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Who plays the strings in newborn analgesia at birth, vasopressin or oxytocin?

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For many years, oxytocin has been viewed as the primary hormone edging endocrinology, behavior, and pain in mothers and infants around parturition. Very recent work puts the vasopressin receptor 1A in the focus of peripheral analgesia and pain relief in respect to circulating vasopressin and oxytocin. Here, we present a concise overview on these new findings, will discuss them in context of parturition, and will outline new avenues.

Both neuropeptides, oxytocin and vasopressin, are synthesized in the hypothalamus from paraventricular and supraoptic nuclei and act either centrally within the brain or peripherally after release by the posterior pituitary gland (Meyer-Lindenberg et al., 2011). In mammals, four receptors have been identified, the oxytocin receptor (OTR) and three receptors that respond primarily to vasopressin, vasopressin receptor 1A (VR1A), VR1B, and VR2. Whereas VR1A and VR2 mediate the vasoactive and antidiuretic action, respectively, in the periphery, central vasopressin functions are mediated by VR1A, VR1B, and OTR. Ligand binding of both centrally acting receptors, OTR and VR1A, activates the phospholipase C beta signal transduction pathway (Jard et al., 1986; Arnaudeau et al., 1994; Ku et al., 1995; Phaneuf et al., 1995). Both the soluble ligands, oxytocin and vasopressin, as well as their receptors, OTR and VR1A, display high sequence homology, hence both ligands can activate both receptors (Chini and Manning, 2007).

In contrast to humans, the development of paraventricular and supraoptic nuclei is late in rodents (Clancy et al., 2001). Synthesis of vasopressin in rats starts between the 16th and 18th day of intrauterine life and that of oxytocin few days after birth (Lipari et al., 2001). As the placenta of rodents is freely passable for both neuropeptides, the newborn rodent oxytocin is mainly provided by the mother. On the contrary, fetal human oxytocin at birth is of fetal origin, because its concentrations are higher in the umbilical artery than in the umbilical vein, and oxytocin is completely absent in cord blood of anencephalic newborns (Chard et al., 1971).

Parturition is a very complex process and oxytocin has its role particularly in contractility of myocytes (Smith, 2007). Exogenous oxytocin administration to pregnant woman strongly induces contractions (Mori et al., 2011) but plasma oxytocin does not cross placenta toward the fetus (Chard et al., 1971; Patient et al., 1999). However, by use of an *in vitro* system with dually perfused isolated cotyledons from term human placenta, bi-directional diffusion of oxytocin has been demonstrated across the maternal-fetal barrier (Malek et al., 1996). Fetal oxytocin concentrations have been found to be either unaffected by vaginal delivery, contractions, and by experimental hypoxic stress (Stegner et al., 1984; Thornton et al., 1993; Patient et al., 1999) or slightly increased (1.5- to 2-fold) in umbilical cord blood after vaginal delivery as compared to elective cesarean section (Marchini et al., 1988; Lindow et al., 1998). Hence, fetal oxytocin release is not subject to birth stress and even if there is some crossing of the maternal-fetal barrier, fetal oxytocin levels are barely altered. This is in sharp contrast to what has been observed for vasopressin. During vaginal delivery, there is an extremely steep rise of circulating vasopressin which is unparalleled by any changes that may occur during the life span of a human being (Chard et al., 1971; Polin et al., 1977; Wellmann et al., 2010; Benzing et al., 2011; Schlapbach et al., 2011). The exceptional surge of circulating vasopressin (approximately 100-fold) is observed in infants born by vaginal delivery but not those born by elective cesarean section.

A perpetually growing body of literature within the last four decades demonstrate analgesic effects in human and rodents of both, oxytocin and vasopressin (Honda and Takano, 2009; Koshimizu and Tsujimoto, 2009; Schorscher-Petcu et al., 2010). Oxytocin was reported to be analgesic when administered into the brain (Ge et al., 2002; Gao and Yu, 2004), the spinal cord (Yu et al., 2003; Miranda-Cardenas et al., 2006; Condes-Lara et al., 2007), or systemically (Lundeberg et al., 1994; Reeta et al., 2006). Very recently, oxytocin was investigated in newborn Wistar rats in the tail-flick pain assay and the vocalization assay of decerebrated newborn pups (Mazzuca et al., 2011). Whereas systemically (intraperitoneally) administered oxytocin was found to augment newborn rat analgesia, while two OTR antagonists, atosiban and SSR126768A, delivered via the same route lowered analgesia (Mazzuca et al., 2011). This is of interest as there is clinical evidence of stress-induced analgesia in spontaneously delivered newborn infants (Bergqvist et al., 2009). It was concluded, that the same hormone (oxytocin) that triggers delivery also acts as a natural pain killer in the fetus at birth (Mazzuca et al., 2011). Of note, the OTR antagonist atosiban employed in these experiments bind more readily to VR1A than to OTR (Akerlund et al., 1999) whereas SSR126768A is more OTR specific (Serradeil-Le Gal et al., 2004).

However, also very recently, elegant experiments with transgenic mice lacking the OTR or VR1A clearly demonstrated the indispensable prerequisite of VR1A for oxytocin-induced analgesia, at least at the peripheral level (Schorscher-Petcu et al., 2010). Systemically administered oxytocin was found to produce robust, dose-dependent analgesia in OTR KO mice but not in VR1A KO mice in a battery of thermal, mechanical, and chemical

nociception assays (Schorscher-Petcu et al., 2010). In addition, the analgesic effects of oxytocin could be fully prevented by a VR1A-selective antagonist, but not by an OTR-selective antagonist at the peripheral level (Schorscher-Petcu et al., 2010).

It is tempting to reinterpret the results of Mazzuca et al. (2011) in the light of the results from transgenic mice (Schorscher-Petcu et al., 2010). In both studies analgesia was studied at the peripheral level, the drugs were administered the same route, intraperitoneally. But there are many disparities between the studies of Mazzuca et al. (2011) and Schorscher-Petcu et al. (2010), including the species applied, rats vs. mice, the different ages, newborn pubs vs. adults, the different pain assays, and the different OTR antagonists, atosiban (Akerlund et al., 1999), and SSR126768A (Serradeil-Le Gal et al., 2004) vs. desGly-NH_2-D$(CH_2)_5$[D-Tyr^2,Thr^4]OVT (Manning et al., 1995), respectively. In processing analgesia the spinal cord is an important switching point. There is convincing evidence from rat studies that the pain-relevant laminae of the dorsal horn express the OTR (Reiter et al., 1994; Tribollet et al., 1997; Veronneau-Longueville et al., 1999) and are a likely target of spinal oxytocin-ergic projections from the PVN of the hypothalamus (Swanson and Kuypers, 1980; Puder and Papka, 2001; Condes-Lara et al., 2007). Schorscher-Petcu et al. (2010) demonstrated a similar distribution of OTR and VR1A in mice and rats by an autoradiographic study on spinal cord sections, suggesting that at the spinal level no species differences exist. However it is not known, whether this receptor distribution is subject to developmental changes from birth to adulthood.

In order to verify the involvement of vasopressin-VR1A-signaling in mediating analgesia in newborn pubs, new studies are warranted. But it has to be considered that the involvement of vasopressin and VR1A in analgesia is even more complex. Recently it was shown in mice and men that pain sensitivity and vasopressin analgesia are mediated by a gene-sex-environment interaction (Mogil et al., 2011). Vasopressin mediated analgesia was ameliorated in subjects with preceding stress-induced analgesia and in those harboring a nucleotide polymorphism in the gene coding for VR1A, which is male-specific (Mogil et al., 2011).

In conclusion, we propose in human newborns a much stronger involvement of vasopressin and VR1A in mediating analgesia than noted so far based on the following reasons: First, no exchange of vasopressin or oxytocin across placenta was demonstrated in humans *in vivo*. Second, human fetuses independently produce both hormones and toward the end of gestation there is marked increase in the vasopressin/oxytocin ratio in the pituitary (Schubert et al., 1981). Third, normal vaginal delivery evokes a dramatic surge in vasopressin and if at all only a minor increase in fetal oxytocin concentrations. Fourth, the VR1A receptor appears to be central in vasopressin- and oxytocin-induced analgesia, but featured with much greater affinity for vasopressin than oxytocin.

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REFERENCES

Akerlund, M., Bossmar, T., Brouard, R., Kostrzewska, A., Laudanski, T., Lemancewicz, A., Serradeil-Le Gal, C., and Steinwall, M. (1999). Receptor binding of oxytocin and vasopressin antagonists and inhibitory effects on 0isolated myometrium from preterm and term pregnant women. *Br. J. Obstet. Gynaecol.* 106, 1047–1053.

Arnaudeau, S., Lepretre, N., and Mironneau, J. (1994). Chloride and monovalent ion-selective cation currents activated by oxytocin in pregnant rat myometrial cells. *Am. J. Obstet. Gynecol.* 171, 491–501.

Benzing, J., Wellmann, S., Achini, F., Letzner, J., Burkhardt, T., Beinder, E., Morgenthaler, N. G., Haagen, U., Bucher, H. U., Buhrer, C., Lapaire, O., and Szinnai, G. (2011). Plasma copeptin in preterm infants: a highly sensitive marker of fetal and neonatal stress. *J. Clin. Endocrinol. Metab.* 96, E982–E985.

Bergqvist, L. L., Katz-Salamon, M., Hertegard, S., Anand, K. J., and Lagercrantz, H. (2009). Mode of delivery modulates physiological and behavioral responses to neonatal pain. *J. Perinatol.* 29, 44–50.

Chard, T., Hudson, C. N., Edwards, C. R., and Boyd, N. R. (1971). Release of oxytocin and vasopressin by the human foetus during labour. *Nature* 234, 352–354.

Chini, B., and Manning, M. (2007). Agonist selectivity in the oxytocin/vasopressin receptor family: new insights and challenges. *Biochem. Soc. Trans.* 35, 737–741.

Clancy, B., Darlington, R. B., and Finlay, B. L. (2001). Translating developmental time across mammalian species. *Neuroscience* 105, 7–17.

Condes-Lara, M., Martinez-Lorenzana, G., Rojas-Piloni, G., and Rodriguez-Jimenez, J. (2007). Branched oxytocinergic innervations from the paraventricular hypothalamic nuclei to superficial layers in the spinal cord. *Brain Res.* 1160, 20–29.

Gao, L., and Yu, L. C. (2004). Involvement of opioid receptors in the oxytocin-induced antinociception in the central nervous system of rats. *Regul. Pept.* 120, 53–58.

Ge, Y., Lundeberg, T., and Yu, L. C. (2002). Blockade effect of mu and kappa opioid antagonists on the antinociception induced by intra-periaqueductal grey injection of oxytocin in rats. *Brain Res.* 927, 204–207.

Honda, K., and Takano, Y. (2009). New topics in vasopressin receptors and approach to novel drugs: involvement of vasopressin V1a and V1b receptors in nociceptive responses and morphine-induced effects. *J. Pharmacol. Sci.* 109, 38–43.

Jard, S., Gaillard, R. C., Guillon, G., Marie, J., Schoenenberg, P., Muller, A. F., Manning, M., and Sawyer, W. H. (1986). Vasopressin antagonists allow demonstration of a novel type of vasopressin receptor in the rat adenohypophysis. *Mol. Pharmacol.* 30, 171–177.

Koshimizu, T. A., and Tsujimoto, G. (2009). New topics in vasopressin receptors and approach to novel drugs: vasopressin and pain perception. *J. Pharmacol. Sci.* 109, 33–37.

Ku, C. Y., Qian, A., Wen, Y., Anwer, K., and Sanborn, B. M. (1995). Oxytocin stimulates myometrial guanosine triphosphatase and phospholipase-C activities via coupling to G alpha q/11. *Endocrinology* 136, 1509–1515.

Lindow, S. W., Hendricks, M. S., Thompson, J. W., and van der Spuy, Z. M. (1998). Effects of morphine administration on the fetal production of oxytocin in labour. *Clin. Sci.* 95, 91–95.

Lipari, E. F., Lipari, D., Gerbino, A., Di Liberto, D., Bellafiore, M., Catalano, M., and Valentino, B. (2001). The hypothalamic magnocellular neurosecretory system in developing rats. *Eur. J. Histochem.* 45, 163–168.

Lundeberg, T., Uvnas-Moberg, K., Agren, G., and Bruzelius, G. (1994). Anti-nociceptive effects of oxytocin in rats and mice. *Neurosci. Lett.* 170, 153–157.

Malek, A., Blann, E., and Mattison, D. R. (1996). Human placental transport of oxytocin. *J. Matern. Fetal Med.* 5, 245–255.

Manning, M., Miteva, K., Pancheva, S., Stoev, S., Wo, N. C., and Chan, W. Y. (1995). Design and synthesis of highly selective in vitro and in vivo uterine receptor antagonists of oxytocin: comparisons with Atosiban. *Int. J. Pept. Protein Res.* 46, 244–252.

Marchini, G., Lagercrantz, H., Winberg, J., and Uvnas-Moberg, K. (1988). Fetal and maternal plasma levels of gastrin, somatostatin and oxytocin after vaginal delivery and elective cesarean section. *Early Hum. Dev.* 18, 73–79.

Mazzuca, M., Minlebaev, M., Shakirzyanova, A., Tyzio, R., Taccola, G., Janackova, S., Gataullina, S., Ben-Ari, Y., Giniatullin, R., and Khazipov, R. (2011). Newborn analgesia mediated by oxytocin during delivery. *Front. Cell. Neurosci.* 5:3. doi: 10.3389/fncel.2011.00003

Meyer-Lindenberg, A., Domes, G., Kirsch, P., and Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat. Rev. Neurosci.* 12, 524–538.

Miranda-Cardenas, Y., Rojas-Piloni, G., Martinez-Lorenzana, G., Rodriguez-Jimenez, J., Lopez-Hidalgo, M., Freund-Mercier, M. J., and Condes-Lara, M. (2006). Oxytocin and electrical stimulation of the paraventricular hypothalamic nucleus produce antinociceptive effects that are reversed by an oxytocin antagonist. *Pain* 122, 182–189.

Mogil, J. S., Sorge, R. E., LaCroix-Fralish, M. L., Smith, S. B., Fortin, A., Sotocinal, S. G., Ritchie, J., Austin, J. S., Schorscher-Petcu, A., Melmed, K., Czerminski, J., Bittong, R. A., Mokris, J. B., Neubert, J. K., Campbell, C. M., Edwards, R. R., Campbell, J. N., Crawley, J.

N., Lariviere, W. R., Wallace, M. R., Sternberg, W. F., Balaban, C. D., Belfer, I., and Fillingim, R. B. (2011). Pain sensitivity and vasopressin analgesia are mediated by a gene-sex-environment interaction. *Nat. Neurosci.* 14, 1569–1573.

Mori, R., Tokumasu, H., Pledge, D., and Kenyon, S. (2011). High dose versus low dose oxytocin for augmentation of delayed labour. *Cochrane Database Syst. Rev.* 10, CD007201.

Patient, C., Davison, J. M., Charlton, L., Baylis, P. H., and Thornton, S. (1999). The effect of labour and maternal oxytocin infusion on fetal plasma oxytocin concentration. *Br. J. Obstet. Gynaecol.* 106, 1311–1313.

Phaneuf, S., Europe-Finner, G. N., Carrasco, M. P., Hamilton, C. H., and Lopez Bernal, A. (1995). Oxytocin signalling in human myometrium. *Adv. Exp. Med. Biol.* 395, 453–467.

Polin, R. A., Husain, M. K., James, L. S., and Frantz, A. G. (1977). High vasopressin concentrations in human umbilical cord blood – lack of correlation with stress. *J. Perinat. Med.* 5, 114–119.

Puder, B. A., and Papka, R. E. (2001). Hypothalamic paraventricular axons projecting to the female rat lumbosacral spinal cord contain oxytocin immunoreactivity. *J. Neurosci. Res.* 64, 53–60.

Reeta, K., Mediratta, P. K., Rathi, N., Jain, H., Chugh, C., and Sharma, K. K. (2006). Role of kappa- and delta-opioid receptors in the antinociceptive effect of oxytocin in formalin-induced pain response in mice. *Regul. Pept.* 135, 85–90.

Reiter, M. K., Kremarik, P., Freund-Mercier, M. J., Stoeckel, M. E., Desaulles, E., and Feltz, P. (1994). Localization of oxytocin binding sites in the thoracic and upper lumbar spinal cord of the adult and postnatal rat: a histoautoradiographic study. *Eur. J. Neurosci.* 6, 98–104.

Schlapbach, L. J., Frey, S., Bigler, S., Manh-Nhi, C., Aebi, C., Nelle, M., and Nuoffer, J. M. (2011). Copeptin concentration in cord blood in infants with early-onset sepsis, chorioamnionitis and perinatal asphyxia. *BMC Pediatr.* 11, 38. doi: 10.1186/1471-2431-11-38

Schorscher-Petcu, A., Sotocinal, S., Ciura, S., Dupre, A., Ritchie, J., Sorge, R. E., Crawley, J. N., Hu, S. B., Nishimori, K., Young, L. J., Tribollet, E., Quirion, R., and Mogil, J. S. (2010). Oxytocin-induced analgesia and scratching are mediated by the vasopressin-1A receptor in the mouse. *J. Neurosci.* 30, 8274–8284.

Schubert, F., George, J. M., and Rao, M. B. (1981). Vasopressin and oxytocin content of human fetal brain at different stages of gestation. *Brain Res.* 213, 111–117.

Serradeil-Le Gal, C., Valette, G., Foulon, L., Germain, G., Advenier, C., Naline, E., Bardou, M., Martinolle, J. P., Pouzet, B., Raufaste, D., Garcia, C., Double-Cazanave, E., Pauly, M., Pascal, M., Barbier, A., Scatton, B., Maffrand, J. P., and Le Fur, G. (2004). SSR126768A (4-chloro-3-[(3R)-(()-5-chloro-1-(2,4-dimethoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-N-ethyl-N-(3-pyridylmethyl)-benzamide, hydrochloride): a new selective and orally active oxytocin receptor antagonist for the prevention of preterm labor. *J. Pharmacol. Exp. Ther.* 309, 414–424.

Smith, R. (2007). Parturition. *N. Engl. J. Med.* 356, 271–283.

Stegner, H., Leake, R. D., Palmer, S. M., Oakes, G., and Fisher, D. A. (1984). The effect of hypoxia on neurohypophyseal hormone release in fetal and maternal sheep. *Pediatr. Res.* 18, 188–191.

Swanson, L. W., and Kuypers, H. G. (1980). The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double-labeling methods. *J. Comp. Neurol.* 194, 555–570.

Thornton, S., Charlton, L., Murray, B. J., Davison, J. M., and Baylis, P. H. (1993). The effect of early labour, maternal analgesia and fetal acidosis on fetal plasma oxytocin concentrations. *Br. J. Obstet. Gynaecol.* 100, 425–429.

Tribollet, E., Barberis, C., and Arsenijevic, Y. (1997). Distribution of vasopressin and oxytocin receptors in the rat spinal cord: sex-related differences and effect of castration in pudendal motor nuclei. *Neuroscience* 78, 499–509.

Veronneau-Longueville, F., Rampin, O., Freund-Mercier, M. J., Tang, Y., Calas, A., Marson, L., McKenna, K. E., Stoeckel, M. E., Benoit, G., and Giuliano, F. (1999). Oxytocinergic innervation of autonomic nuclei controlling penile erection in the rat. *Neuroscience* 93, 1437–1447.

Wellmann, S., Benzing, J., Cippa, G., Admaty, D., Creutzfeldt, R., Mieth, R. A., Beinder, E., Lapaire, O., Morgenthaler, N. G., Haagen, U., Szinnai, G., Buhrer, C., and Bucher, H. U. (2010). High copeptin concentrations in umbilical cord blood after vaginal delivery and birth acidosis. *J. Clin. Endocrinol. Metab.* 95, 5091–5096.

Yu, S. Q., Lundeberg, T., and Yu, L. C. (2003). Involvement of oxytocin in spinal antinociception in rats with inflammation. *Brain Res.* 983, 13–22.

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