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Neuronal activity and remyelination: new insights into the molecular mechanisms and therapeutic advancements

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This article reviews the role of neuronal activity in myelin regeneration and the related neural signaling pathways. The article points out that neuronal activity can stimulate the formation and regeneration of myelin, significantly improve its conduction speed and neural signal processing ability, maintain axonal integrity, and support axonal nutrition. However, myelin damage is common in various clinical diseases such as multiple sclerosis, stroke, dementia, and schizophrenia. Although myelin regeneration exists in these diseases, it is often incomplete and cannot promote functional recovery. Therefore, seeking other ways to improve myelin regeneration in clinical trials in recent years is of great significance. Research has shown that controlling neuronal excitability may become a new intervention method for the clinical treatment of demyelinating diseases. The article discusses the latest research progress of neuronal activity on myelin regeneration, including direct or indirect stimulation methods, and the related neural signaling pathways, including glutamatergic, GABAergic, cholinergic, histaminergic, purinergic and voltage-gated ion channel signaling pathways, revealing that seeking treatment strategies to promote myelin regeneration through precise regulation of neuronal activity has broad prospects.

KEYWORDS

neuronal activity, remyelination, oligodendrocytes, molecular mechanism, therapeutic advances

1 Introduction

Oligodendrocytes play a substantial role in the central nervous system by forming myelin sheaths and maintaining their structure. Myelin accelerates nerve impulse conduction, increases neural signal processing capacity, maintains axon integrity, and supports axonal nutrition. Demyelination is characterized by the loss of myelin sheaths around the axon, leading to oligodendrocyte death, which is common in clinical disorders such as multiple sclerosis (MS), chronic cerebral hypoperfusion, stroke, dementia, and schizophrenia (Fields, 2008). Though spontaneous remyelination occurs in demyelination diseases, it is generally incomplete and does not contribute to functional recovery in conditions like MS and chronic cerebral hypoperfusion (Zhou et al., 2017; Maas and Angulo, 2021; Deng et al., 2023). Several clinical trials have investigated a variety of molecules that have the potential to enhance remyelination, but their outcomes have been unsatisfactory (Lubetzki et al., 2020). Thus, effective and precise therapeutic approaches for demyelination disorders are crucial.

Multiple research groups have provided the evidences suggesting that neuronal activity could trigger increased myelin formation (Gibson et al., 2014; Mitew et al., 2018). Activation

of signaling pathways between neurons and oligodendrocytes could modulate several developmental stages of oligodendrocytes, including oligodendrocyte precursor cells (OPCs) proliferation, differentiation, and maturation, as well as integrations of neural pathways (Thornton and Hughes, 2020; Deng et al., 2023). Evidence suggests that controlling neuronal excitability may be an appropriate novel intervention for clinical therapy of demyelination conditions. Neuronal activity can be stimulated directly or indirectly by various methods such as optogenetics, chemogenetics, transcranial stimulation, and sensory stimulation (Nagy et al., 2017; Maas and Angulo, 2021; Mooshekhian et al., 2022). In this review, we focus on recent advances in neuronal activity and remyelination, as well as the related mechanisms of neural signaling pathways. This outlook will help to translate experimental findings into therapeutic strategies and clinical trials aimed at enhancing remyelination and neuroprotection associated with demyelination diseases.

2 The role and molecular mechanisms of neuronal activity on remyelination

Remyelination is a crucial process for restoring the function of nerves following damage. It involves the proliferation, migration, and differentiation of OPCs, which eventually wrap around axons to create new myelin sheaths (Figure1) (Smith et al., 1979; Horner and Gage, 2000; Mei et al., 2016).

Studies have shown that neuronal activity plays an essential role in myelin formation and remyelination. Previous studies indicated that electrical stimulation of neuronal activity promotes OPCs proliferation and myelination *in vitro* (Demerens et al., 1996; Bergles and Richardson, 2015). In contrast, inhibiting neuronal action potential generation using tetrodotoxin impeded the progression of myelination. Recent advances in biomolecular and genetic technologies have revealed that the precise activation and transmission of neurotransmitters within neurons have positive effects on myelin formation. Activation of cortical neurons promotes the proliferation and differentiation of OPCs, and it has even been shown to improve mobility in healthy mice (Demerens et al., 1996; Gibson et al., 2014; Pan and Chan, 2021). Similar evidence has been observed in both humans and mice, that the activation of neurons through enriched environments and complex motor skills hastens the formation of newborn myelin and myelin ultrastructure in white matter (McKenzie et al., 2014; Bacmeister et al., 2020; Bacmeister et al., 2022; Nicholson et al., 2022). In addition, the knockout of myelin regulatory factor (MYRF) in OPCs resulted in reduced motor learning ability and restraint of

FIGURE 1
The process of remyelination. A diagram illustrating myelination in normal condition **(A)**, demyelination **(B)**, and remyelination **(C)**, showing OPC proliferation, migration into the lesion, differentiation into myelinating oligodendrocytes, and remyelination of naked axons by neuronal activity or translational approaches stimulation. Blue: neurons, Green: OPCs, Yellow: myelinating oligodendrocytes, Orange: mature oligodendrocytes. Dark red with spotted shape: dying oligodendrocytes.
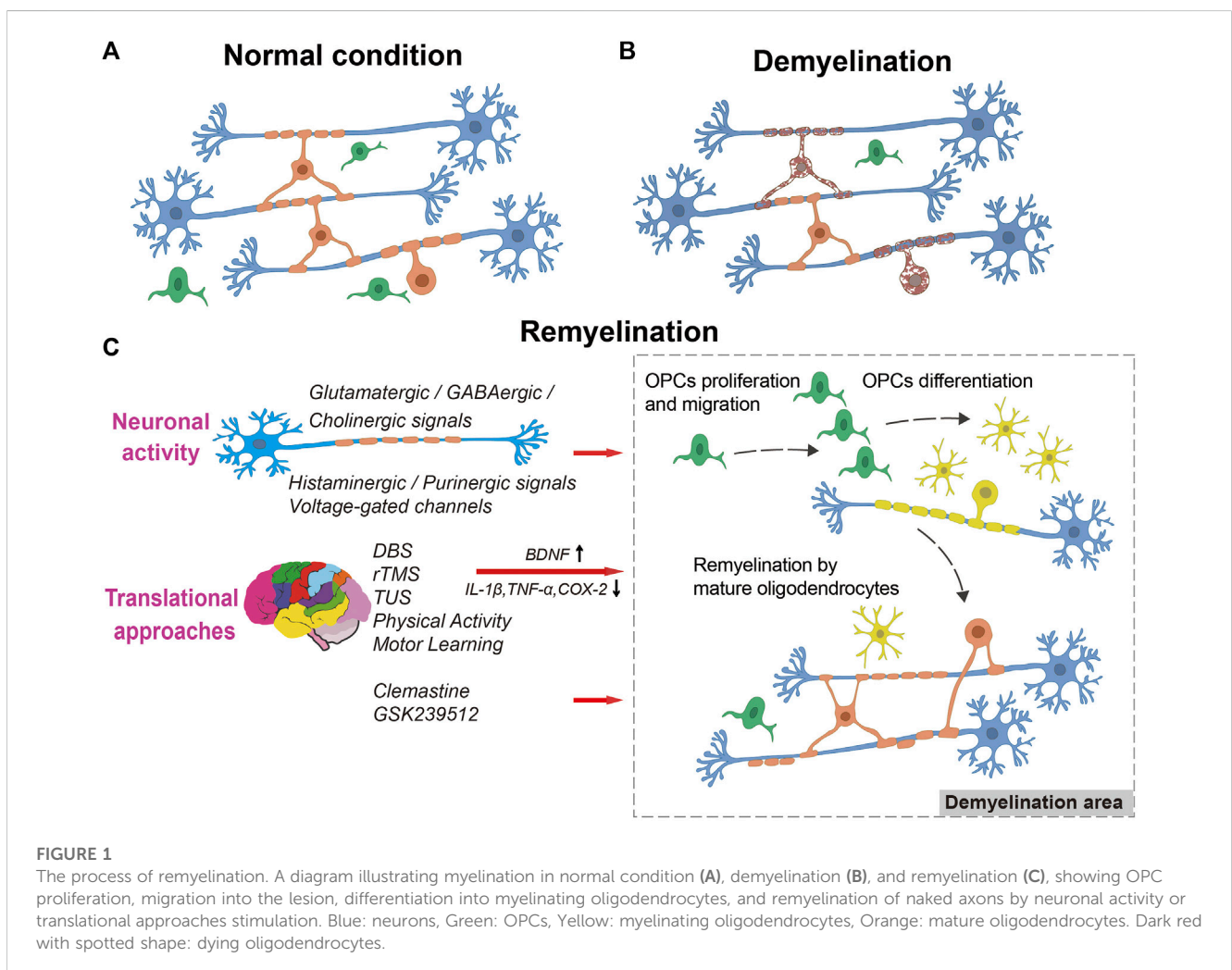
TABLE 1 Effects and molecular mechanisms of neuronal activity on remyelination.

	Targets	*In Vitro*	*In Vivo* demyelination models
Glutamate	General glutamatergic receptors	Proliferation↓ (Spitzer et al., 2016)	Proliferation↑ and myelination↑ in cerebral hypoperfusion model (Zhou et al., 2022)
			Differentiation↑ and myelination↑ in chronic ischemia/LPC-induced model (Ortiz et al., 2019; Deng et al., 2023)
	AMPA receptors	Proliferation↓ and differentiation↓ (Fannon et al., 2015)	Proliferation↑ and myelination↑ in ethidium bromide-induced model (Gautier et al., 2015)
		Differentiation↑ and myelination↑ (Kukley et al., 2007; Barron and Kim, 2019)	Survival↑ and myelination↑ with GluA2/3/4 deficient mice (Kougioumtzidou et al., 2017)
	NMDA receptors	Myelination↓ (Salter and Fern, 2005; Christensen et al., 2016; Macrez et al., 2016)	Myelination↑ in EAE, ethidium bromide/stroke-induced model (Lundgaard et al., 2013; Doyle et al., 2018)
			Myelination↓ in EAE model (Macrez et al., 2016)
GABA	GABAA receptors	Proliferation↑ and differentiation↓ (Hamilton et al., 2017)	Proliferation↓ and myelination↑ in chronic neonatal hypoxia-induced model (Zonouzi et al., 2015; Bai et al., 2021)
	GABAB receptors	Myelination↑ (Serrano-Regal et al., 2022)	Differentiation↑ and myelination↑ in LPC-induced model (Serrano-Regal et al., 2022)
			Myelination↑ in MS patients (Cawley et al., 2015)
Acetylcholine	mAChRs	Proliferation↑ (Fields et al., 2017)	Differentiation↓ and myelination↓ in EAE/cerebral hypoxic model (Deshmukh et al., 2013; Cree et al., 2018)
		Differentiation↓ and Myelination↓ (De Angelis et al., 2012; Deshmukh et al., 2013)	
	nAChRs	Differentiation↑ (Imamura et al., 2015)	Myelination↑ in EAE model (Piovesana et al., 2022)
			Myelination↓ in EAE model/nAChR (α9/α10) knockout mice (Liu et al., 2019)
Histamine	H1 receptors		Myelination↓ in EAE model with H1 receptor knockout mice (Dimitriadou et al., 2000; Ma et al., 2002)
	H2 receptors		Differentiation↓ and myelination↓ in cerebral hypoxic model with Hrh2fl/fl; CNPase-Cre mice (Jiang et al., 2021a)
			Myelination↑ in EAE model with H2 receptor knockout mice (Saligrama et al., 2014)
	H3 receptors		Myelination↑ in EAE model with H3 receptor knockout mice (Teuscher et al., 2007; Shi et al., 2017)
			Myelination↓ in EAE model (Imeri et al., 2021)
	H4 receptors		Myelination↑ in EAE model (Ballerini et al., 2013)
	HDC		Myelination↑ in EAE model with HDC knockout mice (Saligrama et al., 2013)
Adenosine	General	Differentiation↑ and myelination↑ (Stevens et al., 2002)	
	P1 receptors		
	A2a/A2b receptors	Differentiation↓ (Coppi et al., 2013; Coppi et al., 2020)	
	A1 receptors		Myelination↓ in brain hypoxia model (Cherchi et al., 2021b)
	A3 receptors	Apoptosis↑ (Cherchi et al., 2021b)	
ATP/ADP	P2X7 receptors		Myelination↓ in EAE/cerebral ischemia model (Domercq et al., 2010; Illes, 2020)
			Overexpressed in the brains of patients with demyelination (Rivera et al., 2021)
K⁺	Kir4.1	Proliferation↑ (Rivera et al., 2021)	Differentiation↑ and myelination↑ in cerebral ischemia model (Song et al., 2018)
		Myelination↑ (Maldonado et al., 2013)	
	Kv1.3	Proliferation↑ (Rivera et al., 2021)	

TABLE 1 (*Continued*) Effects and molecular mechanisms of neuronal activity on remyelination.

	Targets	*In Vitro*	*In Vivo* demyelination models
		Proliferation↓ and differentiation↓ (Liu et al., 2021)	Proliferation↓ and differentiation↓ in Interleukin 17-induced model (Liu et al., 2021)
	Kv1.6	Proliferation↓ (Rivera et al., 2021)	
Ca²⁺	Cav1.2	Myelination↑ (Li et al., 2020)	Myelination↑ in cuprizone-induced model with Cav1.2 defective mice (Santiago Gonzalez et al., 2017; Paez and Lyons, 2020)
	PDE7	PDE7 inhibitors induce survival↑, differentiation↑ and myelination↑. (Medina-Rodriguez et al., 2013; Zorn and Baillie, 2023)	PDE7 inhibitors induce myelination↑ in EAE/cuprizone/LPC-induced model (Martin-Alvarez et al., 2017; Medina-Rodriguez et al., 2017)

newborn myelin formation (McKenzie et al., 2014; Xiao et al., 2016). With 7 weeks of motor learning training, MYRF and Myelin Basic Protein (MBP) expression in wild-type mice increased by 1.4-fold, emphasizing the critical role of neurons in myelin genesis (Yoon et al., 2016). These studies provide the foundation for investigating the dynamic interactions of signaling pathways between neurons and oligodendrocytes.

Pharmacological blockade of neuronal activity in the demyelination model led to an increase in the number of OPCs within the lesions, but also a decreased proportion of differentiated oligodendrocytes, which impairs the regeneration of myelin *in vitro* (Gautier et al., 2015). Recent *in vivo* experiments demonstrated the neuroprotective effect of neuronal activity on remyelination (Ortiz et al., 2019; Zhou et al., 2022; Deng et al., 2023). Repetitive transcranial magnetic stimulation (rTMS) and transcranial ultrasound stimulation (TUS), non-invasive methods for controlling neuronal activity, encouraged OPC survival and differentiation, which aided in myelin repair and the restoration of cognitive function (Darmani et al., 2022). Precise modulation of neurons in the cerebral cortex utilizing optogenetics and chemogenetics promoted OPCs proliferation and differentiation and contributed to extensive remyelination, recovery of nerve conduction, and cognitive impairment in chronic hypoperfusion and lysophosphatidylcholine (LPC)-induced demyelination model. These effects were mediated through the Wnt2 pathway and neuron-OPC functional synapses. These findings provide novel insights into clinical treatments for demyelinating diseases via precise regulation of neuronal activity. However, it is uncertain whether remyelination is entirely dependent on neuronal activity since it may also affect other neurons and glia cells, not just oligodendrocytes and remyelination (Maas and Angulo, 2021). Further investigation is needed to identify the mechanisms involved in the interactions between neuronal activity and remyelination. In Table 1, the effects and molecular mechanisms of remyelination *in vitro* and *in vivo* by neurotransmitters and neuromodulators known to regulate neuronal activity are summarized.

2.1 Molecular mechanisms of glutamatergic signaling pathways

OPCs are distinguishable from mature oligodendrocytes and other types of glial cells, as they contain voltage-gated potassium (K⁺), sodium (Na⁺), and calcium (Ca²⁺) channels on their cell surface that can initiate action potentials (Paez et al., 2009). OPCs in the hippocampus can receive projections of glutamatergic neuron fibers, respond to nerve impulses, and generate action potentials (Bergles et al., 2000; Gautier et al., 2015). The synaptic connections between glutamatergic neurons and OPCs play a critical role in myelin formation, and synaptic vesicle release has been shown to affect the myelination process. Inhibition of glutamate release from neurons resulted in a significant decline of approximately 39% in myelination (Mensch et al., 2015). Neuronal activity in cultured neurons stimulated the synaptic release of glutamate, which increased the myelination of axons. Conversely, inhibition of vesicle release or glutamate receptor activity decreased myelination (Li et al., 2013). With the development of neuronal precision control technology, *in vivo* optogenetic and pharmacogenetic stimulations of glutamatergic neurons in mice have been demonstrated to boost OPCs proliferation, differentiation in white matter, and contribute to the formation of thicker myelin (Gibson et al., 2014; Mitew et al., 2018; Deng et al., 2023). Additionally, activating cortical glutamatergic neurons with optogenetics in the LPC-induced demyelination model and cerebral hypoperfusion enhanced OPCs proliferation and differentiation in regions of demyelination, leading to remyelination and cognitive function recovery (Ortiz et al., 2019; Zhou et al., 2022). Furthermore, functional synaptic connections between glutamatergic neurons and OPCs, marked by synaptic markers VgluT1 and VgluT2, were formed in areas of demyelination injury (Etxeberria et al., 2010; Gautier et al., 2015; Zhou et al., 2022). These studies indicated that the precise control of the glutamatergic neuron-OPC neuronal circuit to increase functional synaptic connections is necessary to protect against demyelination. However, the functional synaptic connections between OPCs and glutamatergic neurons were significantly altered in the LPC-induced demyelination injury models, resulting in a lack of VGlut1 puncta and neuron-OPC synaptic connections, especially in proliferating OPCs (Sahel et al., 2015). After reaching their proliferation peak, OPCs obtained synaptic connections from neurons during the subsequent differentiation and remyelination stages. These findings further support the notion that elevated glutamate neuronal activity positively impacts remyelination, although the specific mechanisms and processes involved in glutamatergic neuron-OPC functional synapses in this neuroprotective effect require further validation.

Glutamate receptors such as AMPA and NMDA are expressed on the cell membranes of OPCs, and glutamatergic signaling pathways are known to regulate OPCs development and myelin regeneration via regulation of these receptors. There have been multiple studies that revealed the signaling pathway mechanisms between glutamatergic neurons and OPCs, which improve the formation of myelin and remyelination (Krasnow and Attwell, 2016; Spitzer et al., 2016; Doyle et al., 2018). AMPA receptors are identified as the dominant receptor involved in remyelination. Gautier et al. reported that electrical stimulation of glutamatergic neurons, which senses neuronal activity by AMPA receptors, increases OPCs proliferation and promotes remyelination in demyelination lesions induced by ethidium bromide (Gautier et al., 2015). Actually, the role of AMPA receptors in OPCs proliferation is still controversial. In contrast to those findings, studies have reported that blocking AMPA receptors activity by pharmacological means or genetic knockout of subunits GluA2/3/4 does not appear to significantly impede OPCs proliferation *in vivo* or *in vitro* (Fannon et al., 2015; Kougioumtzidou et al., 2017). The AMPA receptors consistently exhibit significant effects on the later stages of myelin regeneration. Excitation of glutamatergic neurons and subsequent release of glutamate from activated axons led to OPCs depolarization and AMPA receptor activation on oligodendrocytes, which contribute to the positive influence of OPCs differentiation and myelination (Kukley et al., 2007; Barron and Kim, 2019). Conversely, blocking AMPA receptor activity arrested OPCs differentiation and subsequent remyelination (Gautier et al., 2015; Chen et al., 2018).

NMDA receptors are another key receptor involved in glutamatergic signaling pathways. Research has shown that excitation of NMDA receptors in OPCs, which are dependent on glutamatergic signaling, is essential for accelerating and improving myelin formation, while blockade of NMDA receptors with MK-801 results in the suppression of myelin formation (Lundgaard et al., 2013). The authors also reported that remyelination following white matter injury is reliant on NMDA receptors *in vivo*. Inhibiting NMDA receptors with MK-801 after demyelination led to a significant decrease in the number of myelinated axons and the thickness of the myelin sheath (Lundgaard et al., 2013). In addition, in both rat and mouse models of stroke-induced demyelination, stimulation of glutamatergic neurons resulted in the release of glutamate into myelin-wrapped axons and the activation of myelin NMDA receptors, which can protect myelin basic proteins from ischemic damage (Doyle et al., 2018). NMDA receptors maybe greatly correlated with OPCs differentiation and remyelination. These receptors were found to be rapidly upregulated at 14 days following demyelination injury in differentiating OPCs, implying their important roles in the differentiation phase of myelin repair (Salter and Fern, 2005; Gautier et al., 2015). However, it is worth noting that both the myelin and axonal structures underwent damage after a 3-h activation of NMDA receptors in dorsal roots incubation (Christensen et al., 2016). Additionally, the authors discovered that pretreatment with NMDA receptor antagonists can attenuate the pathological changes in demyelination disorders (Micu et al., 2006; Macrez et al., 2016). In light of the above conflicting data, further studies are imperative to ascertain whether NMDA receptors can indeed have beneficial effects on remyelination. In general, the glutamatergic signaling pathways exhibit complex actions in OPCs development and produce varying effects on myelin generation and remyelination stages.

2.2 Molecular mechanisms of GABAergic signaling pathways

OPCs express both the GABAA and GABAB receptors, which allow for GABAergic inhibitory and glutamatergic excitatory regulation (Zonouzi et al., 2015). Modulation of GABA receptors and GABAergic signaling pathways is implicated in the regulation of OPCs development, myelination, and remyelination (Bai et al., 2021; Serrano-Regal et al., 2022). In mouse cerebral slices, the presence of endogenous GABA elevated the rate of OPCs and decreased their maturation, an effect that could be nullified by the administration of gabazine, an antagonist of the GABAA receptor (Hamilton et al., 2017). These findings suggest that GABAA receptor-mediated signaling pathways can obstruct myelin synthesis. In contrast, studies have found that GABAA receptor-mediated signaling pathways are downregulated in OPCs in brains under chronic hypoxia and are associated with increased OPCs proliferation, disrupted initiation and progression of oligodendrocytes, and anomalous myelination (Zonouzi et al., 2015). Thus, impeding the metabolism or uptake of GABA can facilitate the differentiation of OPCs into mature oligodendrocytes, which facilitates myelin synthesis by improving the response to hypoxia. This difference in the role of GABAA receptor-mediated signaling pathways during myelination may be due to distinct physiological and pathological conditions. GABAB receptors also play a crucial role in regulating myelin synthesis and the regeneration of myelin. Intracerebral injection of GABAB receptor antagonists in neonatal rats increased OPCs proliferation as well as decreased MBP expression and myelin production in the cingulate cortex (Pudasaini et al., 2022). Baclofen, a GABAB receptor-specific agonist commonly used as a muscle relaxant in MS patients, heightened remyelination by prompting GABA to amplify Myelin-associated glycoprotein (MAG) and MBP expression levels *in vitro* in optic nerve explants and cerebral slices (Serrano-Regal et al., 2022). Serrano-Regal and colleagues further assessed the effects of Baclofen treatment on remyelination *in vivo* using the LPC-triggered demyelination mouse model. Their findings showed that such treatment encouraged the differentiation of OPCs and increased the prevalence of nascent axons in demyelinated lesions, thus indicating a beneficial impact on remyelination (Serrano-Regal et al., 2022). Studies on patient brains depicting progressive demyelination with MS revealed significantly decreased GABAergic signaling pathways and reduced GABA expression in the sensorimotor cortex and hippocampus relative to normal individuals (Cawley et al., 2015). Furthermore, lower GABA levels in the sensorimotor cortex were associated with diminished limb movement, and decreased GABA expression may indicate disruptions in physical abilities and neurodegenerative mechanisms. The findings of this study underscore the significance of regulating GABAergic signaling pathways as a promising prevention approach for neurodegenerative diseases involving demyelination. Overall, GABAergic receptors and signaling pathways play a vital role in promoting myelin synthesis and facilitating remyelination.

2.3 Molecular mechanisms of cholinergic signaling pathways

The involvement of acetylcholine (ACh) in myelin formation has been extensively reported. However, the specific impacts of cholinergic neurons and cholinergic signaling pathways on oligodendrocytes are yet to be clearly defined. Several investigations have substantiated the presence of ACh receptors in oligodendrocytes. Additionally, these studies have validated that the activation of signaling pathways in OPCs and other cells related to the oligodendrocyte lineage is induced by ACh receptors (Takeda et al., 1995; Larocca and Almazan, 1997). The oligodendrocytes express two types of ACh receptors, including muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs) (Bernardini et al., 1999; De Angelis et al., 2012). The transcriptional regulation of cholinergic signaling pathways, activated by Ach receptors, may influence oligodendrocyte development and function. mAChRs, especially M1, M3, and M4 subtypes, were highly expressed on OPCs, suggesting that mAChRs are involved in the initial phases of oligodendrocyte development (Ragheb et al., 2001; De Angelis et al., 2012). According to Fields et al. revealed that pharmacological receptor antagonists can reduce the level of phosphorylated CREB and c-fos expression in OPCs and stimulate OPCs proliferation through the activation of cholinergic pathways mediated by mAChRs (Fields et al., 2017). Muscarinic signaling suppressed OPCs differentiation and myelin formation, and it caused a drop in MBP expression, as shown by further studies (De Angelis et al., 2012). Another research group discussed the utilization of the mAChR antagonist benztropine to accelerate OPCs maturation, resulting in a favorable outcome in alleviating demyelination in both *in vitro* and *in vivo* experiments (Wessler et al., 1999; Deshmukh et al., 2013). Additionally, previous studies have disclosed the presence of multiple subtypes of nAChRs in OPCs, localized in regions including the hippocampus and corpus callosum, which exert an impact on OPCs differentiation (Velez-Fort et al., 2009; Imamura et al., 2015; Imamura et al., 2020). The cholinergic anti-inflammatory system regulates internal immunological homeostasis and excessive immune inflammatory responses. Demyelination disorders have been found to exhibit defects in the anti-inflammatory signaling pathways of Ach that are mediated by nAChRs. The study conducted by Piovesana et al. demonstrated that applying of an acetylcholinesterase inhibitor resulted in the relief of neuroinflammation and demyelination induced by Experimental Autoimmune Encephalomyelitis (EAE), as well as an improvement in cognitive behavior deficits (Piovesana et al., 2022). Correspondingly, this neuroprotective effect was diminished by the treatment of α7nAChR antagonists. Nicotine administration or the use of nAChR α9/α10 knockout mice greatly decreased the severity of EAE and postponed the onset of disease symptoms. This study also revealed a decrease in immune cell infiltration, reactive oxygen species levels, and demyelination in the spinal cord and brain of nAChR α9/α10 knockout mice, indicating that nAChRs may play immunomodulatory roles in autoimmune demyelinating disorders (Liu et al., 2019). In addition, a non-selective antimuscarinic drug prevented demyelination-related schizophrenia-like behavior in a cuprizone mouse model and recovered myelin repair (Li et al., 2015). Through its specific actions on mAChR of OPCs, antimuscarinic effects dramatically aided OPCs differentiation and myelin production, reduced ultrastructural myelin degradation, and improved functional recovery after hypoxic brain injury (Cree et al., 2018).

Acetylcholinesterase inhibitors have been shown to improve the myelin regeneration in demyelination diseases, including MS and its animal models. Imamura et al. showed that employing the acetylcholinesterase inhibitor donepezil pharmacologically improves differentiation and maturation of OPCs derived from neural stem cells without affecting their proliferation or survival (Imamura et al., 2015; Imamura et al., 2017). The administration of donepezil resulted in a significant upregulation of critical proteins associated with myelin, such as MAG, Myelin proteolipid protein (PLP), and MBP. The promotion of OPCs maturation by donepezil was obviously inhibited by the nAChR antagonist Mecamylamine. However, a recent study demonstrated that inhibiting the cholinergic signaling pathways might reduce the speed of myelin conduction and myelin thickness in the corpus callosum, leading to the failure of myelin synthesis (Palma et al., 2022). The preexisting data is consistent with the involvement of cholinergic signaling pathways in cognitive dysfunction and demyelination-related white matter diseases. Regulation of cholinergic signaling pathways may offer possible therapeutic treatments to promote myelin regeneration and white matter recovery, but there is still debate in this field.

2.4 Molecular mechanisms of histaminergic signaling pathways

Histamine is a pervasive inflammatory mediator implicated in the pathophysiology of diverse allergy, autoimmune, inflammatory, and neurological disorders (Hu and Chen, 2017; Volonte et al., 2022). Histamine signaling has been reported to regulate the differentiation of OPCs, attenuate demyelination, and improve myelin repair, particularly in MS (Panula and Nuutinen, 2013; Jiang et al., 2021a; Amadio et al., 2022). The effects of histaminergic signaling have been noted to be both beneficial and detrimental through its immunomodulatory properties or direct regulation of histaminergic H1-H4 receptors in MS (Passani and Blandina, 2011; Passani and Ballerini, 2012; Palma et al., 2022). Histamine has the potential to alter the permeability of the blood-brain barrier and increase the number of infiltrating cells in the central nervous system, resulting in detrimental neuroinflammation (Volonte et al., 2022). In EAE model mice, the H1 receptors have the potential to speed up the occurrence of immunological inflammation, demyelination, and behavioral abnormalities (Ma et al., 2002). The most recent research found that H2 receptors, like H1 receptors, has a pro-pathogenic effect through decreasing OPCs maturation following hypoxic brain injury (Jiang et al., 2021a). H2 receptors also exhibited a neuroprotective effect by attenuating demyelination, but it also induced a positive suppression of the immunological inflammatory response (Saligrama et al., 2014). The H3 receptors act as an auto-receptor, modulating the activity of histaminergic neurons and regulating the synthesis and secretion of histamine (Passani and Blandina, 2011). The application of the highly selective histamine H3 receptor agonist Immethridine slowed the progression of the

disease by reducing the expression of inflammatory cytokines such as TNFα and IFN-γ in an EAE model (Teuscher et al., 2007; Shi et al., 2017). Recent researches using methylene amine and two novel piperidine compounds as histamine H3 receptor antagonists validated the beneficial effects of MS treatment (Imeri et al., 2021). In accordance with the conclusions, demyelination, inflammatory infiltration, and the EAE clinical score were all decreased. Moreover, H4 receptors have a neuroprotective effect comparable to that of H3 receptors. H4 receptors deletion or use of the H4 receptors antagonist JNJ7777120 led to increased spinal cord inflammation and IFN- levels, which hindered remyelination (Ballerini et al., 2013; Volonte et al., 2022).

Histidine decarboxylase (HDC) is capable of regulating histaminergic signaling pathways and the release of endogenous histamine. Musio et al. showed that endogenous histamine has an inhibitory effect on immunological damage and myelin breakdown in the central nervous system, promoting the therapeutic efficacy of EAE (Musio et al., 2006). Histamine-deficient HDC knockout mice exhibited more severe neuropathy and EAE symptoms. The transcription of genes associated with oligodendrocytes and myelin production in the basal ganglia was altered in HDC knockout mice with defective histaminergic signaling pathways, which resulted in white matter damage and abnormal mental states (Saligrama et al., 2013). A first-generation antihistamine, Clemastine, showed benefits in promoting oligodendrocyte differentiation and has been evaluated as a remyelinating therapy for multiple sclerosis in clinical trials (Green et al., 2017). The detailed information on Clemastine is in Part 3.5. Serum levels of histamine and its precursor histidine were lower in MS patients than in healthy individuals, especially in women with clinically significant symptoms, indicating that histaminergic signaling pathways play a significant role in MS-related symptoms (Rafiee Zadeh et al., 2018; Loy et al., 2019). Nevertheless, an inverse correlation between histamine levels in the central nervous system and serum has been observed in MS patients by other investigators (Cacabelos et al., 2016a; Cacabelos et al., 2016b). Therefore, additional research is required to elucidate the specific roles of histamine and histaminergic signaling pathways.

2.5 Molecular mechanisms of purinergic signaling pathways

Purinergic signaling pathways have been shown to influence oligodendrocyte growth, myelin formation, and remyelination in both healthy and pathological conditions (Rivera et al., 2016; Butt et al., 2019). Adenosine and ATP are acknowledged as immune function modulators, functioning as activators and chemotactic signals for diverse immune cells (Welsh and Kucenas, 2018). Purines serve as neurotransmitters and facilitate the transmission of neural signals through the activation of purinergic receptors. Oligodendrocytes predominantly express adenosine-binding P1 receptors and ATP- and ADP-binding P2 receptors (Cheng et al., 2023). P1 receptors are subdivided into four distinct types, namely, A1, A2a, A2b, and A3, all of which are G protein-coupled receptors. A1 and A3 exert inhibitory effects on adenylate cyclase, resulting in a reduction of intracellular cyclic adenosine monophosphate (cAMP) levels. Conversely, A2a and A2b

stimulate adenylate cyclase, leading to an elevation in intracellular cAMP concentrations (Welsh and Kucenas, 2018). P2 receptors are classified into ionotropic P2X (P2X1-7) or metabotropic P2Y(P2Y1, P2Y2, P2Y4, P2Y6, and P2Y11-14) subtypes.

Adenosine is involved in the regulation of OPCs development through a dual mechanism. The administration of adenosine and the P1 receptor agonist NECA in co-cultures of OPC-DRG cells exhibited a notable reduction in OPC proliferation in a concentration-dependent manner, while concurrently promoting OPC differentiation and myelin regeneration (Stevens et al., 2002; Welsh and Kucenas, 2018). However, recent studies have reported that the maturation of OPCs can be hindered by A2a receptor and A2b receptor agonists through the inhibition of potassium currents, whereas cell proliferation is unaffected (Coppi et al., 2013; Coppi et al., 2020; Cherchi et al., 2021b). Adenosine is frequently thought to have a protective effect in white matter disease models. Several studies have indicated that the absence of A1 receptors and A2a receptors in mice can intensify white matter damage in EAE models because of the anti-inflammatory properties of adenosine on immune cells and microglia (Tsutsui et al., 2004; Yao et al., 2012; Welsh and Kucenas, 2018). The mechanism of these neuroprotective effects may be attributed to immunomodulation. Contrary to the newborn rat brain hypoxia model, however, treatment with A1 receptor agonists reduces the volume of white matter, causes ventricular enlargement, and lowers MBP expression (Cherchi et al., 2021b). Furthermore, an additional research group has disclosed that the activation of A3 receptors by adenosine may induce oligodendrocyte apoptosis in optic nerve and white matter ischemic injury (Gonzalez-Fernandez et al., 2014). The diverse functions of adenosine on oligodendrocytes and immune cells under distinct pathophysiological conditions are essential for the treatment of demyelination diseases.

P2X7 receptors are the purinergic receptors that have been investigated the most. According to available research, high levels of ATP that constantly activate P2X7 receptors in oligodendrocytes cause oligodendrocyte death and myelin loss in demyelination disorders *in vivo* (Illes, 2020). In addition, P2X7 receptor antagonists were noted to be very effective in preventing oligodendrocyte apoptosis and to be implicated in the modulation of white matter injury in cerebral ischemia (Domercq et al., 2010). In a clinical study, Oyanguren-Desez et al. discovered a gain-of-function mutation of the P2X7 receptors in patients with multiple sclerosis (Oyanguren-Desez et al., 2011). This mutation resulted in an elevated inward flow of cytotoxic calcium. P2X7 receptors were also found to be overexpressed in the brains of patients with white matter atrophy and myelin loss compared to healthy controls (Rivera et al., 2021). Nonetheless, since many neuronal cells and immune cells in the periphery express P2X7 receptors, the effects of P2X7 receptor antagonists cannot be ascribed to direct effects on oligodendrocytes or immunomodulation.

Moreover, changes in the expression of P2Y2 and P2Y12 receptors on oligodendrocytes were seen in the demyelination models, but it is yet unknown if these changes have beneficial or detrimental consequences on myelin (Amadio et al., 2010; Welsh and Kucenas, 2018; Cherchi et al., 2021a).

2.6 Molecular mechanisms of voltage-gated channels

Different voltage-gated ion channels are expressed by OPCs in gray and white matter. These include voltage-gated K^+ channels, Na^+ channels, and Ca^{2+} channels that regulate the OPCs cell cycle and function (Liu et al., 2021). Overexpression of K^+ channel protein subunits Kir4.1 and Kv1.3 stimulated OPCs proliferation *in vitro*, whereas overexpression of Kv1.6 inhibited mitogen-induced cell cycle progression, indicating the involvement of K^+ channels in regulating OPCs proliferation (Larson et al., 2016). Kir4.1 modulated OPCs proliferation and differentiation in response to extracellular K^+ variations during neuronal activity (Maldonado et al., 2013). Increased extracellular membrane K^+ levels activated Kir4.1 channels in OPCs, which could speed up their proliferation and remyelination following ischemic cerebral injury (Song et al., 2018). Correspondingly, Kir4.1 channel defects in OPCs aggravated myelin protein loss and sheath ultrastructure disruption. Kv1.3, an additional prevalent voltage-gated K^+ channel on oligodendrocytes, displayed higher levels of expression in an inflammatory model of myelin injury induced by Interleukin 17 *in vitro* and *in vivo* experiments (Liu et al., 2021). Interleukin 17 accelerated myelin damage by altering Kv1.3 currents and blocking AKT phosphorylation, thereby inhibiting OPCs proliferation and differentiation. The preceding findings suggest that K^+ channels may be a potential intervention target for myelin impairment.

The function of the Na^+ channel remains uncertain. Tong et al. provided evidence that GABA induces activation of GABAA receptors, which in turn causes a sustained elevation of Na^+ currents in the OPCs, resulting in Ca^{2+} influx via the $Na^+/Ca2^+$ exchanger. This particular Ca^{2+} signaling pathway was linked to OPCs migration and myelination (Tong et al., 2009). GABA and glutamate transmitters are released by neurons, activating AMPA and GABA receptors in the OPCs. Sun and colleagues found that activation of the majority of AMPA and GABA receptors is correlated with an increase in intracellular Ca^{2+} signaling (Sun et al., 2016). With Ca^{2+} signaling pathways, these activated receptors communicate with neurons and OPCs to generate myelin sheaths (Li et al., 2020). The frequency of the Ca^{2+} signal transient was found to correspond with the extension of the myelin sheath when it was caused by high-frequency stimulation (Baraban et al., 2018; Krasnow et al., 2018). In contrast, low-frequency stimulation and less Ca^{2+} release shorten the myelin sheath. In a cuprizone demyelination model, animals with a specific deletion of Ca^{2+} channel subtype Cav1.2 on OPCs suffered remyelination disorder (Santiago Gonzalez et al., 2017). Cav1.2 defective mice revealed a reduction in OPCs number, myelin proteins MBP synthesis, myelinated axons, and myelin thickness, which indicated that Ca^{2+}singaling activation and Ca^{2+} inflow of OPCs were needed for myelin repair (Paez and Lyons, 2020). On the whole, the modulation of voltage-gated ion channels expression and activity is a promising therapeutic strategy for promoting OPCs proliferation and differentiation and improving remyelination after injury.

Along with the aforementioned neural signaling pathways, small-molecule agents like Phosphodiesterase 7(PDE7) inhibitors can also improve myelination and remyelination by affecting neuronal activity and immunomodulation (Huang et al., 2023). The study conducted by Zorn and Baillie et al. found that increased PDE7 expression and a subsequent decrease in cAMP levels were substantially correlated with MS disease development and symptoms in animal models (Zorn and Baillie, 2023). PDE7 inhibitors VP1.15 and VP3.15 enhanced motor function and alleviated demyelination and disease pathology in EAE, cuprizone, and LPC-induced demyelination models by increasing intracellular cAMP and reducing pro-inflammatory cytokines (Martin-Alvarez et al., 2017; Medina-Rodriguez et al., 2017). PDE7 inhibitors have also been demonstrated in *ex vivo* studies to prevent neuronal degeneration, encourage OPCs survival, differentiation, and remyelination (Medina-Rodriguez et al., 2013; Zorn and Baillie, 2023). Therefore, in the future, treating demyelination diseases by targeting PDE7 might be an innovative strategy.

3 Translational approaches and drugs

Modulation of neuronal signaling pathways that directly impacts on neuronal activity could promote OPC survival, proliferation, and differentiation, thus making neuronal activity as a potent extrinsic regulator of remyelination in demyelination disease. Neuronal activity can be modulated by invasive way such as deep brain stimulation (DBS) and noninvasive ways like repetitive rTMS, TUS and behavioral training (Darmani et al., 2022). In addition to directly stimulating neuronal activity, alternative pathways can be sought, such as medicines that modulated neuronal axonal signaling during OPCs differentiation and remyelination.

3.1 DBS

Currently, DBS has been FDA-approved for the treatment of several conditions, including Parkinson's disease, dystonia, essential tremor, obsessive-compulsive disorder, and medically refractory epilepsy. Although the underlying mechanisms were largely unknown, DBS was well tolerated and improved the mean tremor rating scale scores of multiple sclerosis patients at 6 months (Oliveria et al., 2017). Memory and cognitive ability are dependent on regulating the fornix, a white matter tract in the Papez circuit. Lee et al. have conducted clinical trials in phases 1 and 2, which focus on fornical DBS as a treatment for disorders of the nervous system and schizophrenia that involve white matter (Lee et al., 2019). However, invasive methods of brain stimulation may result in lesions of the white matter and an impairment in verbal fluency (Costentin et al., 2019).

3.2 rTMS

It is reported that low intensity rTMS in an intermittent theta burst stimulation pattern upregulated oligodendrocytes survival and promoted myelination. Four weeks of daily rTMS has been demonstrated to enhance oligodendrocyte myelination in both healthy adult mice and demyelinated mice, while also reducing

depression-like symptoms and facilitating cognitive recovery in demyelinated mice (Cullen et al., 2019; Wang et al., 2021; Mooshekhian et al., 2022). Recently, a randomized controlled trial has been conducted to assess the safety and remyelination in multiple sclerosis patients (Makowiecki et al., 2022). But not only neuronal cells were affected by magnetic stimulation, glial progenitor cells could also be influenced directly. Gamma frequency low-field magnetic stimulation daily for five consecutive days *in vitro* was reported to promote the differentiation of OPCs (Dolgova et al., 2021). The underlying molecular mechanism of remyelination has been linked to elevated brain-derived neurotrophic factor (BDNF) levels and decreased Interleukin-1 beta (IL-1β) and Tumor necrosis factor alpha (TNF-α) levels during rTMS treatment (Zhao et al., 2019).

3.3 TUS

Ultrasound treatment was demonstrated to enhance remyelination in the LPC-induced demyelination model of MS by alleviating neuroinflammation, enhancing mature oligodendrocyte density, and promoting BDNF expression (Yang et al., 2022). TUS has higher spatial resolution and deeper penetration, which can induce short-term and long-term changes in neuronal excitability and spontaneous firing rates. Also, it has the ability to selectively target small subcortical structures compared to other non-invasive stimulation methods (Darmani et al., 2022). Another advantage of TUS is that it can be safely combined with MRI-related neuroimaging techniques such as diffusion tensor imaging, which could reflect the effects of TUS treatment on white matter fiber tracts. In all, it seems that TUS could serve as a potential treatment for demyelinated disorders that needs modulation of neuronal activity. But TUS is still in the research stage, and further clinical trials are needed to evaluate its safety and efficacy (Darmani et al., 2022).

3.4 Physical activity and motor learning

Motor learning, the progressive acquisition of a specific novel motor skill, showed influences on adaptive myelin formation in both the healthy and demyelinated central nervous system. While physical activity, a planned, structured, and repetitive movement of the body that expends energy and improves one's fitness, could promote remyelination of the nervous system pathological process (Bloom et al., 2022). White matter integrity affects cognitive performance, and conversely, behavioral training could also promote white matter regeneration. Behavior-induced neuronal activity could have influences on circuit-specific changes in myelination (Bacmeister et al., 2022). Exercise and motor skills training contribute to remyelination. It has been reported that precisely timed motor learning following the commencement of remyelination enhances remyelination from newly generated and persisting oligodendrocytes, improving recovery from demyelinating injury (Bacmeister et al., 2020). In the LPC or cuprizone model of demyelination, voluntary exercise may inhibit demyelination or encourage remyelination (Jensen et al., 2018;

Mandolesi et al., 2019). And physical exercise was also reported to have an influence on astrocytes polarization, which facilitated the clearance of myelin debris and promoted remyelination (Jiang et al., 2021b). Therefore, individualized behavioral therapies are being employed more frequently in clinical settings to improve motor function in myelin disease patients.

3.5 Clemastine

It has been demonstrated that Clemastine, a first-generation antihistamine and M1/M3 muscarinic receptor antagonist, may stimulate OPCs development and remyelination *in vitro*, in several myelin degeneration models, and in human cells (Li et al., 2015; Liu et al., 2016; Tong et al., 2022). In a randomized, controlled, double-blind, crossover trial, it was evaluated as a remyelinating therapy for multiple sclerosis. The trial was carried out in a single center and encompassed a cohort of 50 patients with relapsing multiple sclerosis with chronic demyelinating optic neuropathy on stable immunomodulatory therapy. The administration of Clemastine resulted in a reduction of the latency delay by 1.7 ms/eye, when the trial was analyzed as a crossover. Treatment with Clemastine was linked to fatigue, but no significant adverse events were observed. The findings revealed that myelin repair is possible even in the presence of extensive injury (Green et al., 2017).

3.6 GSK239512

H3 receptors are highly expressed in the presynaptic region of neurons containing histamine, and moderately expressed in oligodendrocytes (Chen et al., 2017). It can directly regulate the synthesis and release of neurotransmitters in the central nervous system, which are important for processes of cognition, sleep, and homoeostatic neuronal regulation. GSK239512 is a highly effective and capable H3 receptor antagonist/inverse agonist. It has been specifically designed for the purpose of addressing cognitive impairment in neurological disorders, as increasing acetylcholine release could be one mechanism (Wilson et al., 2013). GSK239512 is a highly effective and capable H3 receptor antagonist/inverse agonist that has been specifically designed for the purpose of addressing cognitive impairment in neurological disorders. The benefits of the treatment for patients diagnosed with relapsing-remitting multiple sclerosis were evaluated through a clinical trial. The trial was conducted in a single center and involved 131 patients with relapsing-remitting multiple sclerosis on stable immunomodulatory therapy. The primary outcome was normalization of magnetization transfer ratio (MTR) changes in gadolinium-enhancing and Delta-MTR lesions. The outcome showed GSK239512 treatment was associated with a modest yet favorable impact on remyelination (Schwartzbach et al., 2017; Wooliscroft et al., 2019). However, we cannot rule out the possibility that GSK239512 could directly act on oligodendrocytes. Because it has been demonstrated that H3R antagonists can accelerate the differentiation of isolated OPCs *in vitro* (Chen et al., 2017).

4 Conclusion

Remyelination occurs in various clinical disorders, but it does not contribute to full functional recovery. Several clinical trials have been conducted to enhance remyelination, but they have been unsatisfactory (Lubetzki et al., 2020). Recent evidence suggests that increased myelin formation and remyelination can be stimulated by neuronal activity, which can aid in the development of therapeutic strategies for demyelination diseases (Maas and Angulo, 2021). Pharmacological blockade of neuronal activity impairs myelin regeneration, while non-invasive methods for controlling neuronal activity encourage OPC survival and differentiation, aiding myelin repair and cognitive function restoration (Darmani et al., 2022).

OPCs development, myelin formation, and remyelination depend on glutamatergic signaling pathways. The synaptic connections between glutamatergic neurons and OPCs positively influence remyelination by regulating the expression of AMPA and NMDA receptors on OPCs. AMPA receptors exhibit significant effects on the later stages of myelin regeneration, while NMDA receptors are essential for accelerating and improving myelin formation (Gautier et al., 2015; Chen et al., 2018). However, the effects of NMDA receptors on myelin and axonal structures are conflicting, and further studies are necessary to ascertain their beneficial effects on remyelination (Christensen et al., 2016).

GABAergic signaling pathways refer to the regulation of cells in the brain known as OPCs. The GABAA receptor-mediated signaling pathways obstruct myelin synthesis, their impacts on myelination may alter due to normal and pathological circumstances (Zonouzi et al., 2015). GABAB receptors also play an important role in regulating myelin synthesis and remyelination, as evidenced by studies using GABAB receptor antagonists and agonists (Pudasaini et al., 2022; Serrano-Regal et al., 2022). Furthermore, lower levels of GABA in patient brains with neurodegenerative diseases involving demyelination suggest the importance of regulating GABAergic signaling pathways for prevention (Cawley et al., 2015).

The involvement of ACh in myelin formation and remyelination has been extensively studied, and the activation of cholinergic signaling pathways mediated by ACh receptors affect the development and function of oligodendrocytes. Myelin regeneration and OPC differentiation are inhibited by muscarinic signaling, whereas nicotinic signaling boosts OPC maturation (Imamura et al., 2020; Piovesana et al., 2022).

Histamine has been found to regulate the differentiation of OPCs and attenuate demyelination, leading to improved myelin repair. Activation or inhibition of histaminergic H1-H4 receptors can result in different effects on demyelination and immunological inflammation (Piovesana et al., 2022). Histaminergic signaling pathways contribute to MS-related symptoms, as MS patients have lower serum histamine and histidine levels than healthy people (Rafiee Zadeh et al., 2018; Loy et al., 2019).

Purinergic signaling pathways influence oligodendrocytes development, myelin formation, and remyelination in both healthy and pathological conditions. Purines act as neurotransmitters, while adenosine and ATP regulate the immune response. Oligodendrocytes express P1 and P2 receptors, which regulate OPCs development through a dual mechanism (Welsh and Kucenas, 2018; Cherchi et al., 2021b). Adenosine has a protective effect in white matter

disease models, and its anti-inflammatory properties may be attributed to immunomodulation (Coppi et al., 2013; Coppi et al., 2020). P2X7 receptors are the most investigated purinergic receptors, and their effects on oligodendrocyte death and myelin loss can't be traced back to direct effects on oligodendrocytes or changes in the immune system (Illes, 2020).

Voltage-gated ion channels in OPCs influence the cell cycle and remyelination. Kir4.1 and Kv1.3 overexpression promote OPCs proliferation and myelination regeneration, but Kv1.6 inhibits it (Song et al., 2018; Liu et al., 2021). Myelin repair also requires Cav1.2 activation and Ca^{2+} signal transients. Modulation of voltage-gated ion channels may improve OPC proliferation and remyelination following damage (Paez and Lyons, 2020).

Modulating neuronal activity can promote remyelination in demyelination disease, using invasive methods like DBS or noninvasive methods like rTMS, TUS, as well as physical activity and motor learning. In therapeutic settings, individualized behavioral therapies are utilized to improve motor function in myelin disease patients (Makowiecki et al., 2022). Except for rTMS and TUS, the underlying molecular mechanisms of exercise have also been linked to the increased expression of BDNF (Wrann et al., 2013). BDNF, a member of the neurotrophic family, was demonstrated to impact oligodendrocyte lineage cells throughout development (Vondran et al., 2010). Lack of BDNF restricted proliferation and differentiation of OPC in the demyelination model (VonDran et al., 2011; Fulmer et al., 2014; Tsiperson et al., 2015). And several studies revealed that MS patients have lower levels of BDNF in their serum or cerebrospinal fluid (Azoulay et al., 2005; Azoulay et al., 2008). BDNF could also alleviate neuroinflammation by downregulating Cyclooxygenase-2 (COX-2) and pro-inflammatory cytokines in microglia (Lai et al., 2018; Nociti and Romozzi, 2023). In clinical trials for the treatment of multiple sclerosis, Clemastine and GSK239512 have demonstrated encouraging results in increasing myelination (Wooliscroft et al., 2019; Tong et al., 2022). To evaluate the effectiveness and safety of these techniques, nevertheless, more studies and trials are required.

These recent investigations have emphasized the potential of neuronal activity to promote myelin synthesis and repair. The use of optogenetics and chemogenetics to modulate neuronal activity possesses high cellular selectivity and exact spatiotemporal responses, allowing for the precise excitation or inhibition of specific neurons (Deisseroth, 2015; Roth, 2016). Non-invasive techniques, including DBS, rTMS, and TUS, offer potential avenues for clinical translation as new therapeutic strategies for demyelination diseases (Darmani et al., 2022). In contrast to pharmacological methods directly manipulating oligodendrocytes, a novel mechanism of action promotes the establishment of functional synaptic connections between OPCs and neurons by precisely modulating neuronal circuits (Etxeberria et al., 2010; Sahel et al., 2015; Zhou et al., 2022). The interaction between neurons and oligodendrocytes is increasingly recognized as one of the essential components of remyelination.

In this review, we emphasize the need for further research to develop effective therapeutic strategies for enhancing remyelination and neuroprotection associated with demyelination. We focus on recent developments in neuronal activity and remyelination, as well as their associated molecule mechanisms of neural signaling pathways and advanced clinical methods, which may potentially

contribute to the development of therapeutic approaches for demyelination diseases.

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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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