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The promiscuity of the oxytocin–vasopressin systems and their involvement in autism spectrum disorder

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Abstract

Oxytocin and vasopressin systems have been studied separately in autism spectrum disorder (ASD). Here, we provide evidence from an evolutionary and neuroscience perspective about the shared mechanisms and the common roles in regulating social behaviors. We first discuss findings on the evolutionary history of oxytocin and vasopressin ligands and receptors that highlight their common origin and clarify the evolutionary background of the crosstalk between them. Second, we conducted a comprehensive review of the increasing evidence for the role of both neuropeptides in regulating social behaviors. Third, we reviewed the growing evidence on the associations between the oxytocin/vasopressin systems and ASD, which includes oxytocin and vasopressin dysfunction in animal models of autism and in human patients, and the impact of treatments targeting the oxytocin or the vasopressin systems in children and in adults. Here, we highlight the potential of targeting the oxytocin/vasopressin systems to improve social deficits observed in ASD and the need for further investigations on how to transfer these research innovations into clinical applications.

INTRODUCTION: OXYTOCIN AND VASOPRESSIN SYNTHESIS, GENE STRUCTURE, AND FUNCTION

Oxytocin (*OT*) and vasopressin (*VP*) are neuropeptides produced mainly in the supraoptic and the paraventricular nucleus (PVN) of the hypothalamus (Lucassen et al., 1997). They are released in the capillaries of the posterior pituitary and then distributed peripherally, acting as hormones, or to other brain regions, onto neurons containing their receptors, acting as neurotransmitters/neuromodulators (see Bakos et al., 2018 and references therein). Central release of *OT* and *VP* can occur through dendritic and axonal release. The dendritic release (Ludwig and Leng, 2006) is notably important to induce a positive feedback mechanism.

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The axonal release was discovered 40 years ago when *OT* and *VP* synapses were observed in the limbic regions of the rat brain (Buijs and Swaab, 1979).

The recent use of an optogenetic technique to induce local activation of oxytocin or vasopressin fibers (Knobloch et al., 2012; Smith et al., 2016; Hung et al., 2017) supports the idea that these peptides can be locally released in the brain. Furthermore, retro dialysis studies performed mainly in rats demonstrated that oxytocin and vasopressin can be released locally in response to social stimuli (Veenema and Neumann, 2008): for example, oxytocin is released in the PVN but not the amygdala or the lateral septum (LS) of lactating females defending their nest (Bosch et al., 2004).

Both the oxytocin and vasopressin genes are comprised by three exons that give rise to a prepropeptide (Fig. 9.1). For oxytocin, the first exon encodes the signal peptide, the oxytocin hormone, the tripeptide processing signal (GKR), and the NH_2-terminal residues of neurophysin I; the second exon encodes the central part of neurophysin I; and the third exon encodes the COOH-terminal region of neurophysin I. For vasopressin, the three exons also give rise to a prepropeptide: the first exon encodes a signal peptide, the vasopressin hormone, and the NH_2-terminal region of neurophysin II; the second exon encodes the central region of neurophysin II; and the third exon encodes the COOH-terminal region of neurophysin II and the glycopeptide copeptin (Melmed, 2011). The products of these processes, *OT* and neurophysin I, on the one hand, and *VP*, copeptin, and neurophysin II, on the other, are packaged in granules for axonal transport to the posterior pituitary (Brownstein et al., 1980), until their release is elicited (Renaud and Bourquet, 1991).

OT and *VP* are involved in an array of functions that go beyond their traditional implication in uterine contractions (Magalhaes et al., 2009) and antidiuresis (Walter et al., 1967), respectively. Based on our literature review for their functions in mammals, both neuropeptides are involved in grooming (Marroni et al., 2007; Nephew and Bridges, 2008), maternal behavior (Arthur et al., 2008; Leng et al., 2008; Nephew and Bridges, 2008), blood pressure regulation (Petersson et al., 1996; Pavan de Arruda Camargo et al., 2008), social behavior (Heinrichs and Domes, 2008; Lukas et al., 2011), and memory (Weingartner et al., 1981; Larrazolo-López et al., 2008), among other functions. Other prominent functions of *OT* in mammals are mating (Witt and Insel, 1994; Insel and Hulihan, 1995), sperm ejaculation (Filippi et al., 2003), lactation (Leng et al., 2008), heart development (Jankowski et al., 2004), ossification (Elabd et al., 2007), digestive system regulation (Wu et al., 2003), pain perception (Yang et al., 2007), estradiol response (Jirikowski et al., 1988), drinking and eating (Verty et al., 2004), and sensory perception (Marlin et al., 2015). *VP* is also involved in apoptosis regulation (Chen et al., 2008), locomotion (Schank, 2009), arterial, vasoconstriction regulation (Alonso et al., 2008), and thermoregulation (Richmond, 2003).

The diverse functions of *OT* and *VP* depend on the peripheral and brain synthesis sites, release sites, and the *OT* and *VP* receptors (*OTR-VPRs*) distribution. The *OTR-VPRs* are classical seven-transmembrane G protein-coupled receptors. When peptides bind to these receptors, they cause a series of signal transduction cascades with both excitatory or inhibitory actions on Ca^{2+} and other messengers and transcription of specific genes.

EVOLUTIONARY HISTORY OF OXYTOCIN AND VASOPRESSIN LIGANDS AND RECEPTORS

OT and *VP* are adjacent paralogous genes, meaning that they are located next to each other in most vertebrate genomes (except in teleost fish) (Theofanopoulou et al., 2021), and that they likely resulted from a local duplication in the stem of vertebrates. Gwee et al. (2009) first hypothesized that since only *VP* is found in invertebrates and in the first vertebrates (e.g., lampreys), and *OT* is found for the first time in fishes (e.g., elephant sharks), it was *VP* that gave rise to *OT*, and not the other way around. Theofanopoulou et al. (2021) found evidence for this hypothesis, in that they traced DNA TEs around the *OT* region, but not around the *VP* (Fig. 9.1). TEs are known to drive gene duplications through their terminal inverted repeats, which have been found to transpose through a cut-and-paste mechanism creating an extra copy at the donor site (Wicker et al., 2007). In other words, the hypothesized ancestral *VP* copied and pasted itself, creating *OT*, and leaving TEs around it as a "remnant" of this process.

Based on the common evolutionary origin of these genes, which is supported by extensive synteny and phylogenetic analyses' data shown in Theofanopoulou et al. (2021), we second their proposal for a universal vertebrate nomenclature. So far, the use of different gene names for each of the ligands (and receptors) in different species or lineages has brought translation between experiments on different species at a standstill. All the following terms: oxytocin (mammals), mesotocin (birds, turtles, crocodiles, frogs, and some fish), isotocin (fish), glumitocin (fish), valitocin, and aspargtocin (fish) are being used to refer to the same gene that they propose we call "oxytocin" from now on; arginine vasopressin (mammals), lysine vasopressin (mammals), phenypressin (mammals), and vasotocin (*VT*) (birds, crocodiles, turtles, frogs, fish, sharks, lampreys, hagfishes) are being used to refer to the same gene that they propose we call "vasotocin" from now on. Naming them "vasotocin" and "oxytocin" portrays their evolutionary history, as is standard practice for other genes that are orthologous across species (e.g., *FOXP1*) and paralogous within species (e.g., *FOXP2*, *FOXP3*, *FOXP4*). According to this practice, these two peptides would be named vasopressin1 (*AVP1*) and vasopressin2 (*AVP2*), vasotocin1 (*VT1*) and vasotocin2 (*VT2*), or oxytocin1 (*OT1*) and oxytocin2 (*OT2*). Since this would be a far-reaching shift from the existing nomenclature, Theofanopoulou et al. (2021) propose that the common origin of these genes be portrayed through the shared ending name—tocin, and paralogy conveyed through different root names oxy- and vaso-. Vasotocin is a name already used by all nonmammalian scientific communities. Although we support this new nomenclature, we have not adopted it in this chapter to avoid confusion with the nomenclature used in the rest of the chapters. We followed a similar approach for the receptors.

Concerning their receptors, there are six major *OTR-VPRs* in vertebrates (*OTR/OXTR/VT3/MesoR/ITR, VTR1A/AVPR1A/V1AR/VT4/VASR*, *VTR1B/AVPR1B/AVPR3/V3, VTR2A/VT1/V2C/V2BR2/AVPR2.2*, *VTR2B/V2B/V2BR1/OTRL/AVPR2*, and *VTR2C/AVPR2/V2A2/AVPR2AA*; for their nomenclature, we list the names proposed in Theofanopoulou et al. (2021) followed by other traditional names). While in invertebrates, there is only one receptor type (*VTR*), the invertebrate species have more than one receptor

that might have duplicated in a species-specific manner from the same receptor type (Theofanopoulou et al., 2021). Several scientists have hypothesized that the six receptors evolved through the traditional two rounds of whole-genome duplications (Ocampo Daza et al., 2012; Lagman et al., 2013), meaning that two initial ancestral receptors got duplicated twice, making eight receptors, with two of them having been fully lost from the vertebrate genomes. According to more recent hypotheses (Mayasich and Clarke, 2016; Theofanopoulou et al., 2021), the receptors evolved through one round of whole-genome duplication, followed by several segmental duplications, a scenario that is better parsimoniously explained in the context of vertebrate genome evolution (Smith and Keinath, 2015; Theofanopoulou et al., 2021).

These evolutionary findings have direct repercussions on our understanding of the *OT-VP* system, which thus far has been mostly studied as two separate systems that show crosstalk. Specifically, the finding that the *OTR* evolved millions of years before the *OT* ligand suggests that the ancestral *VP* may have originally acted through the *OTR* before *OT* evolved. This suggestion is supported by findings that in some species *OT* and *VP* bind to the *OTR* at similar efficiencies; a greater response of *OTR* to *OT* over *VP* is found for the first time in teleost fish (Yamaguchi et al., 2012). Studying the *OT-VP* system as one and the same system, like for example, the dopamine system or the serotonin system, can frame studies showing crosstalk and interaction between *OT*, *VP*, and *OTR-VPRs* differently, as well as inform the design of new experiments targeting this system in social disorders, like autism spectrum disorders (ASD), which we discuss further.

OXYTOCIN AND VASOPRESSIN LIGAND AND RECEPTOR DISTRIBUTION IN THE HUMAN AND MOUSE BRAIN

We searched in the Human Protein Atlas (Thul et al., 2017) (http://www.proteinatlas.org) for brain gene expression patterns of the *OT* and *VP* ligands and the *OTR-VPRs* present in humans (*Homo sapiens*) and mice (*Mus musculus*) (*OTR*, *AVPR1A*, *AVPR1B*, *AVPR2*). For human data, we used the GTEx and FANTOM5 datasets. For mouse data, we used the HPA mouse brain RNA-Seq dataset. Overall, gene expression was similar in the brain tissues of both human and mice brains. An observation of their profiling combined can shed light to these genes' expression in the mammalian brain.

High *OT* and *VP* expression was found in both the human and mouse hypothalamus. Other regions such as the basal ganglia and the amygdala show instead much less expression. This points to an almost exclusive gene expression in the hypothalamus and to the great reliance of the *OT-VP* system to the synaptic transmission of these products through neurons expressing their receptors, at least in the mammalian brain (Fig. 9.2).

Although *OTR* has a lower region specificity, it shows high expression in several brain regions. In humans, *OTR* is highly expressed in the midbrain, the basal ganglia, and the hypothalamus. In mice, *OTR* is highly expressed in the amygdala, the basal ganglia, and the hippocampus (Figs. 9.3 and 9.4). *OTR* in the hippocampus has been shown to be involved in social recognition and social memory (Raam et al., 2017), something that may point to a species-specific enhancement of such functions.

AVPR1A is overall less detected in the brain. It can be found in the mouse hypothalamus and basal ganglia. In humans and mice, it is expressed, although at low levels, in the amygdala, pons and medulla, and other areas (Figs. 9.3 and 9.4). *AVPR1B* is not enriched in any brain areas in humans. However, in humans, there are low expression levels in the cerebellum, and even lower in the amygdala, basal ganglia, and hypothalamus. In mice, *AVPR1B* expression is the highest in the pituitary gland of the hypothalamus with some expression in the hippocampus (Figs. 9.3 and 9.4). *AVPR1B*'s expression in the hypothalamus has been suggested to have specific functions in the regulation of stress, aggressive, and social behaviors, possibly through interaction with the adrenal axis (Stevenson and Caldwell, 2012).

The less studied *AVPR2* is enriched in the cerebellum of both species. Its functional role is unknown. Some early study in rats (Kato et al., 1995) showed that *AVPR2* is constitutively expressed in the granular layer of the cerebellum throughout brain development, concluding that since the granular layer sends output signals to the Purkinje cells, it is possible that *AVPR2* could have an important role in regulating Purkinje cells (Figs. 9.2 and 9.3).

OXYTOCIN AND VASOPRESSIN REGULATE SOCIAL BEHAVIORS

Gene blockade and activation studies (knockout, pharmacological, chemogenetic, optogenetic)

To investigate the potential role of *OT* and *VP* in social behavior, scientists generated mice lacking *OT*, *VP* or lacking their receptors. More than 20 years ago, transgenic *OT* knockouts (KO) were shown to display social memory deficits that could be reversed by exogeneous administration of oxytocin (Ferguson et al., 2000). Interestingly, *OTR*-KO mice also present a wide range of social deficits with decreased ultrasonic vocalizations and mobility in pups, social discrimination deficits, and increased aggressivity in adults, as well as an alteration of maternal behavior (Takayanagi et al., 2005). The negative social impact of *OTR* deficiency is not limited to mice. *OTR*-KO prairie voles present both decreased interest for social novelty and exaggerated repeated behaviors (Horie et al., 2018), two symptoms that are reminiscent of the deficits observed in ASD. Interestingly, mice lacking only one copy of the *OTR* gene also display decreased sociability, indicating that even a partial decrease of *OTR* expression alters social behavior (Sala et al., 2011). Altogether, these results demonstrate that the activity of the *OT* system is necessary for social behavior.

One naturally occurring deficiency can be found in the Brattleboro strain of rats that have lost their ability to produce *VP* due to a genetic mutation. This strain has been extensively studied and has revealed social discrimination deficits, compared to other strains, which could be restored by intraseptal administration of *VP* (Engelmann and Landgraf, 1994). Similarly, mice lacking the *AVPR1A* present social discrimination deficits that are rescued by restoring *AVPR1A* expression in the LS using a viral strategy (Bielsky et al., 2005). Furthermore, mice lacking *AVPR1B* also show social discrimination deficits (Wersinger et al., 2002), suggesting that some aspects of social behaviors depend on the coordinated activity of different *OTR*-*VPRs*.

Other evidence for the role of *OT* and *VP* in regulating social behaviors come from pharmacological experiments. Pharmacological blockade of the *AVPR1A* in the LS impairs social discrimination, while the administration of exogenous *VP* extends social discrimination in rats (Veenema et al., 2012). The same manipulations also influence juvenile rat play behavior (Veenema et al., 2013) and pair bond formation in prairie voles (Liu et al., 2001). Studies also showed that *OTR* antagonist impairs social recognition in mice when administered in the medial amygdala (Ferguson et al., 2001) and impedes pair bond formation in socially monogamous species, such as zebra finches (Klatt and Goodson, 2013) and prairie voles (Liu and Wang, 2003). In the prairie vole, *OTR* activation is involved in mating-induced increase of correlated activity between the nodes of the social brain neural network (Johnson et al., 2016), as well as in consolation behavior (Burkett et al., 2016). Interestingly, *OT* has other central functions such as regulation of metabolism and feeding (reviewed in Spetter and Hallschmid, 2017). Recent studies suggest that *OT* impact on eating behavior may depend on its psychosocial function as social cues modulate the effect of oxytocin on feeding (Olszewski et al., 2016).

Similarly, studies taking advantage of chemogenomic techniques to manipulate the activity of endogeneous *OT* demonstrated that stimulating *OT* neurons is sufficient to promote social motivation and to reduce anxiety (Grund et al., 2019). It is also sufficient to socially transmit fear in mice (Pisansky et al., 2017). Inhibition of *OT* activity increased fear response in lactating mice (Menon et al., 2018). One recent study in mice used a chemogenetic strategy to specifically inhibit the activity of PVN *OT* neurons projecting to either the amygdala, the nucleus accumbens, or the prefrontal cortex and showed that only the inhibition of neurons projecting to the amygdala does impair emotion recognition (Ferretti et al., 2019). This shows that different *OT* neurons may project to different brain areas and thus regulate specific aspects of social behavior. It also suggests that the *OT* projections from PVN to amygdala are essential for emotional processes.

Other studies used optogenetic techniques to specifically manipulate the activity of endogenous *OT* or *VP* systems in specific brain areas that are part of the social or reward brain network. Knobloch et al. (2012) showed that optogenetic stimulation of oxytocinergic fibers in the amygdala attenuates fear response, while optogenetic stimulation of *OT*-PVN neurons increased social exploration and social memory in rats (Oettl et al., 2016). Optogenetic inhibition of *OT* fibers in the ventral tegmental area decreases sociability, while their stimulation gives rise to the opposite effect (Hung et al., 2017). Optogenetic stimulation of *OT* fibers in the auditory cortex of naïve virgin mice increased their pup retrieval behavior (Marlin et al., 2015), while stimulation of *VP* fibers in hippocampal CA2 enhanced social memory (Smith et al., 2016). Lastly, optogenetic inhibition of *OT* or *VP* fibers in the LS impairs social discrimination in mice (Borie et al., 2019). Interestingly in this study, the authors describe a population of neurons in the LS inhibited by *OT* only if previously exposed to *VP*. This reveals that these two neuropeptides can have a coordinated action and while most studies investigate one or the other, considering both *OT* and *VP* together would broaden our understanding of their function in the regulation of social behaviors (Borie et al., 2019).

Overall, these studies suggest that oxytocin and vasopressin play a key role in the regulation of social behavior. Their role is both necessary (blockade studies) and sufficient (activation studies) to regulate social behavior in general, while the localization and action of specific ligands and receptors in specific brain regions mediate different aspects of this umbrella term (social behavior) that includes behaviors like social recognition, social memory, social discrimination, among others.

Oxytocin/vasopressin concentration and administration studies

Several studies have measured *OT*-*VP* concentration, in an attempt to evaluate whether variation in the concentration correlates with variability in different social tasks. Although the methodology of concentration measurements in different sites (blood vs cerebrospinal fluid (CSF)) is still under debate (Lefevre et al., 2017), there is a general consensus that both *OT* and *VP* show a covariation with an array of social behaviors, like parenting (Apter-Levi et al., 2014) and interpersonal relationships (Gouin et al., 2012). Low oxytocin levels were also associated with introverted personalities and increased volume in the amygdala (Andari et al., 2014).

Beyond merely correlative results, studies have also investigated brain activity and behavioral changes induced by exogeneous administrations of *OT* and *VP*, mostly with an intranasal administration. Intranasal administration of these neuropeptides is the most efficient way of administration given that the spray penetrates the brain and does not affect peripheral organs the same way as peripheral injections would (Quintana et al., 2015). Several studies have shown that intranasal administration of *OT* does increase CSF concentration of *OT* in macaque (Dal Monte et al., 2014; Freeman et al., 2016), in oxytocin knockout mice (Smith et al., 2019), in rats and in mice (Neumann et al., 2013), and in humans (Born et al., 2002; Striepens et al., 2013), indicating that this route of administration is efficient in influencing central pathways. In addition, researchers have developed a sensitive and specific quantitative mass spectrometry assay that can distinguish a labeled *OT* from endogenous *OT* (Lee et al., 2018) and found that an intranasal labeled *OT* reaches the CSF and did not affect the endogenous release of *OT*.

A 24 International Units (IU) of *OT*-intranasal administration was found to increase the time of eye fixation (Guastella et al., 2008), suggesting an important involvement of *OT* in the social attention and emotion recognition mechanisms. Vasopressin plays a role in sociosexual cue recognition. Twenty IU of intranasal *VP* administration increased the speed at which men detected sexual words over other types of words (Guastella et al., 2011), while it also increased the memory for happy and angry but not neutral faces (Guastella et al., 2010b). An important series of results were obtained by studying the response to the “prisoner’s dilemma” and its neural correlates in after intranasal administration of *OT* (24UI) or *VP* (20UI). The prisoner’s dilemma is a standard example of a game where two individuals should testify either by betraying the other or remaining silent. First studies were performed in males and showed that both *OT* and *VP* administration increased the functional connectivity between the amygdala and the anterior insula, both being important components of the decision-making neural network. *OT* administration increases the response of the caudate nucleus in response to unreciprocated cooperation and,

behaviorally, it induces an increased rate of cooperation following noncooperative moves (Rilling et al., 2012). In a replication study involving males and females, they found that while *OT* induces an increase of the activity of the caudate/putamen in males, it induces a decrease of such activity in females when both partners were cooperative. In the same conditions, the intranasal administration of *VP* increased activity in the insula in males, but decreased it in females (Feng et al., 2015). Further studies confirmed that the neural correlates of *OT* administration are sex dependent, with *OT* playing a critical role in the regulation of the activity of the social brain network in this social game, since it significantly changes its nodes' functional connectivity (nucleus accumbens, amygdala, insula, septum, ventral tegmental area, orbitofrontal cortex) (Rilling et al., 2018).

Epigenetic studies

Studies on epigenetic modifications of our genes of interest can shed light on the specific impact these genes might have. DNA methylation patterns have been extensively studied on the *OTR* since it can provide a window for the outcomes of *OTR* transcription repression (Mamrut et al., 2013; Harony-Nicolas et al., 2014). High levels of *OTR* methylation have been associated with a decreased neural response in regions supporting social perception and emotion processing, such as the amygdala or the insula, but also with a decrease in the functional coupling between the amygdala and brain areas involved in emotion regulation (Puglia et al., 2015, 2018). This suggests that the oxytocin system may be involved in the attenuation of fear response and that variation in the methylation of the *OTR* could partially account for the natural variability in emotion processing (Krol et al., 2019). An increase in DNA methylation of the *OTR* was more generally associated with impairments in social, cognitive, and emotional cognition (Maud et al., 2018). Interestingly, epigenetic markers on the *OTR* could be modulated by environmental factors (Kumsta et al., 2013).

Single-nucleotide polymorphism (SNP) studies

Another naturally occurring source of variability in the activity of the *OT-VP* system are single-nucleotide polymorphisms. Different polymorphisms in the *OTR* have been associated with reduced plasma oxytocin levels and a low parental contact (Feldman et al., 2012), or on the contrary, with positive parenting and increased activity in the orbitofrontal and anterior cingulate cortex (Michalska et al., 2014), empathy (Wu et al., 2012), reaction to betrayal (Tabak et al., 2014), and trust (Nishina et al., 2015). Interestingly, *OTR* SNPs have also been associated with interindividual variability in *OTR* expression in specific brain areas, such as the nucleus accumbens in prairie voles (King et al., 2016).

Polymorphisms in the *AVPRs* are linked to variability in social behavior. Variation in the promotor region of the *AVPR1A* was shown to be associated with variation in the mating system of voles. Prairie voles or pine voles, which are socially monogamous, present a repetitive sequence of DNA in 5′ UTR of the *AVPR1A*, while this sequence is absent in the promiscuous montane vole and meadow vole (Hammock and Young, 2002). Interestingly, this variation is also associated with a different pattern of *AVPR1A* brain expression, specifically with an increase in the ventral pallidum, an increase that was also induced in a transgenic mouse that was carrying the 5′ UTR repetitive sequence (Young et al., 1999). Another repetitive sequence in 5′ UTR of *AVPR1A*, called RS3, has been associated with

chimpanzee personality variation: the long form of the gene has been linked to dominance and conscientiousness (Hopkins et al., 2012), while the short form to a higher level of extraversion (Wilson et al., 2017); its influence on personality traits has been similarly reported for bonobo (Staes et al., 2016). Interestingly, a variation of a similar microsatellite region correlates with levels of *AVPR1A* binding in some brain areas of the prairie vole (Hammock et al., 2005). Furthermore, in human, the long RS3 repeat was associated with higher levels of *AVPR1A* RNA in the hippocampus and the length of this region is also associated with levels of altruistic behavior (Knafo et al., 2008).

In humans, polymorphisms in the *AVPR1A* have also been associated with trust and reciprocity (Nishina et al., 2019), and polymorphisms in the *AVPR1B* receptor gene have been associated with levels of aggressivity in children (Luppino et al., 2014) or empathy and prosociality in adults (Wu et al., 2015) (see also Theofanopoulou et al., 2018).

OXYTOCINERGIC AND VASOPRESSINERGIC SYSTEMS ARE IMPAIRED IN ASD AND RELATED ANIMAL MODELS

Nonhuman animal models

In order to understand the pathophysiology underlying deficits observed in ASDs, animal models aiming at recapitulating the main features of ASD have been developed. An ideal animal model would respond to three criteria: construct validity (causes of the pathology are the same in the model and the pathology), face validity (symptoms are similar to the disease), and predictive validity (treatments effective in the models and in the pathology would match). Since the etiology of ASD is not fully understood yet and in the absence of a solid treatment, the second criterion remains the most confident. Indeed, the three aspects of ASD-related deficits are considered to define a good model of ASD: deficits of social interaction, communication, and exaggerated repetitive behaviors.

When it comes to etiology, we can segregate the models into three categories (Bey and Jiang, 2014): genetics (modification of genes or group of genes known for their involvement in ASD), environmental, and naturally occurring strains' variations. Interestingly, while most of these models initially do not directly target the *OT* or *VP* systems, alterations in these systems have often been observed (Peñagarikano, 2017). For example, loss of function of the *FRM1* gene (causing fragile X syndrome in humans; one of the most common genetic form of autism) in mice induces a reduction of social approach, an alteration of communication, and repeated behaviors (Kazdoba et al., 2014), but also a decrease in *OT* and *VP* expression in the PVN (Francis et al., 2014). A reduction of *OT* immunoreactivity in the supraoptic nucleus and of the circulating *OT* levels have also been observed in rats subjected to a neonatal treatment with valproic acid (Dai et al., 2018), a treatment known to induce social behavior deficits relevant to ASD. Furthermore, as previously mentioned, mice lack one (Sala et al., 2013) or both alleles (Sala et al., 2011; Pobbe et al., 2012) of the *OTR* present social behavior deficits, patterns of repeated behavior, and neuronal hyperexcitability, all being features that make them up as a good model of ASD.

Human patients

OT and *VP* have been investigated as potential biomarkers for autism. More than 20 years ago, a first study revealed that plasma *OT* levels were lower in ASD children than in age-matched controls (Modahl et al., 1998). This result was since replicated in a small cohort (Andari et al., 2010), and in a cohort of more than 80 ASD children and 80 age-matched controls which also showed that in the ASD population, the higher the *OT* concentration, the less the impairment of verbal communication (Zhang et al., 2016), suggesting a role of oxytocin in vocal aspects of communication (Theofanopoulou et al., 2017). Nevertheless, other studies did not find differences in plasma *OT* levels between ASD and controls, suggesting that the *OT* system may actually play more of a regulatory role in both the physiology and the pathology (Parker et al., 2014). Lastly, *OT* concentration in saliva was positively correlated with secure attachment in ASD patients, which might be due to differential functional coupling between the amygdala and the hippocampus (Alaerts et al., 2019).

When it comes to *VP*, plasma levels are in many studies similar in children with and without ASD (Carson et al., 2015; Zhang et al., 2016), but according to Shou et al. (2017), plasma levels of *VP* positively correlate with brain morphological alterations in ASD patients, such as increased left amygdala and hippocampal volume, and decreased bilateral hypothalamus volume association between blood *VP* concentrations and behavioral phenotypes in ASD has also been demonstrated: *VP* levels negatively correlated with the visual and listening response score of CARS (Shou et al., 2017) and positively correlated with the theory of mind scores (Carson et al., 2015). To summarize, the association between *OT* and *VP* circulating levels and the diagnosis of autism is still unclear, but in autistic populations, the levels of circulating hormones are predictive of symptoms' severity more often than not. Two studies found decreased CSF *VP* levels in autistic children, compared to controls (Oztan et al., 2018; Parker et al., 2018), something not observed in the case of *OT* (Oztan et al., 2018).

As it follows from our review of SNP studies with respect to social behavior, ASD patients have been shown to present specific variants, compared to controls, in the *OTR*, *AVPR1A*, and *AVPR1B* genes (Yang et al., 2010; Di Napoli et al., 2014; Francis et al., 2016; Uzefovsky et al., 2019). Similarly, specific methylation patterns are present in ASD population with specific behavioral phenotypes. Earlier, in a pilot study, Gregory et al. (2009) found an increased methylation of the *OTR* in ASD patients hand in hand with decreased *OTR* mRNA levels in the temporal cortex of postmortem tissues (Gregory et al., 2009). In a recent functional magnetic resonance imaging (fMRI) study, it has been shown that adults with ASD have a higher level of methylation in the first intron of *OTR*, which was associated with hypoconnectivity between cortical areas implicated in theory of mind and self-awareness deficits in ASD (Andari et al., 2020). Also, the study showed, for the first time, that a variation in a CpG site (not hypermethylated in ASD) in the exon area of *OTR* is associated with ASD symptom severity in social responsiveness, and with a hyperconnectivity between brain networks involved in reward processing (such as the ventral striatum and the ventromedial prefrontal cortex) (Andari et al., 2020). This hyperconnectivity was associated with a subtype of ASD that have restricted patterns of

interests (such as computer, programming, astrophysics). DNA methylation of the *OTR* can become indeed a promising biomarker for ASD and for moderating the effects of *OT* treatment efficacy. More studies are needed to confirm this hypothesis.

TREATMENTS FOR ASD TARGETING THE OXYTOCINERGIC AND VASOPRESSINERGIC SYSTEMS

Treatments targeting the oxytocin system in adults

IN NONHUMAN ANIMAL MODELS—Oxytocin treatments administered to mouse models of ASD improve their social deficits. Mice lacking the *CNTNAP2* gene, whose mutation causes cortical dysplasia and focal epilepsy syndrome with 70% of ASDs comorbidity, present stereotypic movements, behavioral inflexibility, communication and social behavior abnormalities (Peñagarikano et al., 2011), but also a decreased number of *OT* neurons in the PVN (Peñagarikano et al., 2015). In these animals, juvenile social interaction and social preference were improved by *OT* intraperitoneal or intranasal administrations by a mechanism depending on the activation of the *OTR* itself (Peñagarikano et al., 2015). Interestingly, melanocortin four receptor agonists, which activate paraventricular oxytocinergic neurons and induce central *OT* release (Sabatier, 2006), can also improve the social deficits of *CNTNAP2* deficient mice, suggesting that inducing an endogenous release of *OT* can be an efficient strategy. Acute or subchronic *OT* treatment was reported to be efficient in improving the deficits of social interactions in different models of ASD (Peñagarikano, 2017), including *SHANK3* deficient rats (Harony-Nicolas et al., 2017), the prenatal valproic acid-induced mouse model of autism (Hara et al., 2017), or mouse lines that naturally present phenotypes relevant to core ASD symptoms, such as BALB/cByJ and C58/J lines (Teng et al., 2013).

IN HUMAN PATIENTS—As early as 2003, the potential impact of *OT* to improve deficits observed in ASD patients was evaluated. In a cohort of 15 adults with Asperger Syndrome, 4h of continuous synthetic *OT* infusion decreased repetitive behaviors (Hollander et al., 2003). A few years later, the same group showed that intravenous *OT* administration improved the ability of patients to assign emotional significance to speech intonation (Hollander et al., 2007). Acute intranasal *OT* administration to adults with high functioning autism was found to increase eye fixation, cooperative interaction, and trust during social ball games (Andari et al., 2010). This result suggests that *OT* could improve both attention to social cues and social cognition in people with ASD. Also, Andari et al. (2016) found that intranasal administration of *OT* enhances the blood–oxygen level-dependent (BOLD) activity of early visual areas during the perception of facial stimuli in adults with ASD. The authors also found that the treatment modulates the BOLD activity of the amygdala during a social ball-game in a context-dependent manner (Andari et al., 2016). The treatment enhances the activity of reward areas in response to positive stimuli (good player's face) and insula area in response to negative stimuli (bad player's face) (Andari et al., 2016). Since these pioneering studies, more studies have followed investigating the potential of *OT* treatment in ASD, with several replications (Guastella et al., 2010a; Watanabe et al., 2014; Auyeung et al., 2015). Long-term administration of *OT* in ASD improves clinical symptoms based on the oxytocin dosage and genetic background of the *OTR* (Kosaka et

al., 2016). However, continuous administration of *OT* has some contradictory results in the literature (Ooi et al., 2017), with some showing no significant effects of *OT* on primary measures (Anagnostou et al., 2012; Dadds et al., 2014), and others showing improvements in secondary measures (such as RMET) (Anagnostou et al., 2012) and primary measures (Watanabe et al., 2015). Few issues need to be resolved before assessing the true clinical effects of *OT* in ASD. There is a considerable lack of reliable and sensitive clinical measures that can detect changes over time of the core symptoms of ASD. The ability to measure the effects of drugs on objective and quantitative assessments is needed. Also, deciding on the dose and duration of treatment is crucial for enhancing *OT* treatment effects. Also, using a precision medicine approach and targeting specific subtypes of ASD who can benefit the most from *OT* treatment can be essential.

Treatments targeting the oxytocin system during development

In nonhuman animal models—*OT* has an important function in mammals, which is related to birth. Indeed, in mammals, birth is a stressful experience which carries high risks for the brain of the infants because it requires a change in the oxygenation mode. While in adults, GABA is known as the main inhibitory neurotransmitter, during fetal and early postnatal development, it has a depolarizing action and is the main source of excitatory inputs to immature neurons. On the day that precedes birth in rats, the number of cells excited by GABA decreases due to *OT* activity (Tyzio et al., 2006). Interestingly, in two animal models of ASD (rats exposed to valproate in utero and mice carrying the fragile X mutation), this transient switch of GABA is not observed indicating that such abnormality might be due to early alterations in the *OT* system (Tyzio et al., 2014).

Interestingly, early life experiences shape the *OT* system and perinatal manipulation of *OT* has long-term consequences. Neonatal manipulation of male prairie voles on the day of birth can induce a decrease of *OT* immunoreactivity in the paraventricular and supraoptic nuclei and changes in *OTR* binding in the bed nucleus of the stria terminalis or LS. Injection of *OT* on postnatal day 1 can alter anxiety, alloparental behavior, pair bond formation, and *OT* immunoreactivity in the PVN in adults (Carter et al., 2009). Furthermore, a single intraperitoneal administration of an *OTR* antagonist on the first day of life induces a decrease of *AVPR1A* binding sites in brain areas such as the preoptic area, the bed nucleus of the stria terminalis, and the LS (Bales et al., 2007) and an increase of immunoreactivity to *VP* in the PVN, confirming that there is crosstalk between the different types of ligands and receptors.

Scientists investigated the potential of a transient *OT* treatment in early life on the improvement of social behavior deficits of mouse models of autism or other related neurodevelopmental disorders. In *CNTNAP2* deficient mice, while *OT* treatments had an acute impact on social deficits, a daily intranasal *OT* treatment performed from postnatal day 7–21 improved social preference even 9 days after the end of the treatment, an improvement that was associated with a normalization of *OT* immunoreactivity in the PVN (Peñagarikano et al., 2015). A study performed on *MAGEL2* KO mice, a mouse model of Prader–Willi syndrome (PWS) that has an increased prevalence in autism (Schaaf et al., 2013), showed that intranasal *OT* administration during the seven first postnatal days was sufficient to

prevent the social and learning deficits normally developed in adult *MAGEL2* KO mice. In this study, the impact of the treatment was evaluated in adults, 3–4 months after the end of the treatment (Meziane et al., 2015). This treatment also normalized some aspects of the oxytocin system such as *OT* binding in the LS and *OT* immunoreactivity in the amygdala, dorso-vagal complex, and LS. Similar results were recently obtained in the valproic acid rat model, where a treatment during the seven first postnatal days restored communication at the end of the treatment and social preference and self-grooming in young adults, with these effects being associated with a restoration of *OT* immunoreactivity in the paraventricular and supraoptic nuclei (Dai et al., 2018).

In human patients—Early-life treatment of ASD is challenging because the diagnosis of ASD is usually not performed before 2 years. Nevertheless, some neurodevelopmental disorders that are caused by genetic alterations can be diagnosed close to birth. It is the case of PWS, a hypothalamic disorder that is characterized by intellectual disabilities, repeated and compulsive behaviors and hyperphagia, and some comorbidities with autism (Dykens et al., 2011). An early study indicated that *OT* may play a role in the disease as it found a 42% decrease in the density of PVN *OT* neurons in postmortem tissue from PWS patients (Swaab et al., 1995). Furthermore, it was recently shown that 7 days of treatment with intranasal *OT* in PWS infants under 6 months of age improved both feeding and social skills and increased the connectivity in the right superior orbitofrontal area (Tauber et al., 2017). The treated infants were followed for 2 years after the treatment and when compared with age-matched nontreated PWS patients, they displayed higher social skills and engagement in relationships. Interestingly, another study performed on PWS indicates that the beneficial impact of *OT* treatment on social and food-related behavior was dependent on the age of the patients, with the beneficial impact being limited to children less than 11 years old (Kuppens et al., 2016).

In autism patients aged 12–19 years old, a single intranasal *OT* administration enhanced performance in the “reading the mind in the eyes” test, suggesting an acute improvement of emotion recognition (Guastella et al., 2010a). In a study of long-tern administration (7 months) of intranasal *OT*, improvement of both communication and social interaction skills was detected (Tachibana et al., 2013). Furthermore, one study performed in children aged between 12 and 18 years old did not report beneficial effects on primary outcomes (Guastella et al., 2015). Studies involving fMRI provide a structural and functional support for these beneficial effects: studies showed that *OT* increases the activity of areas involved in social reward processing and theory of mind (i.e., striatum, nucleus accumbens, left posterior superior temporal sulcus, and left premotor cortex) when ASD children were presented with pictures of faces, but decreased it when presented with pictures of nonsocial objects (Gordon et al., 2013), suggesting a selective social effect of *OT*. More studies are needed to better understand the chronic effects of *OT* on the brain and behavior in order to maximize treatment efficacy. Also, targeting the endogenous *OT* system with other drugs can be a promising avenue.

Treatments targeting the vasopressin system

In nonhuman animal models—In animal models of autism, *VP* treatments have been less investigated than *OT* treatments. In the *CNTNAP2* deficient mice, *VP* treatment was found to improve the social deficits, but this effect was mainly mediated by the *OTR*, as its blockade abolished the improvement induced by *VP* treatment (Peñagarikano et al., 2015). This is probably due to the important promiscuity of the *O*T and *VP* systems (Song and Albers, 2017). Similarly, in the *OTR* deficient mice, both *OT* and *VP* treatment were found to have a beneficial impact on the social deficits. This is due, in both cases, to the activation of *AVPR1A* (Sala et al., 2011), indicating that when the oxytocin system is impaired, it is possible that the *VP* system takes over to make up for the impairment. It is thus possible that the impact of *OT* treatment partly relies on its binding to *VPRs*. In a recent study performed in *MAGEL2* KO mice, it was found that stimulation of *VP* but not *OT* fibers in the LS could restore social behavior in a social habituation–dishabituation task, suggesting that *VP* also plays a role by itself (Borie et al., 2019).

In human subjects—In recent studies, the vasopressinergic system was targeted in order to improve the social symptoms of ASDs. A 4-week intranasal *VP* administration in children with ASD (6–13 years old) improved social abilities in the social responsiveness scale and decreased anxiety and some repetitive behaviors (Parker et al., 2019). Balovaptan, a *AVPR1A* antagonist that can be administered orally, improved socialization and communication scores in high functioning men with ASD (Bolognani et al., 2019) after a 12-week treatment. Interestingly, both agonists and antagonists of *VPRs* showed the beneficial impact. It is nevertheless important to note that the age of the patients differs in the two cohorts and that more studies are necessary to fully understand how and when to target the vasopressinergic system to improve the phenotype of ASD.

Oxytocin and behavioral therapies—Studies indicate that cognitive behavioral therapy can improve behavioral phenotypes in children with ASD (Remington et al., 2007; Kurz et al., 2018). In a mouse model of autism with blunted reward processing, a behavioral therapy based on the association of positive reinforcement to social interaction rescued mice' social preference behaviors. Interestingly, this behavioral therapy normalized *OT* and *VP* systems in the reward and social circuitry, suggesting that such a behavioral therapy could indirectly modulate the activity of *OT* and *VP* (Pujol et al., 2018). In humans, it has been shown that endogenous *OT* release can occur in response to social interaction. For example, according to a pilot study, a daily 20 min massage performed by the mother of children with ASD was sufficient to increase salivary *OT* concentration in both the children and their mothers (Tsuji et al., 2015). The possibility of shaping the *OT* and *VP* release systems through behavioral therapies alone, or in combination with exogenous treatments, opens a new field of research that is bound to give informative results in the close future.

CONCLUSION

In this chapter, we have reviewed findings on the evolutionary history of oxytocin and vasopressin ligands and receptors that highlight their common origin and clarify the evolutionary background of the crosstalk between them. Understanding both

neuroendocrine systems, although named differently, but evolutionary derived from the same “vasotocinergic” system, helps decipher the neurobiology of social functioning and the establishment of promising treatments. Additionally, we have reviewed the evidence on the brain distribution of the ligands and the receptors in humans and mice, which has shown that they are expressed in regions that have been associated with social behaviors. We have then reviewed studies exhaustively in humans and nonhuman animal models showing how oxytocin and vasopressin regulate social behaviors, including gene blockade and activation studies, studies on their concentration centrally and peripherally, as well administration, epigenetic, and variation studies. We lastly reviewed the literature targeting the involvement/impairment of *OT*, *VP*, and *OTR-VPRs* in ASD, as well as ASD treatments involving these molecules. We conclude that the *OT*/*VP* system is one of the most promising systems to uncover treatments for social disorders given its pivotal role in social cognition and emotional processing.

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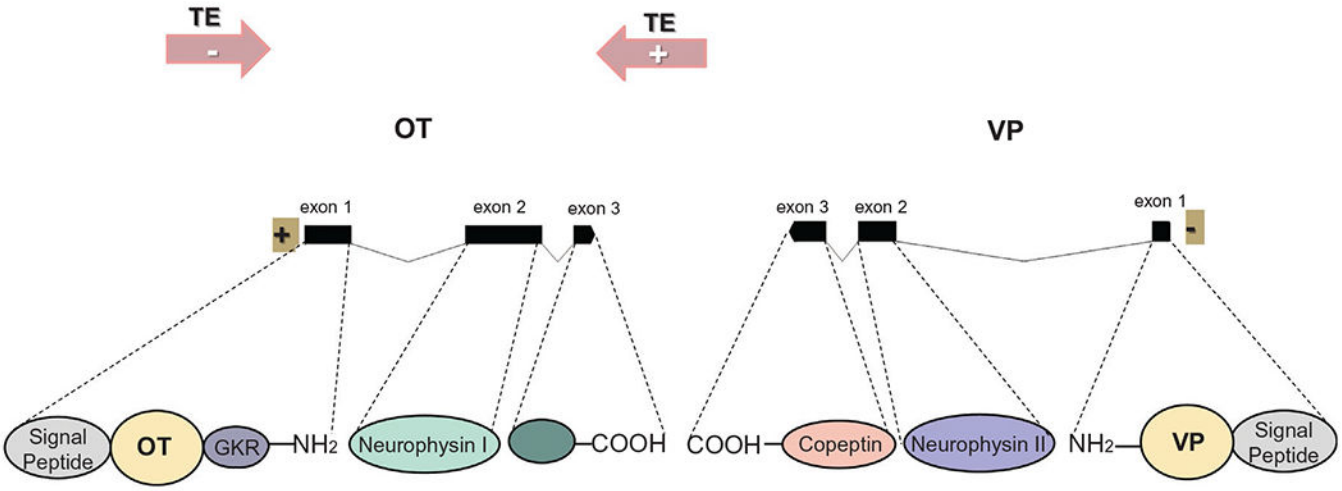

Fig. 9.1.

Oxytocin (*OT*) and vasopressin (*VP*) gene structure and synthesis. Local chromosomal organization of the *OT*-*VP* region. Representation of *OT* and *VP* genes (exons + introns) in human chromosome 12, DNA transposable elements (TE; *pink arrows*), and orientation (+, −). Each exon links with dashed lines to the gene products it encodes. *GKR*, glycine–lysine–arginine. Gene length scale: 100 bases.

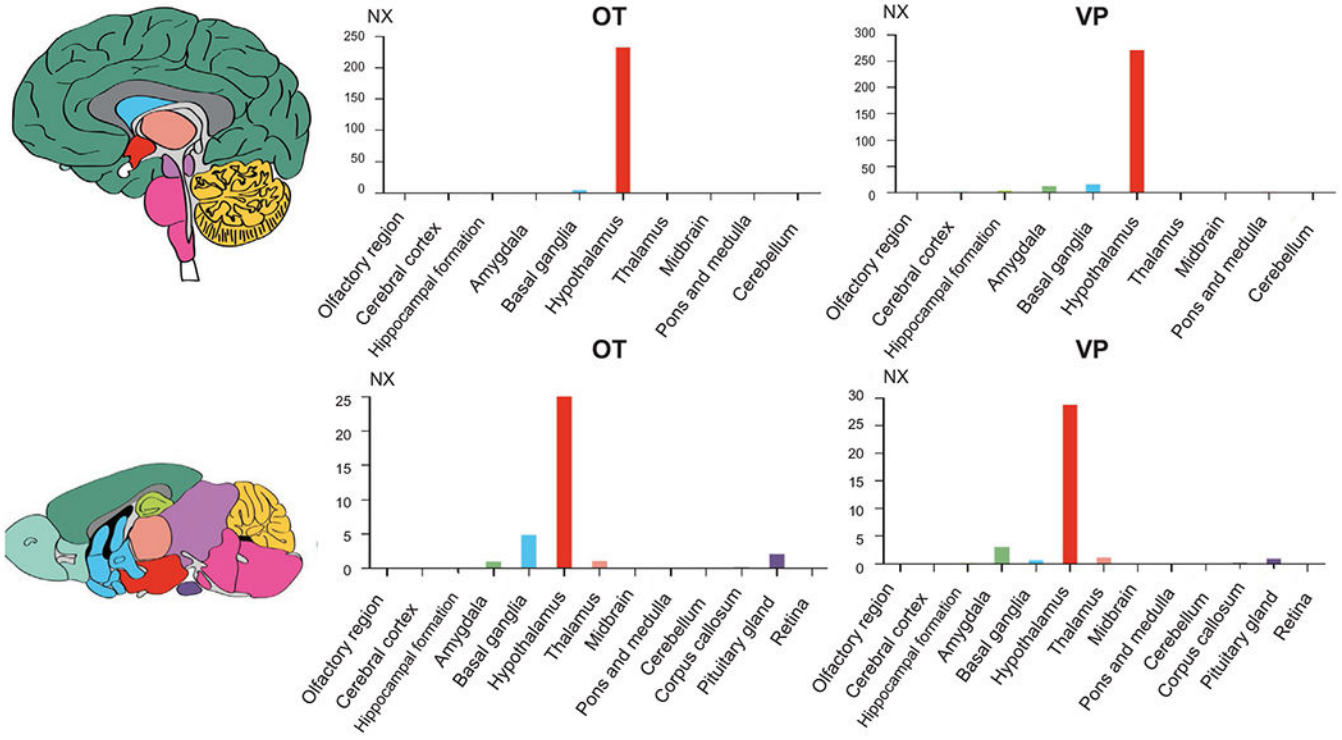

Fig. 9.2.

OT and *VP* gene expression in brain regions of the human (*top*) and mouse (*bottom*) brains. Color coding is based on brain region, and the bar shows the highest expression among the subregions included. Consensus normalized expression (NX) levels were created for the brain regions by combining the data from two transcriptomics datasets (GTEx and FANTOM5) in human and pTPM (protein-coding transcripts per million) of the individual HPA mouse dataset samples in mouse.

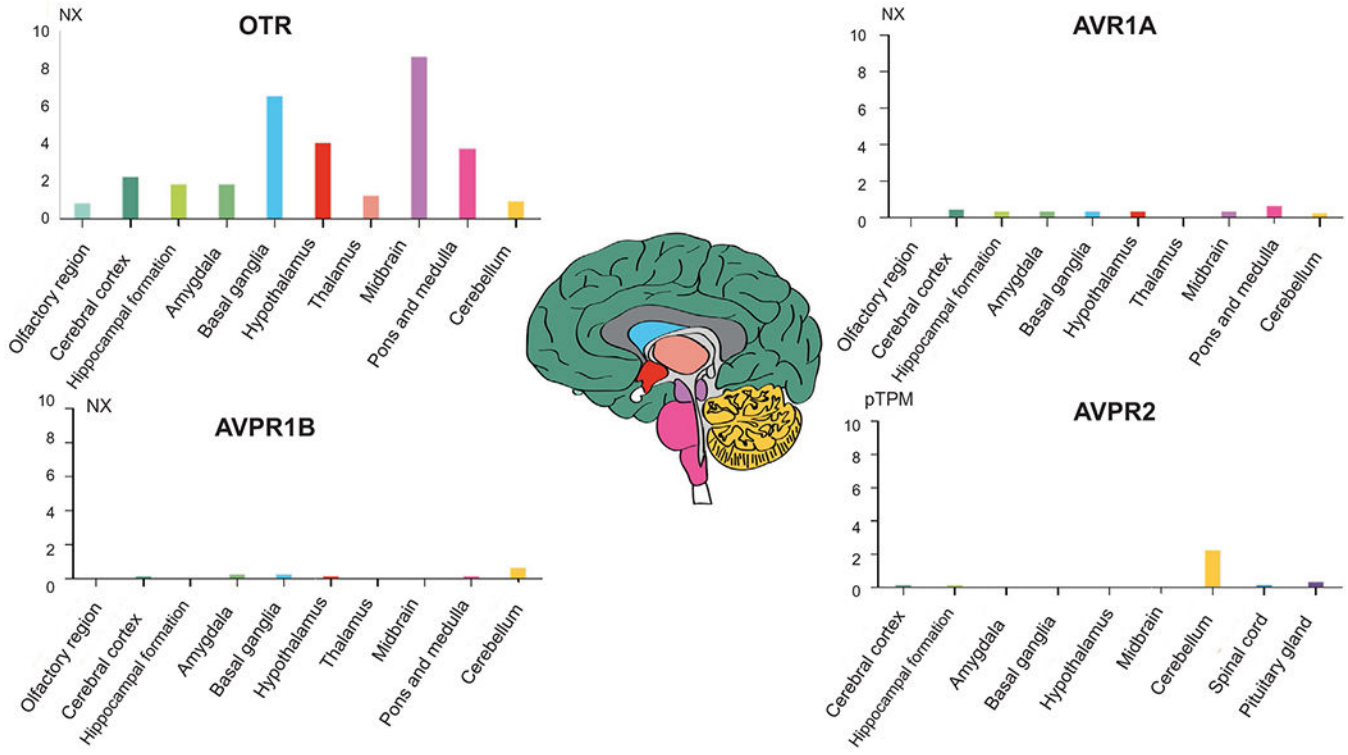

Fig. 9.3.

OTR, AVPR1A, AVPR1B, and *AVPR2* gene expression in the brain regions of the human brain. Color coding is based on brain region and the bar shows the highest expression among the subregions included. Consensus normalized expression (NX) levels were created for the brain regions for *OTR, AVPR1A*, and *AVPR1B* expression by combining the data from two transcriptomics datasets (GTEx and FANTOM5); pTPM (protein-coding transcripts per million) levels, corresponding to mean values of the different individual samples for respective subregions generated by GTEx were created for *AVPR2*.

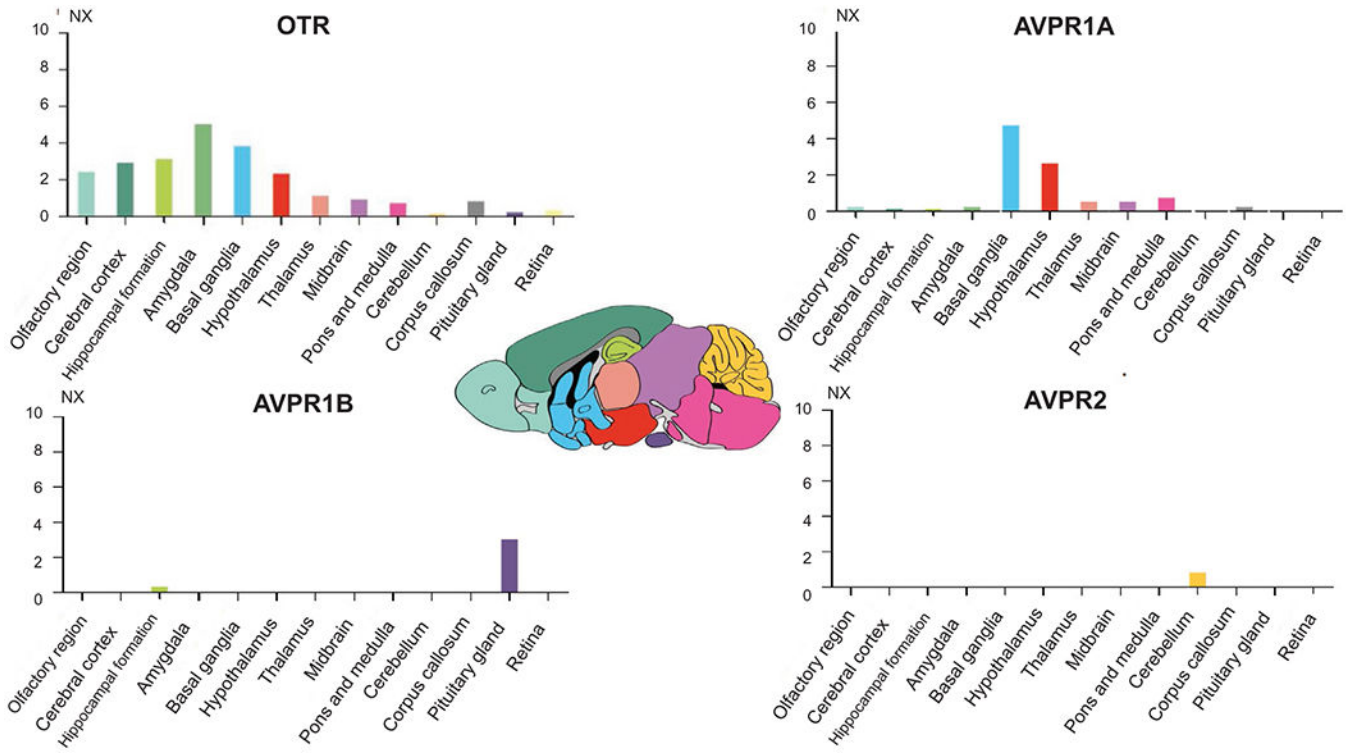

Fig. 9.4.

OTR, AVPR1A, AVPR1B, and *AVPR2* gene expression in the brain regions of the mouse brain. Color coding is based on brain region and the bar shows the highest expression among the subregions included. Consensus normalized expression (NX) levels were created for the brain regions by pTPM (protein-coding transcripts per million) of the individual HPA Mouse dataset samples in mouse.