic and tonic GABAergic inhibition–causes the hyperpolarization and the reduction of the excitability of the CA1 PYRs which lead to a consequent reduction in the genesis of spontaneous spikes (reduction of noise) (**Figure 3C**). On the other hand, the increase in the firing rate of the fast-spiking INs induces a "use-dependent reduction" in the efficacy of the inhibition of the fast-spiking INs on the PYRs (Owen et al., 2013). In these conditions inputs arriving from Schaffer's collaterals cause more effective mono-synaptic excitatory transmission and reduced di-synaptic inhibitory transmission on PYRs, thus entailing the enhancement of the EPSP-spike coupling (increase of signal) (**Figure 3C**). Overall, oxytocin improves the signal-to-noise ratio in the CA1 region of the hippocampus: in this way it improves the fidelity and temporal precision of information transfer through this area.

3.4. Subiculum

The subiculum is the major output structure of the hippocampal formation receiving inputs from CA1 and sending outputs to many subcortical and cortical areas (Amaral and Witter, 1989; Naber and Witter, 1998; Witter, 2006). It expresses the highest density of binding sites for OT (Freund-Mercier et al., 1987; Dreifuss et al., 1989). Very little is currently known about the physiological functions and mechanisms concerning oxytocinergic neuromodulation in this brain region.

Direct OT injection into the ventral subiculum induces penile erection episodes in male rats (Succu et al., 2011), confirming the important role of this hormone for sexual behavior. The subiculum OT-induced penile erection is mediated by the activation of glutamatergic ventral neurons projecting to the ventral tegmental area (VTA) (Melis et al., 2009, 2010; Melis and Argiolas, 2011). The subiculum dependent VTA activation in turn increases the release of dopamine by mesolimbic and mesocortical dopaminergic neurons onto neurons of the nucleus accumbens and of the prelimbic medial prefrontal cortex, supporting the hypothesis that the ventral subiculum is crucial in controlling not only penile erection, but also sexual motivation, arousal, and reward (Succu et al., 2011).

Recently, Hu et al. (2021) investigated the effects of OTR activation on the electrophysiological properties of the two types of subicular pyramidal glutamatergic neurons: intrinsically bursting cells (BCs), which are believed to contribute to synaptic plasticity, and regularly firing cells (RCs) (Cooper et al., 2005; Hu et al., 2017; Simonnet and Brecht, 2019; **Figure 4A**). The authors observed that OT administration directly depolarized the resting membrane

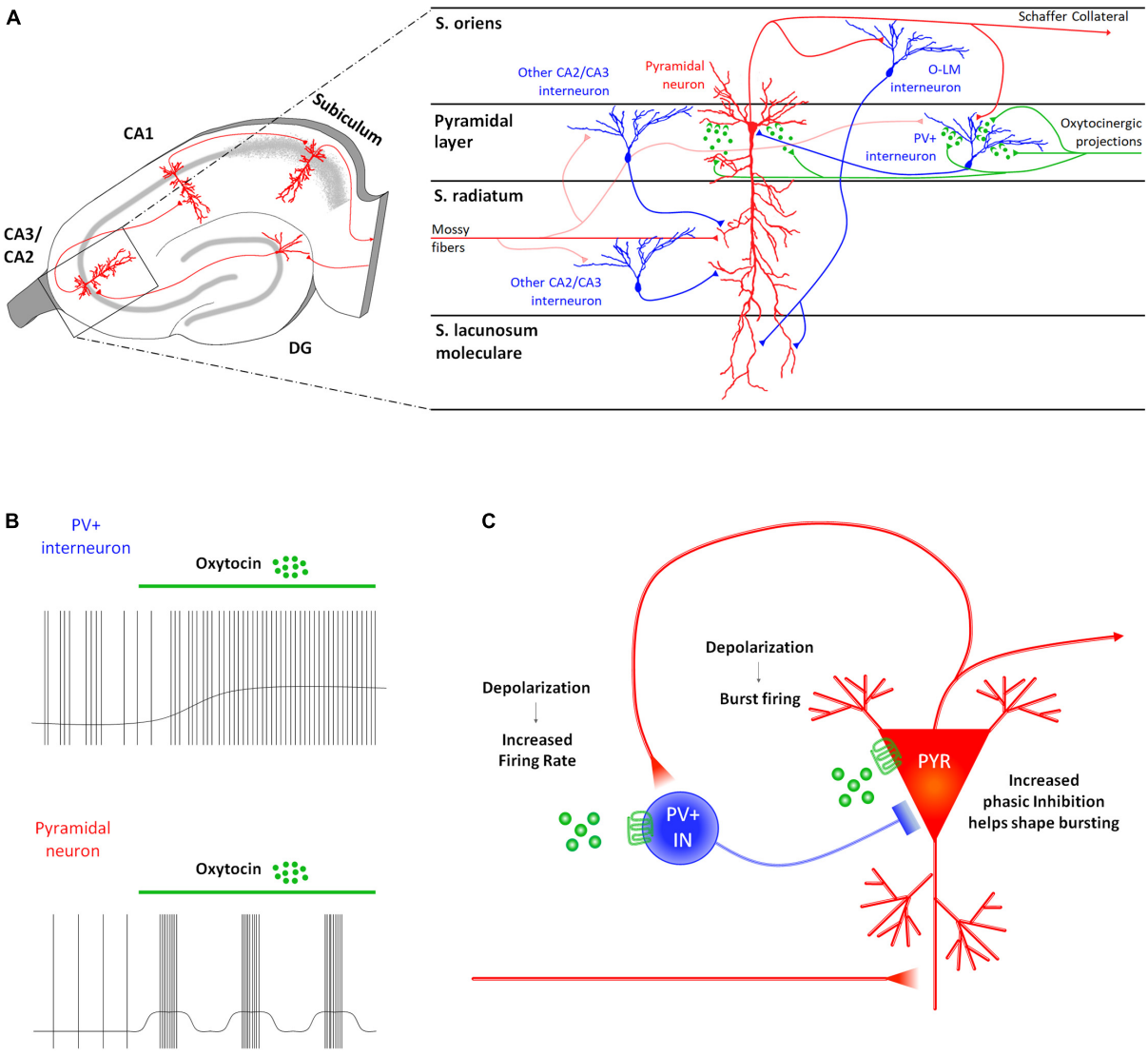

FIGURE 2
Receptor distribution, oxytocinergic projections and main effects exerted by oxytocin (OT) at CA2/CA3 (DG) region of the rodent's hippocampus. **(A)** At the CA2/CA3 region, OTRs are found both on the projective glutamatergic pyramidal neurons (PYR–red) and on parvalbumin positive GABAergic interneurons (PV^+ INs–blue). **(B)** In this region, OT increases the PV^+ IN excitability by depolarizing their membrane potential and by increasing their firing rate. Also, it exerts an excitatory effect on the PYRs by depolarizing their membrane and by promoting the onset of a bursting firing pattern. **(C)** In CA2/CA3, OT induces a reciprocal modulation of the neuronal activity of PYRs and PV^+ INs. Specifically, the OT-dependent increased excitability of the PYRs reverberates on the PV^+ IN by increasing frequency and amplitude of the EPSPs onto the PV^+ IN receiving Schaffer's collaterals. In turn, OT-dependent increased excitability of PV^+ IN supports a GABAergic input onto the PYR that modulates their burst firing and appears to be essential in promoting reliability of synaptic communication in the downstream areas of the hippocampus.

potentials of both subicular BCs and RCs (**Figure 4B**), through two different ionic mechanisms. In about 75% of the OT-responding subicular neurons the depolarization was due to a cationic current flowing through transient receptor potential vanilloid 1 (TRPV1) channels, while in the remaining cells it is induced by the inhibition of a K^+ current (Hu et al., 2021).

It is possible that OT-induced depolarization of the PYRs contributes to facilitate information transmission toward downstream brain areas (**Figure 4C**). However, how OT could affect the E/I balance in this area requires further investigation. For example, there are still no data regarding OTR expression and/or OT effect on subicular GABAergic INs although they are fundamental in the gating function exerted by the subiculum on hippocampal output activity (Benini and Avoli, 2005) and in controlling the recurrent network activity within the subicular network (Harris and Stewart, 2001; Harris et al., 2001; Witter, 2006).

4. Oxytocinergic modulation of hippocampal synaptic plasticity

Oxytocin serves a wide array of neuromodulatory functions in the context of synaptic plasticity in the hippocampus. It plays an important role in mediating long-term synaptic plasticity and is implicated in social, working, spatial, and episodic memory formation (Dubrovsky et al., 2002; Tomizawa et al., 2003; Lin et al., 2012, 2018; Chini et al., 2014; Park et al., 2017; Lin and Hsu, 2018; Rajamani et al., 2018; Abramova et al., 2020;

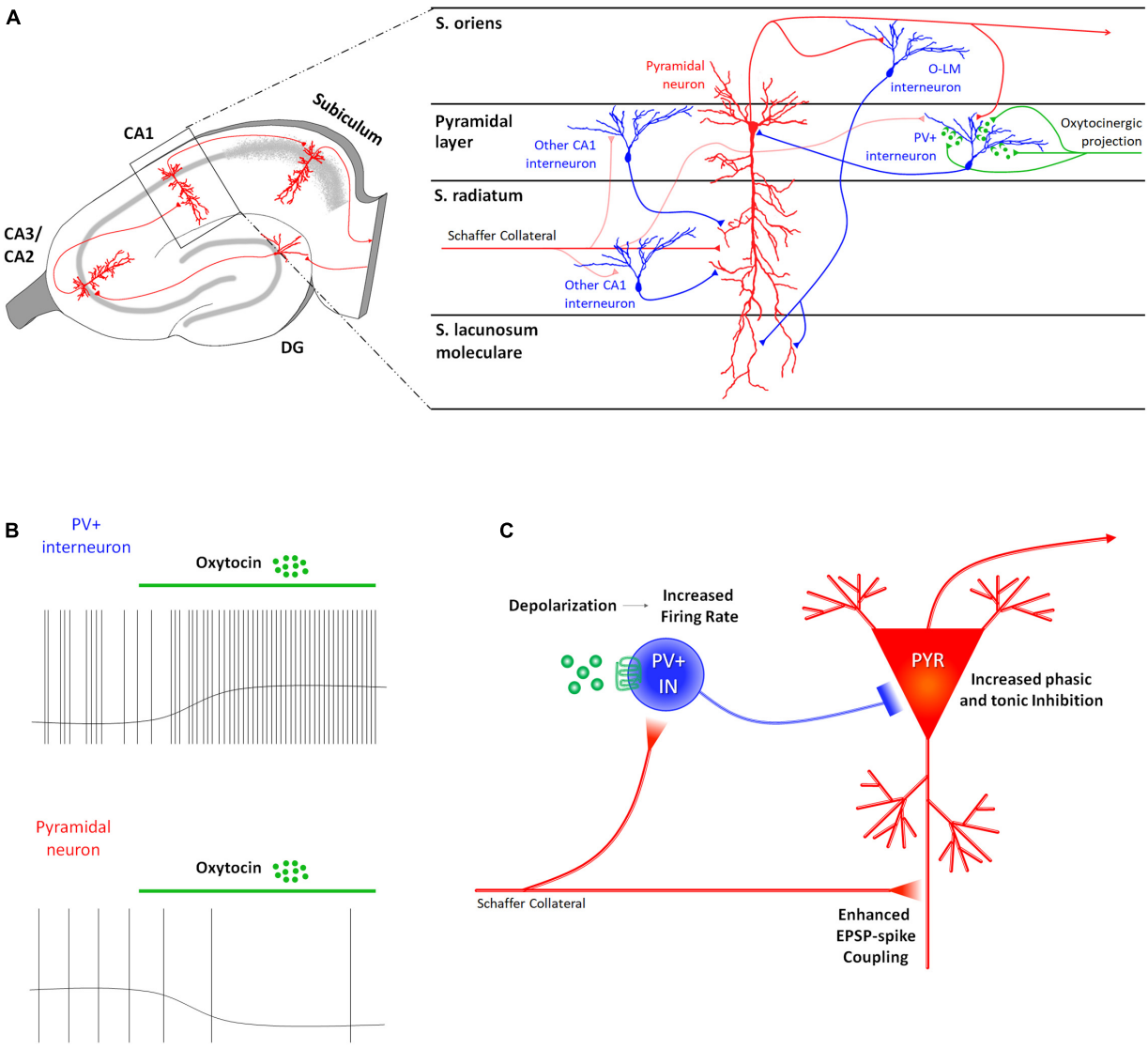

FIGURE 3
Receptor distribution, oxytocinergic projections and main effects exerted by oxytocin (OT) at CA1 region of the rodent's hippocampus. **(A)** At the CA1 region, OTRs are expressed only by parvalbumin positive GABAergic interneurons (PV^+ INs–blue) that receive direct oxytocinergic terminals (green) and whose cell body is located in the pyramidal layer. **(B)** In CA1, OT directly depolarizes PV^+ INs by increasing their firing rate and indirectly (by interposition of PV^+ INs) hyperpolarizes pyramidal neurons (PYR) by determining a reduction in their firing rate. **(C)** The OT-dependent increased excitability of the PV^+ INs indirectly modulates the excitability of the PYRs by increasing both phasic and tonic inhibition onto them, suppressing in turn spontaneous firing of the PYRs (reduction of noise). At the same time, OT-dependent increase in the firing rate of the PV^+ INs determines a "use-dependent reduction" of efficacy of the inhibition resulting in a more effective mono-synaptic excitatory transmission and a reduced di-synaptic inhibitory transmission arriving from Schaffer collaterals, entailing the enhancement of the EPSP-spike coupling (increase of signal). These two effects improve the fidelity and temporal precision of the information transfer through this area.

Pekarek et al., 2020; Hu et al., 2021). OT application on cultured glutamatergic hippocampal neurons drives dendritic and synaptic remodeling confirming that plasticity processes occur at these synapses (Ripamonti et al., 2017). Also, OT regulates neurogenic plasticity by stimulating adult neurogenesis and by driving adult-born neural circuit integration in the hippocampus (Leuner et al., 2012; Lin et al., 2017). Systemic administration of exogenous OT in rats increases the neuronal proliferation, differentiation and complexity of dendrites on newborn neurons (Sánchez-Vidaña et al., 2016). Accordingly, when OTR is removed from the hippocampus, there is a dramatic reduction in newly generated neurons together with a marked reduction in dendritic complexity and a delay in the excitatory-to-inhibitory GABA switch (Lin et al., 2017). Thus, OT-mediated development in newborn neurons is thought to govern the response of the animal to critical social stimuli.

Interestingly, OT seems to exert different effects on long-term synaptic plasticity in each specific hippocampal region (**Figure 5**). *In vivo* experiments on anesthetized rats showed that, unexpectedly, tetanic stimulation of the perforant path following intracerebroventricular injection of OT caused long-term depression (LTD), instead of long-term potentiation (LTP), in granule cells of DG (Dubrovsky et al., 2002). A similar effect of OT was reported in the medial nucleus of the amygdala (MeA) in rats (Gur et al., 2014). On the contrary, OT signaling is necessary for LTP induction in the EC-CA2 pathway: TGOT application during high-frequency tetanic stimulation of the perforant path

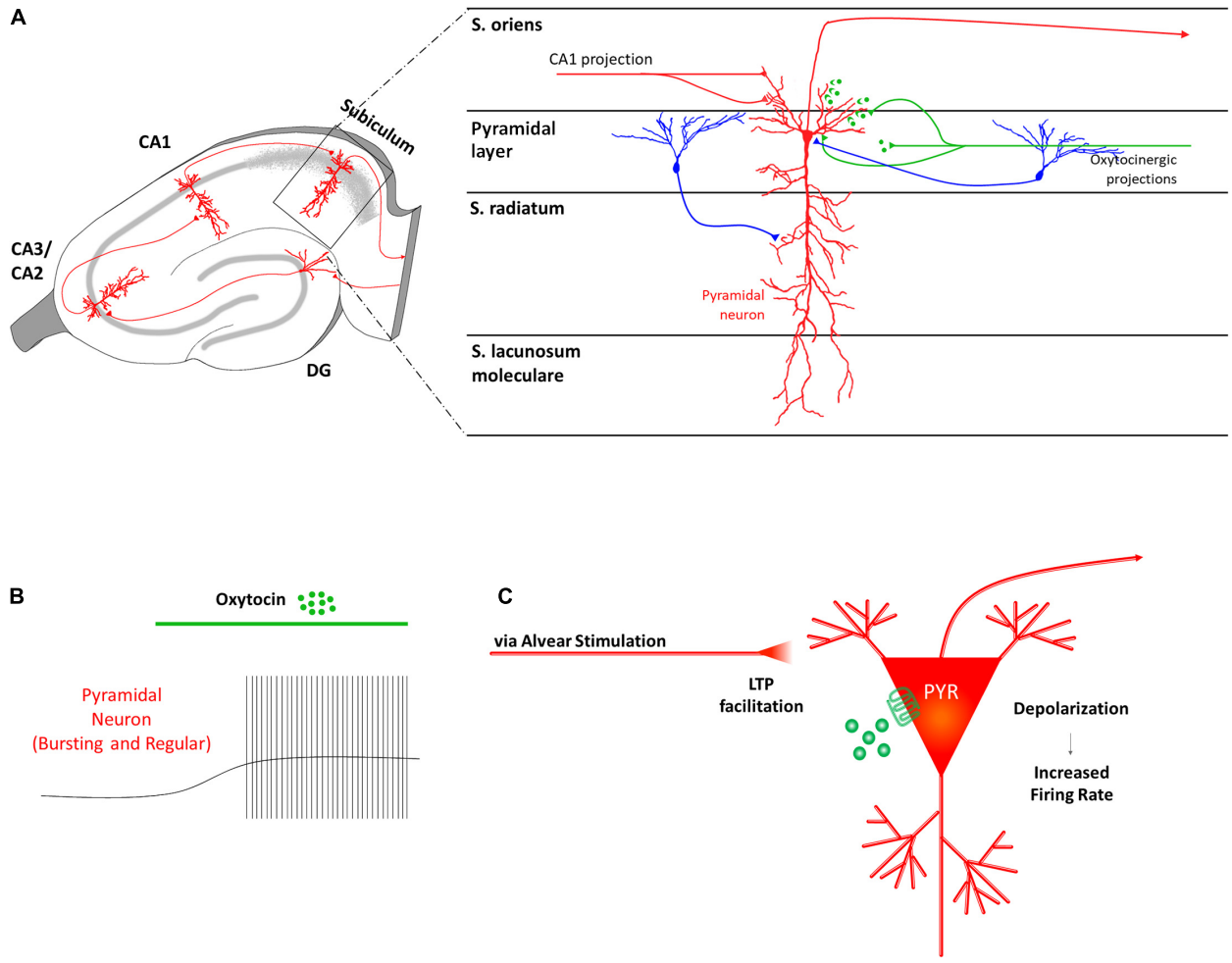

FIGURE 4
Receptor distribution, oxytocinergic projections and main effects exerted by oxytocin (OT) at subiculum region of the rodent's hippocampus. **(A)** In the subiculum, OTRs are known to be expressed by glutamatergic pyramidal neurons (PYR–red) that receive oxytocinergic afferent fibers (green). **(B)** OT causes a significant depolarization of the membrane potential and increases the firing rate of the subicular PYRs. **(C)** The OT-dependent increased excitability of the PYRs in the subiculum is thought to be crucial in transmitting information exiting the hippocampus.

resulted in an acute and lasting potentiation of excitatory synaptic responses in CA2 PYRs (Lin et al., 2018). Consistently, mice with conditional deletion of hippocampal CA2/CA3 OTRs display defects in the induction of LTP in the EC-CA2 synapses (Lin et al., 2018). Despite the apparently opposite effects on synaptic potentiation, impaired oxytocinergic neuromodulation affects both of these pathways to drastically alter social recognition memory (Lin et al., 2018; Rajamani et al., 2018).

At hippocampal Schaffer's collateral-CA1 synapses, OT enhances the ability of subthreshold synaptic stimulation to cause long-lasting LTP (Tomizawa et al., 2003; Lin et al., 2012), with the result of improving long-term spatial learning (Tomizawa et al., 2003). This result is of particular interest in light of the spatial memory enhancement that occurs in female mice during pregnancy, delivery, and lactation, when OT levels are increased both centrally and peripherally (Kinsley et al., 1999). At these synapses OT contributes to the maintenance of the late phase of LTP, but not to the early phase (Lin et al., 2012). An OT-dependent enhancement of LTP has also been reported at CA1-subiculum synapses (Hu et al., 2021).

Consistent with the central role played by OT in long-term plasticity in the hippocampus, impairments in the oxytocinergic system are associated with various pathological conditions involving deficits in learning and memory. OTR deletion in specific subregions and neurons of the hippocampus causes defects in LTP associated with hippocampal synaptic malformation and impaired long-term social recognition memory (Raam et al., 2017; Lin et al., 2018). It has been reported that an acute high-fat diet (HFD) in juvenile rats results in impaired LTP in CA1 of the dorsal hippocampus, which was related to a significant decrease in OT levels in this brain region. Systemic injection of a high dose of OT rescued HFD-induced LTP impairments (Khazen et al., 2022). Moreover, OT administration reversed synaptic plasticity impairments in other pathological conditions. Mutations in the contactin-associated protein-like 2 (CNTNAP2) are implicated in cortical dysplasia-focal epilepsy syndrome, epilepsy, attention-deficit hyperactivity disorder and autism spectrum disorders (Strauss et al., 2006; Elia et al., 2010; Mefford et al., 2010; Rodenas-Cuadrado et al., 2014). Intraperitoneal or intranasal application of OT in mice lacking CNTNAP2 transiently rescued their social behavior deficits (Peñagarikano et al., 2015). Intracerebroventricular injection of OT in a Shank3-deficient rat model of Phelan-McDermid syndrome (PMS) reduced the *in vitro* and *in vivo* synaptic plasticity impairments, partially rescuing

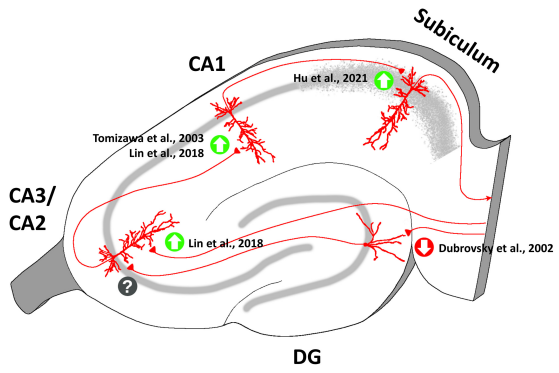

FIGURE 5
Oxytocinergic modulations of the synaptic plasticity at the different regions of the rodent's hippocampus. OT plays a crucial role in mediating long-term plasticity at the hippocampal synapses exerting different effects in each specific hippocampal region (enhancement of long-term potentiation = green upward arrow; emergence of long-term depression = red downward arrow; unknow OT effect on plasticity = question mark). The figure shows the main bibliographic references in which the OT-dependent modulations of synaptic plasticity in the specific regions of the hippocampus have been described.

long-term social recognition memory and attention deficits (Harony-Nicolas et al., 2015). Amyloid β peptides – that typically accumulate in the brain in Alzheimer's Disease – strongly suppress LTP in the hippocampus, but OT administration has been found to reverse this pathological effect (Takahashi et al., 2020). Stress-induced impairments in hippocampal synaptic plasticity and spatial memory in rats can be rescued by intranasal OT administration before or after the stress event (Lee et al., 2015; Park et al., 2017).

5. Oxytocin-mediated intracellular signaling in the hippocampus

The action of OT in the brain is conveyed through the OTRs, which are 7-transmembrane domain G protein-coupled receptors that can activate different intracellular signaling pathways depending on their coupling to G_q, G_o/G_i, or G_s proteins (Alberi et al., 1997; Gravati et al., 2010; Busnelli et al., 2012; Busnelli and Chini, 2018). It has been demonstrated that different OT concentrations determine the specific coupling of OTRs to different G_q and G_o/G_i protein subtypes (Busnelli et al., 2012). In the hippocampus, OTRs seem to be coupled to $G_{q/11}$ proteins (Lin and Hsu, 2018; Cilz et al., 2019; Froemke and Young, 2021) that can activate multiple signaling cascades with a variety of downstream effects (**Figure 6**).

The principal OTR signaling cascade involves a G-protein mediated increase in the activity of phospholipase C β (PLCβ), which in turn hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP2) to generate inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG). IP3 increases intracellular Ca^{2+} release and DAG activates protein kinase C (PKC). The increase in intracellular Ca^{2+} together with the phosphorylation of various receptors and/or ion-channels are at the basis of the depolarizing effects identified in different populations of hippocampal neurons. The $G_{q/11}$ pathway also transactivates epidermal growth factor receptors (EGFRs) and the mitogen-activated protein kinase (MAPK) cascade that culminates in the extracellular signal-regulated kinase 1/2 (ERK1/2) translocation to the nucleus and the activation of transcription factors involved in long-term plasticity processes (Tomizawa et al., 2003).

Specifically, the direct depolarization of the hilar GABAergic INs of the DG has been proposed to be due to an IP3-mediated increase in the intracellular Ca^{2+} and/or an increase in the sodium permeability mediated by IP3-DAG cascade (Harden and Frazier, 2016). In parallel, an OT-induced inhibition of the enzymes of the (Ca^{2+} + Mg^{2+}) ATPase family complex (Soloff and Sweet, 1982) probably underlies the LTD in the EC-DG pathway by limiting the availability of the phosphate groups required for LTP induction at these synapses (Dubrovsky et al., 2002).

The ionic mechanism underlying the direct depolarization of CA2 OT-responding neurons has been proven to rely on a reduction of the M-current mediated by the PIP2 cascade, whereas the mechanism underlying the modulation of spike shape in the same neurons is determined by the PKC-dependent phosphorylation of the Na^+-channels that are responsible for the action potential generation (Tirko et al., 2018). In parallel, the increase of the intracellular Ca^{2+}, synergistically with N-methyl-D-aspartate receptors (NMDARs) opening, determines the activation of calcium/calmodulin-dependent protein kinase II (CAMKII) which promotes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) recruitment in the EC-CA2 synapses to support synaptic potentiation (Lin et al., 2018). Interestingly, a similar mechanism of synaptic potentiation–modulated by arginin-vasopressin and involving activation of NMDARs and CaMKII–has also been described at Schaffer collateral-CA2 synapses (Pagani et al., 2015).

The mechanisms of OT-induced depolarization of the CA1 GABAergic INs are controversial. On one hand, Maniezzi et al. (2019) describe an up-modulation of L-type Ca^{2+} channels mediated by TGOT application. On the other hand, Owen et al. (2013) confirm the involvement of a G protein mediated modulation operated by OT, but suggest a calcium-independent mechanism. This shows that further studies are required to dissect the exact processes underlying the OT-induced depolarization of FS-INs in this area are needed. Maniezzi et al. (2019) speculate that multiple mechanisms may be involved (i.e., upregulation of L-type Ca^{2+} channels, modulation of P/Q-type calcium Ca^{2+} channels that are selectively expressed by FS-INs, inhibition of inward rectifier potassium channels, etc.), which converge the same final depolarizing effect. It is instead established that OT-induced LTP at hippocampal Schaffer collateral-CA1 synapses involves the activation of an EGFR-mediated pathway (Tomizawa et al., 2003; Lin et al., 2012). This pathway determines–through the activation of ERK1/2 signaling–the translation of an atypical PKC isoform, the protein kinase Mζ (PKMζ) (Lin et al., 2012), that has been found to be both necessary and sufficient for the maintenance of LTP and memory storage in the hippocampus (Sacktor et al., 1993; Ling et al., 2002; Pastalkova et al., 2006; Serrano et al., 2008; Hardt et al., 2010).

In the subiculum, two different ionic mechanisms underlie the OTR-induced depolarization. In most of the subicular neurons (∼75%), OTR-mediated depolarization derives from PKC-dependent activation of a cation conductance flowing through TRPV1 channels, while in a small population of subicular neurons (∼25%) it is induced by inhibition of a K^+ current (Hu et al., 2021). The OTR-dependent depolarization is required to induce synaptic plasticity in the CA1-subiculum synapses. Two possible mechanisms to explain OTR-elicited augmentation of LTP have been proposed. Since LTP at the CA1-subiculum synapses is NMDA dependent (Wozny et al., 2008),

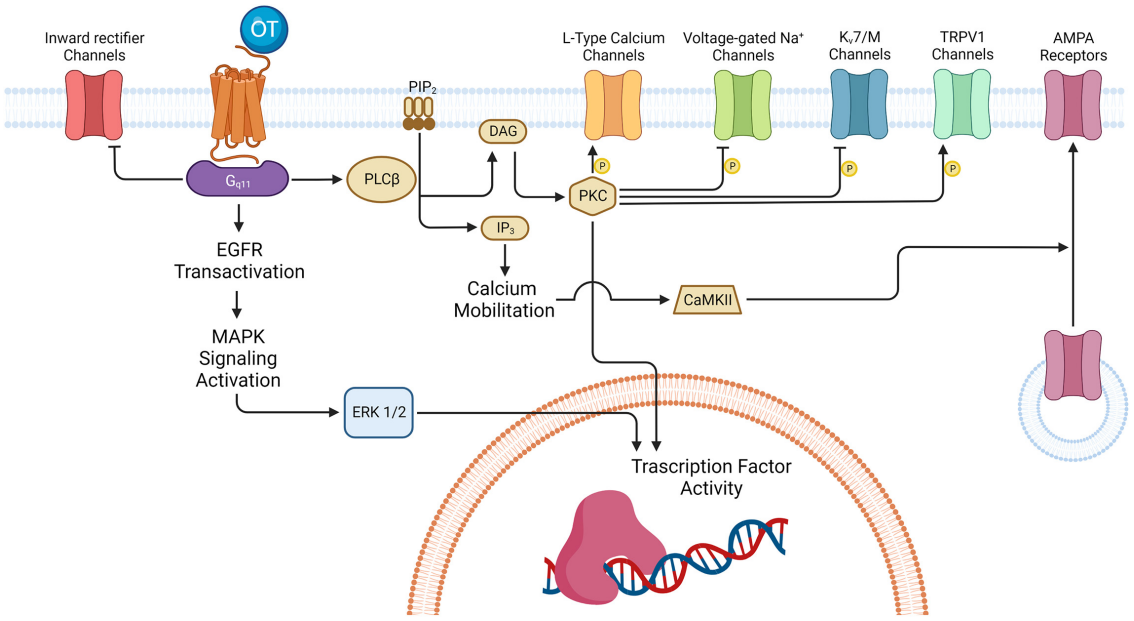

FIGURE 6
Oxytocinergic-mediated intracellular signaling in hippocampus. The various effects exerted by OT in the several regions of the hippocampus are all ascribable to the activation of the 7-transmembrane domain G protein-coupled receptors for oxytocin (OTR). In the hippocampus, OTR is usually coupled to $G_{q/11}$ that activates various signaling cascades with different downstream effects, depending on the hippocampal region and neuronal type involved. One of the pathways activated by $G_{q/11}$ leads to the inhibition of the inward rectifier K^+ channels: this is one of the mechanisms possibly implicated in the depolarization of the CA1 FS-INs. Also, $G_{q/11}$ can induce activation of the mitogen-activated protein kinase (MAPK) cascade culminating in the extracellular signal-regulated kinase 1/2 (ERK1/2) translocation to the nucleus and the activation of transcription factors involved in long-term plasticity processes. Besides, $G_{q/11}$ determines activation of phospholipase C β (PLCβ) which leads to protein kinase C (PKC) activation and the subsequent phosphorylation of different targets (i.e., L-Type Ca^{2+} channels in CA1 GABAergic interneurons, voltage-gated Na^+ channels and the Kv7 channels in the PYR neurons of CA2/CA3; TRPV1channels in the PYR of the Subiculum). In some cases, PKC can also activate different transcription factors thus promoting gene expression. In parallel, PLC can also bring IP3-mediated increase in the intracellular Ca^{2+} which, by activating calcium/calmodulin-dependent protein kinase II (CAMKII), promotes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) recruitment at the entorhinal (EC)-CA2 synapses to support synaptic potentiation. DAG, diacylglycerol; IP_3, inositol 1,4,5-trisphosphate; PIP_2, phosphatidylinositol 4,5-bisphosphate. Created with BioRender.com.

OTR-induced depolarization facilitates NMDA receptor opening and thus augments LTP. In parallel, since TRPV1 are Ca^{2+} permeant channels, OTR-elicited activation of TRPV1 channels increases intracellular Ca^{2+}, thus inducing LTP (Hu et al., 2021).

6. Conclusion and open questions

The hippocampus is a key structure for learning, memory formation, and spatial navigation. Furthermore, it is essential for processing information that regulates social behaviors in primates and other mammals (Maaswinkel et al., 1997; Rubin et al., 2014). As in other brain regions, the hippocampus is highly modulated by multiple neurotransmitters and peptides. Among them, OT has been found to play a primary role in regulating neuronal activity in the different anatomical districts of the hippocampus, thus providing a possible neurobiological correlate for the origin of some of the functions located in this area.

In the last 10 years considerable progress has been made in unraveling the neuromodulatory functions exerted by OT on the specific hippocampal neurons and networks, that have been comprehensively summarized in this review. Although the stimulation of OTRs can lead to the activation of multiple intracellular signaling cascades, with different downstream effects depending on the hippocampal region and neuronal type involved, their overall results are (i) improvement of long-term plasticity at hippocampal synapses and (ii) facilitation of signal processing and the fidelity of information transfer through the stations of the hippocampal tri-synaptic circuit. These effects exerted by OT on hippocampal neuronal networks likely underlie many neuromodulatory functions of this peptide on specific aspects of important cognitive and behavioral phenomena such as sexual receptivity, maternal attachment, stress and fear extinction, social exploration, recognition, and memory. However, the hippocampus is not a homogenous functional unit since differences in anatomy, connectivity, and gene expression exist between the dorsal and ventral hippocampus. In particular, the dorsal region is principally involved in cognitive and memory processes whereas the ventral region is manly involved in emotional functions (Moser and Moser, 1998; Fanselow and Dong, 2010; Bannerman et al., 2014). A difference in OTR density was observed between the ventral and dorsal hippocampus, with the former presenting a higher number of OTR-expressing cells than the latter (Lin and Hsu, 2018). These differences suggest a possible differential neuromodulatory action exerted by OT on these two regions that deserves to be investigated further. OT seems to be involved in consolidation of social memory traces in the dorsal hippocampus (Raam et al., 2017; Lin et al., 2018; Bazaz et al., 2022), while there is a knowledge gap concerning the role of OT in ventral hippocampus and it would be worthwhile to investigate the effect on emotion and affection that this neuropeptide could have specifically

in this hippocampal portion. Besides, these complex behaviors result from interactions between multiple brain areas. Despite the reported advancement, further studies are needed to deepen our understanding of the relationships between the oxytocinergic modulation of the hippocampal networks and other brain areas that express high levels of OTRs, such as amygdala or striatum. Extending knowledge in this field could be crucial in determining pharmacological targets and approaches for the treatment of neuropsychiatric disorders such as autism or schizophrenia, that have been reported to be associated with impairments in the oxytocinergic system.

Another crucial point that remains to be investigated concerns the specific contributions of different sources of endogenous OT reaching the hippocampus. OT is released in the hippocampus by the OT-producing parvocellular and magnocellular neurons of the PVN and the magnocellular neurons of the SON (Gimpl and Fahrenholz, 2001; Ross and Young, 2009; Knobloch et al., 2012; Stoop, 2012; Mitre et al., 2016, 2018; Son et al., 2022), but it is also secreted in the bloodstream by axon terminals of the magnocellular neurons of the same nuclei that reach the neurohypophysis and release OT into the neuro-hypophyseal capillaries (Kiss and Mikkelsen, 2005). OT in the blood circulation has a primarily peripheral role, especially in parturition and in lactation. However, there are pieces of evidence suggesting that OT could be re-captured at the neuronal level by crossing the blood-brain barrier thanks to the binding with a dedicated (RAGE) transporter present in endothelial cells at this interface (Yamamoto and Higashida, 2020). Verification that this mechanism exists would be of great importance for determining the relationship between the birth event and the modifications that occur in the mothers' brain in the peri- and post-partum, which are aimed at favoring the care of the offspring and reinforcing the parental bond. In this case, indeed, not only the central release of OT, but also the reuptake from the blood could contribute to neuromodulation in new mothers. Also, OT seems to be absorbed on intestinal epithelial cells at the blood-intestinal barrier (Yamamoto and Higashida, 2020). OT passing to the milk during lactation could then be implicated in the attachment of offspring to parents, again through re-capture at neuronal level in the pups. These mechanisms could explain how several OT-related behaviors are sex-dependent (i.e., pup distress calls, somatosensory stimuli for lactation and nursing) (Donaldson and Young, 2008; Heinrichs et al., 2009; Dumais and Veenema, 2016; Brown et al., 2020), although the organization of the oxytocinergic system in the brain apparently does not vary between sexes or individuals (Knobloch et al., 2012; Son et al., 2022). Is the concentration of OT in the hippocampus and the whole brain comparable between virgin females and new mothers? Are there brain areas where the post-partum concentration of OT is higher in mothers and/or pups? Are there differences between males and females in oxytocinergic neuromodulation in specific behavioral contexts? Do different levels of OT involve the expression of different levels of OTRs? These are only a few examples of open questions in this area of research that need to be addressed. The exact course of the hypothalamic oxytocinergic projections directed to the hippocampus also remains to be investigated. Do oxytocinergic inputs to different hippocampal areas originate from a uniform neuronal population or is there a topographic organization of the inputs? In this sense, retrotracing and optogenetic experiments may help, which will also reveal other brain areas that receive simultaneous neuromodulation with the hippocampus from divergent inputs of the hypothalamus.

Finally, the interaction between OT and other neuromodulators in the hippocampus deserves more in-depth exploration. The function of the hippocampus is highly regulated by various neurotransmitters and accumulating evidence indicates that OT has the potential to interact with other neurotransmitter systems. For example, dopamine D2 receptor (D2R)/OTR heterocomplexes (de la Mora et al., 2016) and OTR/serotonin 2C receptor (5-HTR2C) heterocomplexes (Chruścicka et al., 2019, 2021) have been described in striatum and amygdala, which are brain areas functionally connected to the hippocampus. The formation of these heteroreceptors modifies the standard response to the neuromodulatory molecules, by enhancing or reducing signaling when co-release occurs. Similar mechanisms are also likely to occur in the hippocampus, where numerous dopamine and serotonin receptors are expressed, but to our knowledge they have never been investigated or described so far.

Author contributions

GB, FT, and CM conceptualized the manuscript. GB, FT, PS, AC, CM, and FR wrote the initial manuscript and designed the figures. GB and FT critically revised the manuscript. GB and GS handled the funding. FT, PS, AC, CM, FR, GT, GS, AP, and GB contributed to the manuscript, approved the final version, and ensured that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship and all those who qualify for authorship are listed and contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The neural connections of oxytocin-mediated parental behavior in male mice

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1. Introduction

The adult brain can flexibly adapt behaviors to specific life-stage demands, and a classical example of this plasticity of neural circuits is the emergence of infant-rearing behavior in male mice. Both physically and mentally, the care that fathers provide is necessary for the growth of pups (Svetaz et al., 2014). Fathers' influence on pups can be subtle and far-reaching (Schorr et al., 2021; Scott et al., 2021). When male mice are sexually naive, they usually ignore or even attack cubs. In contrast, after becoming sexually mature, they will display caring behavior toward their own young. However, it remains unclear how caregiving behavior plasticity is implemented at the level of neural connections.

A recent study reported that this significant alteration might be due to the effect of oxytocin (OT) on mammals (Froemke and Young, 2021). OT is a neuropeptide elaborated by the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei. It is mainly involved in the promotion of childbirth and milk ejection (Uvnas-Moberg et al., 2019; Perkinson et al., 2021). Moreover, the link between OT and social behavior has been extensively studied in recent years (Bosch and Young, 2018). Research has revealed that OT can increase mutual trust among humans (Strauss et al., 2019) and reduce the risk of mental illnesses such as anxiety and depression (Naja and Aoun, 2017). In addition, increased OT secretion can reduce aggressive behavior of male mice (Steinman and Trainor, 2017). Exploring the specific mechanism of the intrinsic neural circuit between OT secretion and caring behavior in male mice is of great significance.

2. OT is indispensable for the parental caregiving behaviors of male mice

Recently, Kazunari Miyamichi's team from Japan's RIKEN Research Institute published an article in *Neuron* that revealed the neural circuit plasticity mechanism of OT in regulating the parent-child behavior of male mice (Inada et al., 2022). The authors used chemogenetic viruses to activate OT neurons in the PVN of virgin male mice and found that they exhibited parenting behaviors and reduced aggression toward pups. In addition, viral tracer results showed that excitatory connections from the lateral hypothalamus (LHA) to OT neurons in PVN were enhanced when virgin male mice became fathers. These connections are

functionally relevant, as their activation can induce parental behavior in virgin male mice (Figure 1). The adult brain can flexibly adapt behaviors to specific life-stage demands. These discoveries help providing scientific support for the mitigation of mental health conditions in children that are caused by a lack of parental caregiving behaviors. However, it remains unclear how caregiving behavior plasticity is implemented at the level of neural connections.

First, to explore the relationship between parenting behavior and OT in male mice, they used CRISPR-Cas9-mediated gene editing technology and Cre-expressed adeno-associated virus to conditionally knock out OT ($OT^{-/-}$) in the PVN. Then, they established a behavioral assay and applied it to wild-type ($OT^{+/+}$) and $OT^{-/-}$ mice to assess caregiving behaviors; three unfamiliar pups from different families were put into three cages, and a father mouse that was unrelated to these pups was allowed to interact with them freely. While the $OT^{+/+}$ mice displayed caring behavior, a large percentage of the $OT^{-/-}$ male mice ignored the young mice. This result indicates that OT neurons in the PVN are necessary to exert parental behaviors in fathers. Further examination of expectant fathers illustrated that the activity of OT neurons is essential for the first appearance of paternal caregiving behaviors.

Does OT have the same effect on virgin male mice? To address this, the authors used the chemogenetic virus hM3Dq-mCherry to activate OT neurons in the PVN of virgin male mice. They found that these mice exhibited more pup-care-related behaviors and less aggression. Moreover, Ucn3+ neuronal (related to infanticide) activities in the perifornical area (peFA) were inhibited, whereas the neural activities of Calcr+ neurons (a center for parental behaviors) in the medial part of the MPN (MPNm) were elevated. These outcomes illustrate that OT neurons could regulate the limbic neural populations related to parental and infanticidal behaviors in virgin male mice.

Moreover, OT neurons can release non-OT neurotransmitters and neuropeptides. To identify their role in parenting behavior in the PVN, they used hM3Dq-myc driven by an OT promoter (OTp) to activate OT neurons in virgin male mice. After injection of clozapine N-oxide, which can lead to the release of neurotransmitters or neuropeptides other than OT in $OT^{-/-}$ mice, increased caregiving behaviors were displayed by the $OT^{+/+}$ mice but not the $OT^{-/-}$ virgin male mice. Nevertheless, pup-directed attacks between these two genotypes were suppressed after the injection. Taken together, these data suggest that, compared to the significant promotion from OT, other neurotransmitters are also conducive to caregiving behaviors.

To further investigate the change in neural connections of paternal behavior, the authors concentrated their work on PVN OT neurons. Using rabies virus-based retrograde trans-synaptic tracing, OT neurons in the fathers displayed more input from the LHA and MPNm without a change in the number of neurons compared to virgin males. Interestingly, the increased inputs observed 5 days after the birth of the pups returned to a level similar to that of virgin males after 5 weeks of isolation, revealing that the enhanced connection was temporary and reversible. Moreover, histochemical methods and further analysis of cell-type-specific marker genes demonstrated that the inputs to PVN OT neurons were mostly excitatory neurons from the LHA and MPNm, especially melanin-concentrating hormone-producing excitatory neurons in the LHA.

To examine the electrophysiological properties of excitatory inputs to OT neurons, they injected the AAV-OTp-mCherry virus into the PVN and AAV-FLEx-ChR2 (H134R) virus into the LHA, MPNm, and dorsomedial hypothalamus (DMH) of *vesicular glutamate transporter type 2* (*vGluT2*)-Cre mice. Consistent with the trans-synaptic tracing results, the excitatory postsynaptic currents evoked by the optogenetic stimulation of LHA and MPNm inputs were slightly, but not statistically significantly, larger in the fathers. However, the response to the DMH stimulation remained unchanged. Furthermore, optogenetic activation of excitatory neurons in the LHA evoked more spikes in PVN OT neurons, which would be even more when MPNm was activated concomitantly. These results demonstrate that the enhanced excitatory connectivity from the LHA to OT neurons is associated with life-stage transition.

Finally, what was the specific relationship between excitatory connections from the LHA to OT neurons and parental behavior? Through the use of *in situ* staining, they found that fathers who interacted with pups expressed *c-fos* at a higher ratio in the LHA than those who were not exposed to pups. Notably, most *c-fos*+ neurons were *vGluT2*-positive and Pmch-expressing excitatory neurons. They focused on the functional contributions of this connection. Chemogenetic inhibition of *vGluT2*+ LHA neurons only slightly increased aggressive behaviors toward the pups in virgin male mice. Conversely, targeted hM3Dq-myc in the *vGluT2*+ LHA neurons of $OT^{+/+}$ and $OT^{-/-}$ virgin males showed a reduction in aggression toward the pups of virgin males without evoking caregiving behaviors. More importantly, $OT^{+/+}$ virgin males were significantly less aggressive than their $OT^{-/-}$ counterparts. Taken together, OT release mediated by excitatory LHA neurons provokes the parental behaviors of fathers by suppressing infanticide.

3. Discussion

Fathers play a unique role in the growth of their children (Volling et al., 2019). The specific mechanisms of neural connections in male animals' parenting behaviors have been extensively explored for decades but remain unclear.

Miyamichi et al. first established a behavioral assay to test the paternal caregiving behaviors of male mice, enabling the analyses between behavior and basic neuroscience to be more visual and precise. In addition, they chose OT, a neuropeptide that modulates numerous brain functions and utilized rabies-virus-mediated unbiased screening and cell-type analysis to comprehend the neural connections of OT. Interestingly, their study revealed that the structural plasticity of adults might be greater than expected. Furthermore, their research findings may not be just limited to paternal caregiving behavior but may also be applied to other life-stage transitions or even transient behavior changes.

OT, acts in the brain as a non-canonical neurotransmitter or neuromodulator, has been long known to shape behavior in rodents (Cherepanov et al., 2021; Zhang et al., 2021). OT originating from the PVN modulates various social behaviors,

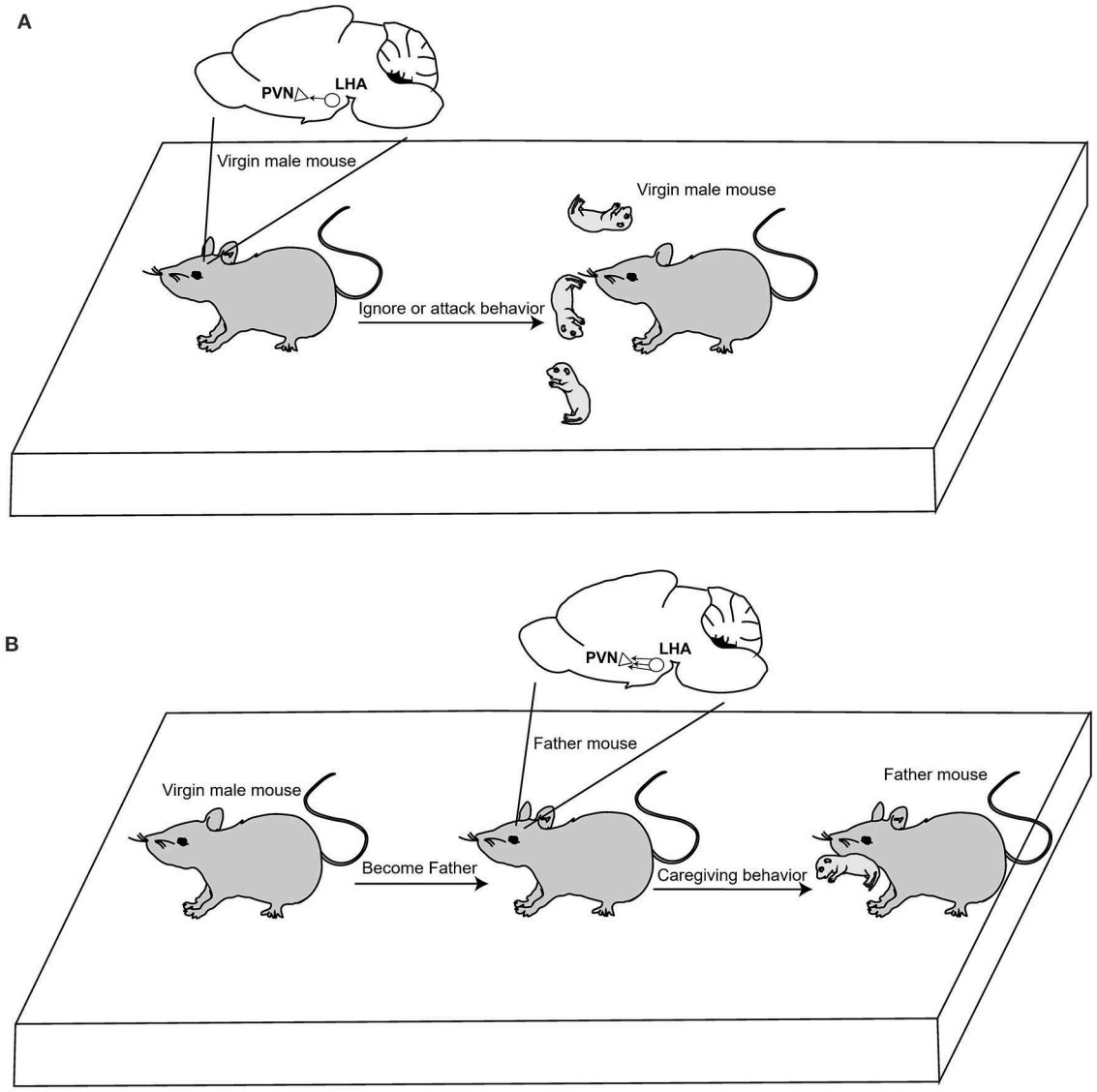

FIGURE 1
OT neuron activation facilitates caregiving behavior in virgin male mice. **(A)** In normal conditions, virgin male mice attack and ignore pups; they do not display parental caregiving behavior. **(B)** Neural connections originating from the LHA to the PVN OT neurons were drastically strengthened when male mouse became father. Activation of OT neurons in the PVN can induce caregiving behavior.

such as social recognition, fear memory, parental behavior (Hasan et al., 2019). Disorders in OT secretion involve in many psychiatric disorders including depression, anxiety, schizophrenia, and autism spectrum disorders (Lefevre et al., 2021). Notably, OT can have different modulatory effects on the same function under different conditions. Such divergence may derive from different neural connections (Wang et al., 2022). Recently, Scott et al. (2015) showed that tyrosine hydroxylase (TH)-expressing neurons in the anteroventral periventricular nucleus of the rodent hypothalamus are related to parental behavior. TH^+ cells have been shown to relay monosynaptic inputs to oxytocin expressing neurons and are thought to regulate oxytocin secretion. TH^+ anteroventral periventricular nucleus (AVPV) neurons can facilitate OT release from OT^+ PVN neurons into central nervous system and blood, leading to parental behavior. Although OT modulation in rodents' behaviors have been extensively studied, little is known on its mechanism in the regulation of parental caregiving behaviors of virgin male mice.

Lack of parental caregiving behaviors can cause mental diseases, such as social behavior, dysfunction, depression, anxiety and so on. The oxytocinergic systems in the CNS are associated with or influence processes implicated in depressive and anxiety disorders as well as those underlying stress, making OT potentially relevant to the development, maintenance, and treatment of these conditions. OT has been shown to exert anxiolytic and antidepressant effects (Slattery and Neumann, 2010; MacDonald and Feifel, 2014). Acute and chronic administration of intranasal OT have been extensively utilized in both animal models and human preclinical and clinical studies to treat various related mental diseases (Rae et al., 2022).

However, several issues related to this research need to be explored further. For instance, what is upstream of the LHA and downstream of PVN OT neurons? Why and how is the connection between the LHA and PVN OT neurons strengthened after virgin male mice become fathers? What is the specific molecular mechanism? Could both inhibition of LHA and peFA suppress pup-directed attack? The role of non-OT neurotransmitters/neuropeptides in this function remains unclear. Besides, some paternal behaviors that indirectly contribute to offspring fitness, such as provisioning and the connection between territorial defense and OT, have not been well-elucidated.

Intranucleus OT release from PVN neurons and into the bloodstream from the nerve terminals of this nucleus in the posterior pituitary (Eliava et al., 2016). OT neurons from PVN project centrally to forebrain regions can modulate neurocircuitry related to learning and memory, anxiety, fear, social approach and reward to treat diseases (Stoop, 2014). OT delivering *via* the intranasal (IN) is a major clinical drug delivery route, which is a more easier, more efficient administration way and can protect the body from systemic toxicity (MacDonald et al., 2011). However, OT's short half-life becomes an obstacle to its treatment of diseases. The application of nano-based delivery system not only improves the penetration of OT inside brain but also increases its half-life by the application of encapsulation and extends release (Al-Suhaimi et al., 2021).

In conclusion, Miyamichi et al. demonstrated that PVN hypothalamic oxytocin neurons and OT ligands are key regulators of parental caregiving behaviors in male mice. The plasticity of the hypothalamic neural connections is related to life stages, long distances, and specific cell types. These considerable discoveries help to provide scientific support for the mitigation of mental health conditions in children that are caused by a lack of parental caregiving behaviors and present a pattern for investigating other behavioral changes.

Author contributions

ZC, QW, XX, ZH, and YW wrote and edited the manuscript. All authors have contributed to the manuscript and approved the submitted version.

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Conflict of interest

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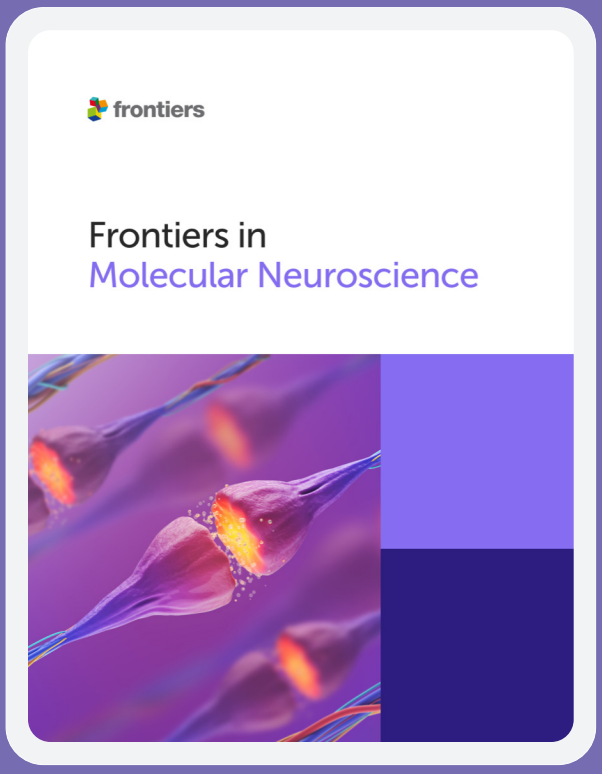

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