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The Contribution of Oxytocin and Vasopressin to Mammalian Social Behavior: Potential Role in Autism Spectrum Disorder

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Abstract
Oxytocin (OT) and arginine-vasopressin (AVP) are 2 peptides that are produced in the brain and released via the pituitary gland to the peripheral blood, where they have diverse physiological functions. In the last 2 decades it has become clear that these peptides also play a central role in the modulation of mammalian social behavior by their actions within the brain. Several lines of evidence suggest their involvement in autism spectrum disorder (ASD), which is known to be associated with impaired social cognition and behavior. Recent clinical trials using OT administration to autistic patients have reported promising results. Here, we aim to describe the main data that suggest a connection between these peptides and ASD. Following a short illustration of several major topics in ASD biology we will (a) briefly describe the oxytocinergic and vasopressinergic systems in the brain, (b) discuss a few compelling cases manifesting the involvement of OT and AVP in mammalian social behavior, (c) describe data supporting the role of these peptides in human social cognition and behavior, and (d) discuss the possibility of the involvement of OT and AVP in ASD etiology, as well as the prospect of using these peptides as a treatment for ASD patients.
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Autism Spectrum Disorder

Symptoms

Autism is a broadly-defined developmental disorder that mainly affects behavior and cognition. It is diagnosed by symptoms in 3 categories: impairments in social behavior, verbal and nonverbal communication deficits, and repetitive movements and stereotyped behavior [1]. Social interaction impairments are the most characteristic deficits in autism spectrum disorder (ASD). These impairments include a failure to use standard nonverbal behaviors (eye contact, affective expression) to regulate social interactions with others, failure to share enjoyment, interests and achievements with others, and a lack of social and emotional reciprocity. Individuals with ASD have difficulties in showing empathy, recognizing faces and processing the affective states of others. Because the

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severity and the age of onset of symptoms can vary greatly among different individuals, autism is highly heterogenic, hence the term 'autism spectrum disorder'.

In recent decades, there has been a sharp increase in the number of children diagnosed with autism. This increase is at least partially due to changes in the diagnosis processes and greater public awareness, but it may also reflect an actual increase in ASD cases [2, 3]. Unlike many other brain disorders, ASD, which is 3–5 times more common in males than in females [4], lacks any clear unifying pathology at the molecular, cellular or system levels [5]. This fact makes the exploration of the biological basis of ASD extremely challenging [6].

Etiology

Despite the intense research focus on ASD in recent years, the underlying etiology remains obscure. Genetic research involving twins and family studies strongly supports a significant contribution of genetic factors to ASD etiology [7, 8]. Nevertheless, no particular model of genetic transmission has been implicated in ASD and no single gene has been found to cause the disorder [9]. Moreover, in recent years it has been shown that dozens of distinct genetic disorders, ranging from single nucleotide mutations to chromosomal abnormalities, can result in ASD symptoms [10]. However, these genetic disorders are only responsible for about 10% of ASD cases [11]. Thus, the genetic basis underlying ASD appears to be very complex, and could be attributed either to the combinational effects of common genetic variants or to rare mutations [12], such as chromosomal deletions and duplications that lead to the autistic phenotype [8].

In addition to the possible contributions of genetic factors, environmental elements may also play a role in causing ASD [13]. Such environmental factors may include certain foods, infectious diseases, environmental toxins, prenatal stress and others [12]. However, no single environmental factor has been shown to be a definite cause for ASD [14].

Recently, several investigators have suggested that the pathogenesis of ASD may involve epigenetic regulatory mechanisms [15, 16]. The term 'epigenetic' is defined as heritable alterations in gene expression caused by mechanisms other than changes in DNA sequence [17]. The 2 main molecular epigenetic mechanisms are posttranslational histone modifications and DNA methylation [18]. Methylation of DNA is a direct chemical modification of a cytosine that is immediately followed by a guanine [19]. These *CpG* dinucleotide sequences are highly underrepresented in the genome, and often occur in small clusters known as CpG islands [20]. Hypermethylation of CpG islands in the vicinity of genes is usually considered to be a transcription-suppressing mechanism [19], although it has been shown in some cases to be associated with transcription activation [21].

In 2 different monogenetic disorders associated with ASD, Rett syndrome [22] and fragile X syndrome [23], an epigenetic component was shown to be involved in the etiology of the disorder. Rett syndrome is a complex neurological disorder caused by a mutation in the methyl-CpG-binding protein 2 [24, 25], one of the key regulators of epigenetic processes in the brain [26]. Fragile X syndrome occurs through an expansion of a *CGG* repeat in the 5′-untranslated region of the *FMR1* gene, rendering the region susceptible to epigenetic silencing [27, 28]. Additional evidence for the involvement of epigenetic modifications in ASD arises from studies demonstrating a link between genomic imprinting, which is an epigenetic process responsible for the parental monoallelic expression of some genes, and susceptibility to autism [29, 30]. Thus, it seems likely that a complex interaction between multiple genetic, environmental and epigenetic factors determines the etiology of ASD [31].

Oxytocin and Vasopressin

Structure, Function and Location

Oxytocin (OT) and arginine-vasopressin (AVP) are 'twin' 9-amino acid peptides (nonapeptides) that in mammals are produced mainly in the brain [excellently reviewed in 32, 33]. They have variable hormonal actions in the periphery and the CNS. Peripheral functions of OT include regulation of uterus contractions during labor and modulation of milk ejection during suckling. Thus, OT is strongly connected to maternal functions. AVP, in contrast, is responsible for very different physiological functions, including the regulation of water absorption in the kidney. As depicted in figure 1a, these peptides are quite similar, differing from each other in only 2 positions of their 9-amino acids sequence. They are both produced by nonoverlapping populations of neurons in the same hypothalamic nuclei, the supraoptic nucleus and the paraventricular nucleus (PVN). The supraoptic nucleus and PVN contain large magnocellular peptidergic neurons that send their axons to the posterior pituitary (neurohypophysis) where they release AVP and OT into the blood (fig. 2) [34].

The PVN also harbors smaller parvocellular neurons, each expressing OT or AVP, which project to certain ar-

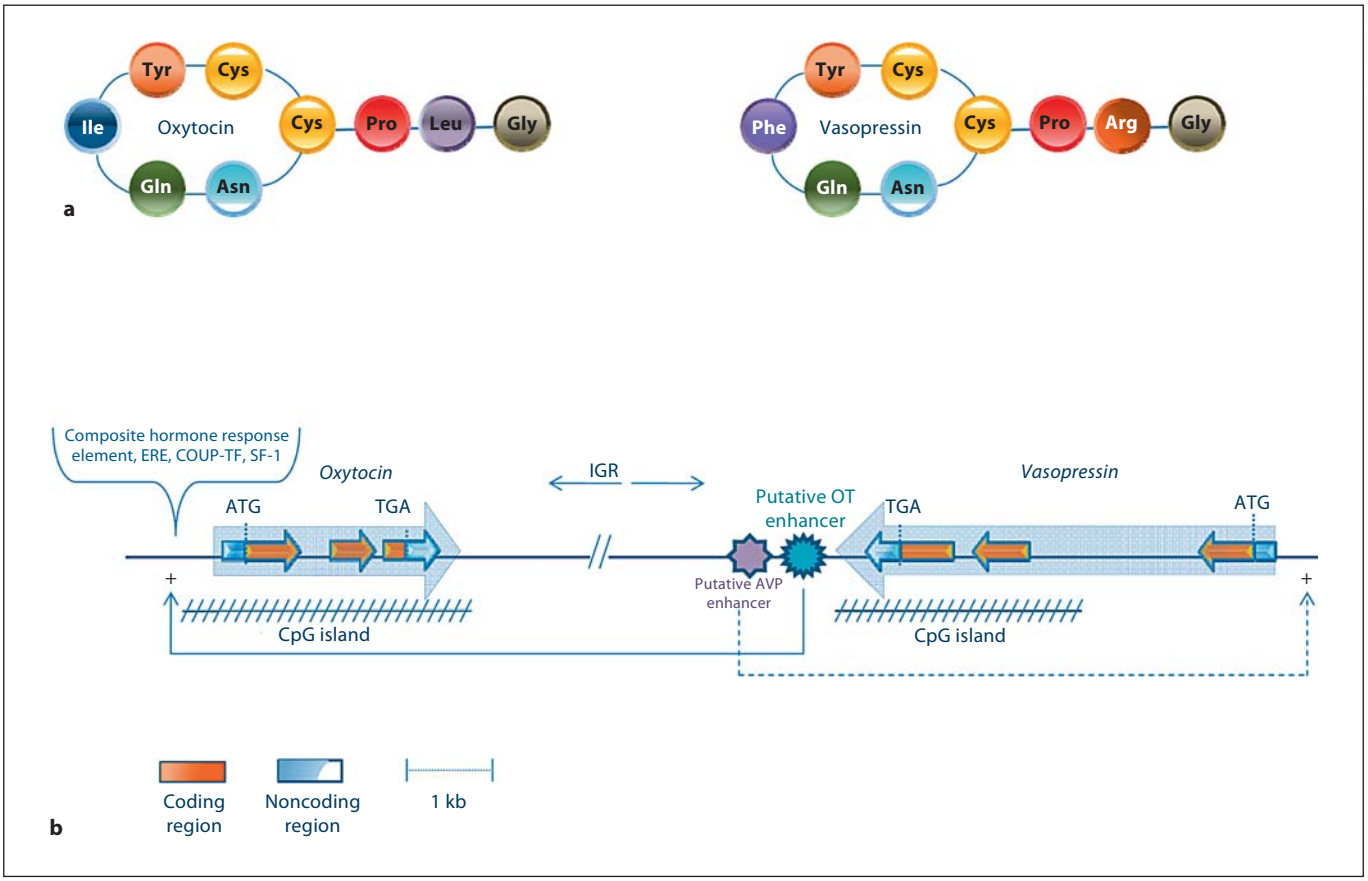

Fig. 1. The OT and AVP peptides and their genes: **a** Schematic structure and sequence of the OT (left) and AVP (right) peptides. Only 2 amino acids differ between these nonapeptides, both of which contain a disulfide bond between Cys residues in positions 1,6. **b** The genes coding for OT and AVP, which are thought to be a product of a gene duplication event, are located near each other on the genome with opposite transcription orientations. The relatively short intergenic region (3.6 kb in mouse) harbors enhancer elements that are important for the proper expression of both genes. The location of a CpG island, which may be involved in epigenetic regulation of gene expression, is depicted for each of the genes. A composite hormone response element which may mediate the effects of estrogen was found upstream to the *OT* gene.

eas of the CNS. AVP is also produced in a few other brain areas, including the suprachiasmatic nucleus, the brain's circadian pacemaker, as well as the medial amygdala (MeA) and the bed nucleus of the stria terminalis (BNST) [35], which both send AVP-containing projections to the lateral septum (LS). The expression of AVP in the MeA and BNST, and hence its release in the LS, is known to be androgen-dependent, with significantly higher levels in males [36].

Genes

OT and AVP are coded by homologous genes that are thought to have emerged from a gene duplication incident prior to vertebrate divergence [37]. Accordingly, almost all invertebrates have only 1 *OT/AVP* homolog while vertebrates have 2 [38, 39]. As illustrated in figure 1b, the mammalian *OT* and *AVP* genes are located near each other in the genome. For example, in the mouse genome they are both located on chromosome 2 [40], separated only by an intergenic region of 3.6 kb that contains several regulatory elements important to the proper expression of both genes [41, 42]. The mRNAs of both peptides are translated into a precursor preprohormone that, besides the nonapeptide itself and a signal peptide, contains a common polypeptide named neurophysin. This precursor is processed and cleaved in dense-core vesicles during its transport to the release sites.

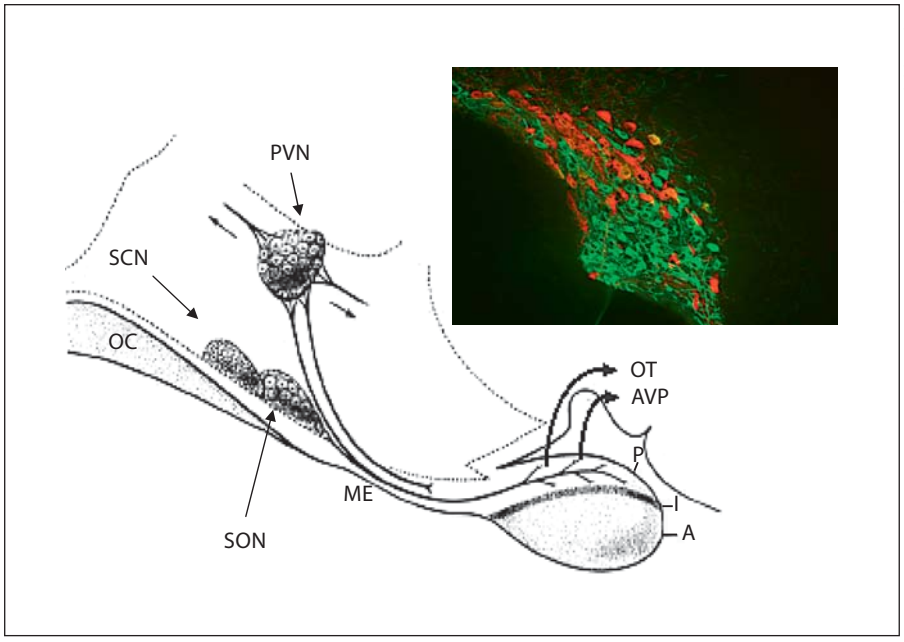

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Fig. 2. The hypothalamo-neurohypophysial system: a schematic illustrating the 2 hypothalamic nuclei, the PVN and the supraoptic nucleus (SON), both of which synthesize and release OT and AVP. Also depicted is a 3rd nucleus, the suprachiasmatic nucleus (SCN), wherein AVP alone is synthesized. The magnocellular neurons of the PVN and SON, which are the main source of OT and AVP, release these 2 peptides into the blood via their projections to the posterior pituitary (neurohypophysis). The magnocellular neurons of the SON are pictured in the inset, stained for OT (red) and AVP (green) using immunocytochemical labeling.

Release in the CNS

Since the blood-brain-barrier is almost impermeable to these peptides, their concentration in the CNS is independent of the magnocellular nerve terminals located in the neurohypophysis. The mechanisms by which OT and AVP are released in the CNS are still a matter of debate and were excellently reviewed by Landgraf and Neumann [43]. Generally speaking, it is agreed that these neuropeptides do not act in a synaptic cleft-dependent manner like classical neurotransmitters, such as GABA or glutamate [44]. OT and AVP may be released from neuronal terminals in discrete brain areas and act in a paracrinic fashion, or they may be released into the cerebrospinal fluid and act globally in the brain as neurohormones on cells that express their receptors [45].

Paracrinic action of OT and AVP in the CNS may emerge from several distinct sources. Axon terminals of PVN parvocellular neurons are probably responsible for OT and AVP release in the specific brain areas to which they project. Additionally, AVP is produced by neurons located at a few nuclei besides the supraoptic nucleus and PVN, such as the MeA and BNST, and is released by these neurons at specific brain areas such as the LS.

Recently, another source for paracrinic action of these peptides was suggested, one that involves direct axonal innervations of certain brain areas by magnocellular neurons [46, 47]. Nevertheless, as discussed below, the receptors of these peptides are spread widely throughout the CNS, suggesting a much wider presence of the peptides themselves. Thus, OT and AVP are likely to also have a neurohormonal action mediated by the release of the peptides from dendrites of the PVN magnocellular neurons, which are located in close proximity to the 3rd ventricle, into the ventricle, which works to change the global concentrations of OT and AVP in the CNS in response to various stimuli [43, 48].

Receptors

The AVP and OT signals are transuded into physiological effects via their respective AVP and OT receptors. The 3 major types of the AVP receptor (AVPR) have been typified: AVPR1a, AVPR1b and AVPR2 [32, 49]. For OT, only a single receptor type (OTR) has been identified [50]. Since the AVPR2 receptor is hardly expressed in the brain and was not shown to influence social behavior, it will not be referred to in this review.

All OT and AVP receptors are members of the G protein-coupled receptor family. Both AVPR1a and AVPR1b couple to the same type of G protein. Their ligand-binding leads to the activation of protein kinase C through the effector enzyme phospholipase C (PLC). In contrast to the pathway-specific coupling of the AVP receptors, the OTR binds various G proteins and can therefore activate diverse 2nd messenger machineries in the same cell type [51].

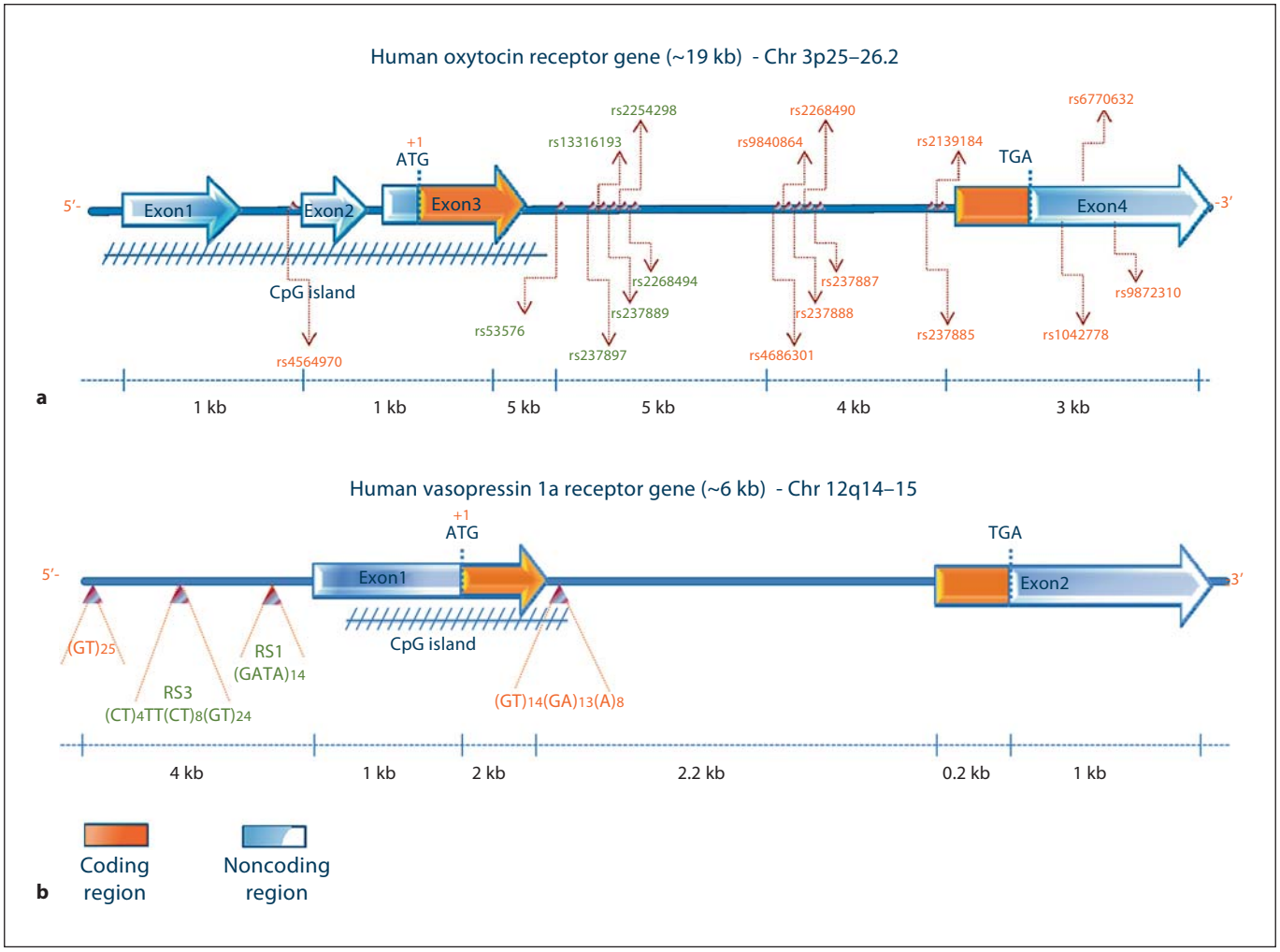

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Fig. 3. The human *OTR* and *AVPR1a* genes: the locations of exons and introns, as well as CpG islands, are illustrated. Also depicted are locations of the polymorphisms (orange), some of which (green) are suspected to be genetically associated with ASD. These elements include intronic SNPs of the *OTR* gene (**a**) and microsatellite elements of the *AVPR1a* gene (**b**).

In humans, the OTR (fig. 3a) is transcribed from a single copy gene on chromosome 3p25–3p26.2 and consists of 3 introns and 4 exons [52]. The *AVPR1a* and *AVPR1b* genes, which are each comprised of 2 exons separated by 1 large intron, are situated on distinct chromosomes in the human genome. The *AVPR1a* gene (fig. 3b) is located on chromosome 12q14–15 [53], while the *AVPR1b* gene has been mapped on chromosome 1q32 [54]. All 3 receptors are expressed in different organs in the periphery. The OTR is expressed in the uterus, mammary gland, placenta, amnion, ovary, testis, thymus, heart and kidney [55]. The AVPR1a is mainly found in the kidney, liver and in the vascular system [53]. The AVPR1b is prominent in the anterior pituitary, but was also detected in various peripheral organs including the kidney, thymus, heart, lung, spleen, uterus and breast [56]. In addition to their peripheral distribution, OTR and AVPR1a are widely expressed in the brain while AVPR1b brain expression is much more restricted [57].

Distribution of OT and AVP Receptors in the Brain

The OTR and AVPR1a expression profiles in rat and hamster brains have been investigated by several research groups. Results [reviewed in 33, 55] have indicated that the expression profile of both receptors is not only brain-region specific, but also sex-specific and influenced by

gonadal steroids. Moreover, studies that focused on these receptors' expression patterns in the brain revealed that they exhibit highly species-specific distribution profiles. For example, in the rat brain, OTR is highly expressed in the hippocampal ventral subiculum [58]. However, no such expression has been detected in the hamster, guinea pig, rabbit or human brains. These facts suggest a complex regulation of the expression of these receptors. In the human brain, OTR was found to be expressed in several subcortical areas including the basal nucleus of Meynert, areas of the basal nuclei such as the globus pallidus, limbic areas such as the lateral septum, hypothalamic areas such as the mammillary nuclei, and in brainstem areas such as the substantia nigra pars compacta [55].

Overall, the sharp contrast between the evolutionarily conserved, spatially restricted expression of the peptides themselves and the widespread, species- and sex-specific expression of their receptors lends credence to the notion that it is the receptor distribution which governs the OT and AVP influence on the highly variable mammalian social behavior [59, 60].

Expression Regulation of OT and AVP Receptors

As previously mentioned, sex steroids seem to be part of the mechanisms regulating the brain's oxytocinergic and vasopressinergic systems [61]. Estrogen is the most well-studied gonadal steroid in respect to its effect on the receptors' expression. For example, OTR levels in the uterine and mammary myoepithelium increase markedly in response to estrogen at late pregnancy [62]. In the rat *OTR* promoter region, there is a classical estrogen response element that likely mediates the sex-specific effects of estrogen on the gene transcription [63]. Moreover, the *OTR* promoter includes other regulatory elements such as IL-1β, IL-6, AP-1 and APRE, all of which could be vital for the transcriptional regulation of the *OTR* gene [55, 64, 65].

Repeated elements or microsatellites within gene promoters could also regulate transcription. Such elements exist in the *AVPR1a* promoter region, and were found to determine the species-specific expression pattern of the AVPR1a in the vole brain [66], as will be discussed in detail below.

In addition to genetic regulatory elements, transcription is also regulated by epigenetic mechanisms that may mediate tissue and sex-specific gene expression [18]. So far, 3 different studies have supported the hypothesis that OTR expression is regulated by DNA methylation. The 1st study confirmed that hypermethylation of a regulatory element within the 3rd intron of the human *OTR* gene is associated with its low levels of expression in non-expressing tissues [67]. The 2nd study demonstrated that growing the human hepatocellular carcinoma cells with the demethylating agent, 5-azacytidine, dramatically increases OTR mRNA levels. This research pointed to a CpG island located between 140 bp upstream and 2,338 bp downstream of the human *OTR* transcription start site where a 400-bp region was found to be highly methylated in the liver, a tissue in which the *OTR* gene is constitutively silenced [68]. A 3rd study found that hypermethylation of several *CpG* sites within the human *OTR* promoter was associated with decreased levels of the OTR mRNA in the temporal cortex tissue of individuals with ASD as compared to age-matched controls [69]. This study strengthens the association between DNA methylation of the *OTR* promoter and the expression of the gene, and suggests a role for *OTR* gene methylation in ASD.

OT, AVP and Animal Social Behavior

As mentioned above, OT and AVP are highly conserved in the animal world, with homologs existing at least 700 million years ago [38, 39]. Studies in widely diverse animal species, ranging from worms to humans, have shown that the role of OT/AVP homologs in modulation of social and reproductive behavior was also conserved during evolution [70]. Overall, AVP seems to play a larger role in male behavior, especially those behaviors related to reproductive functions, while OT is more frequently associated with female activities [61]. Both peptides, however, have behavioral roles in males and females. Below we will discuss a few of the most compelling studies which demonstrate the central role of OT and AVP in the social behavior of several distinct mammalian species.

Maternal Behavior in Rats and Sheep

During birth, the female body undergoes a series of extreme physiological changes within a short period of time. In most mammals, these physiological changes are accompanied by a rapid onset of maternal behaviors, which are primed by the high level of plasma estrogen during late pregnancy. In rats, maternal behavior is initiated only after parturition as virgin females avoid pups. Rat maternal behavior includes nest building, lactation and maternal aggression towards intruders, as well as pup licking, grooming and retrieval [71].

Several brain areas have been implicated in postpartum maternal behavior, including the hypothalamic

MPOA, the BNST and the LS. OTR mRNA levels in these areas are higher around the time of birth, probably due to the high estrogen level [72–74], and were found to be correlated with the level of maternal behavior displayed by female rats [75]. Peripheral and central levels of OT are highest postpartum due to induction of OT release from the brain by a combination of vaginocervical stimulation during birth and the lactation activity immediately following it [55]. Thus, OT was suspected of having a role in the postpartum induction of mammalian maternal behavior [76]. Indeed, following priming with estrogen, virgin female rats centrally infused with OT display full maternal behavior [77]. Accordingly, infusion with an OTR antagonist could block the postpartum onset of maternal behavior in rats [78, 79]. Using fMRI imaging Febo et al. [80] showed that OT administration to postpartum female rats initiated activity in brain areas which are active during pup suckling. In sheep too, central OT administration, as well as endogenous OT release induced by vaginocervical stimulation, stimulate maternal behavior in estrogen-primed nonpregnant females [81]. Moreover, a ewe is able to recognize and selectively feed its own lamb from the moment it is born. This olfactory memory of the lamb was shown to be facilitated by central OT release in the olfactory bulb [82]. These studies implicate OT in the induction of maternal behavior in mammals.

Pair Bonding in Voles

Voles (genus *Microtus*) show a diverse social structure amongst their different species. Prairie voles, for example, are monogamous, a behavior rarely seen among mammals. Male and female prairie voles form long-term bonds that typically last until one partner dies. In the lab, sexually inexperienced voles exhibit nonselective affiliation behavior. However, following mating, both the male and female show behavioral changes indicative of pair bonding, such as sharing a nest and displaying extensive parental behavior [83].

Most importantly, prairie voles show a strong preference for a familiar mate versus a stranger, a preference that is used for a quantitative test assessing pair bonding. During the test the examined animal is placed in a central chamber, which is connected by tubes on both sides to lateral chambers. Two stimulus animals, usually a mate and a stranger, are placed in the lateral chambers. The time spent by the examined animal in each of the chambers serves as an indication of the animal's preference. Several studies demonstrated that following mating, prairie voles spent much more time with their mate than with a stranger [84].

In contrast, members of nonmonogamous vole species, such as meadow and montane voles, do not show any preference towards a mate. The fact that these evolutionarily close species show such divergent social behavior provides an excellent opportunity for comparative investigations into the biological mechanisms underlying pair bonding [83–85].

Early studies have shown that CNS infusion with OT or AVP enhances mate preference, while infusion of OTR and AVPR1a antagonists impairs mate preference [86]. These effects seem to be sex-dependent: AVP is more effective in males, and OT is more effective in females. In addition, neuroanatomical studies have found that while monogamous and nonmonogamous species have very similar distribution patterns of OT and AVP cells and projections, major differences exist in the distribution patterns of their receptors in the brain, mainly in limbic areas. For example, the monogamous prairie voles express significantly more OTR in the nucleus accumbens and AVPR1a in the ventral pallidum, while the nonmonogamous montane and meadow voles express higher levels of both receptors in the LS and ventromedial hypothalamus. These studies [reviewed in 87, 88] suggest that pair bonding, which differs markedly between vole species, is regulated by central OT and AVP.

Indeed, functional studies have shown that OT and AVP actions in specific brain areas are responsible for certain aspects of the voles' social behavior. For example, local infusion of OTR antagonist into the nucleus accumbens of female prairie voles or AVPR1a antagonist into the ventral pallidum of male prairie voles inhibited their mate preference. Most astonishing, overexpression of the *AVPR1a* in the ventral pallidum of meadow vole males induced partner preference behavior in these nonmonogamous animals [89]. These results [reviewed in 59, 60, 83, 87, 88, 90, 91] suggest that a change in the expression of a single gene (the *AVPR1a*) in a specific area of the adult brain may create a robust change in the animal's social behavior.

One genetic factor that may be responsible for the difference in the AVPR1a brain expression pattern between prairie and meadow voles is a microsatellite DNA element located 660 bp upstream to the transcription start site of the *AVPR1a* gene. This repetitive DNA is on average 500 bp long in prairie voles, but only 50 bp long in the nonmonogamous meadow and montane voles [66, 92]. Moreover, even within prairie voles, interspecies differences in the microsatellite length seem to have an impact on the animal's social behavior: it was found that animals with a longer microsatellite are more prosocial than those with a shorter microsatellite [83, 93]. These results suggest that

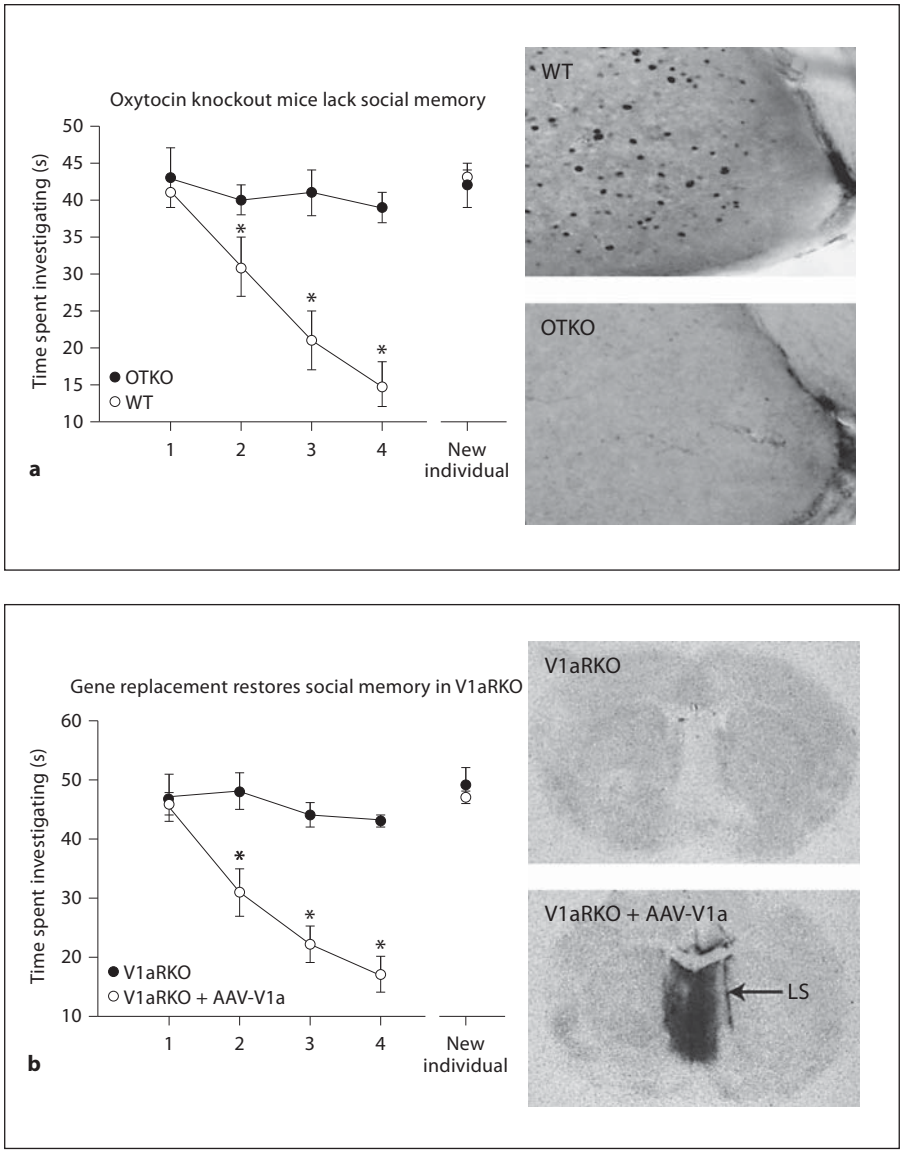

Fig. 4. Social recognition memory in mice depends on OT activity in the MeA and AVP activity in the lateral septum. **a** Left: Social recognition memory paradigm with wild-type (empty dots) and *OT*-knockout mice (black dots) show that *OT*-knockout mice are impaired with regard to social recognition memory, and therefore investigate familiar and novel conspecifics for the same duration of time. Right: Fos immunostaining shows the lack of activity in the MeA of an *OT*-knockout mouse (lower picture) following an encounter with a novel juvenile, as compared to a wild-type mouse (upper picture). **b** Left: While *AVPR1a*-knockout mice (black dots) are impaired in their social recognition memory, overexpression of the gene in the lateral septum using a viral vector (empty dots) is sufficient to restore social memory. Right: Autoradiography shows the lack of AVPR1a-binding sites (dark staining) in the brain of a knockout mouse (upper picture) compared to the strong expression of binding sites following viral-mediated gene delivery to the lateral septum (lower panel). Adapted from Lim and Young [60].

diverse alleles of genetic untranscribed elements may influence the variability in social behavior within a population of animals.

Social Recognition Memory in Rats and Mice

The ability of an animal to recognize a familiar individual is critical for many aspects of mammalian social behavior, especially for establishing family relationships and clan organization. In some cases, recognizing only general characteristics of the individual – such as strain, gender or reproductive state – may be sufficient. In other cases, it is advantageous to recognize the specific individual by remembering its specific features.

Most mammals rely primarily on olfactory cues for social recognition. A meeting between 2 unfamiliar rats or mice usually starts with a period of intensive olfactory investigation, mainly at the face and anogenital regions, which precedes further social interactions such as mating or aggressive interaction.

Based on the natural tendency of rats and mice to closely investigate novel individuals, a simple laboratory test to investigate social recognition memory capacities was developed [94]. In this test, an unfamiliar juvenile conspecific is introduced into the cage of a resident adult rat for a period of 5 min. The time spent by the adult rat on olfactory investigation of the juvenile is measured.

Then, following an interval (usually 30–120 min) the same juvenile is reintroduced into the cage and again, the time spent by the adult rat on olfactory investigation of the juvenile is measured. If the 2 measured times do not differ significantly, it can be deduced that the adult rat did not recognize the juvenile. If, however, the adult rat spent less time investigating the juvenile on the 2nd meeting, it can be deduced that the adult rat had a memory trace of the juvenile.

In a more elaborate version of the test, this procedure is repeated several (usually 4) times with the same juvenile, until the adult displays a very short investigation time. The last (5th) encounter is with an unfamiliar juvenile to control for fatigue or stimulus-unspecific habituation. Following this type of habituation-dishabituation paradigm, the adult rat can remember the tested juvenile for at least a week (Wagner, unpubl. results).

Both OT and AVP were found to be crucial for social recognition memory in rats and mice (reviewed in [95–97]). As shown in figure 4a, *OT*-knockout [98] (and *OTR*-knockout [99]) male and female mice showed a specific loss of social recognition memory even though they displayed a normal sense of smell [100]. In the case of *OT*-knockout mice, injection of OT into the MeA prior to the first exposure to the juvenile enabled social recognition memory in the injected adult [101]. Thus, OT action in the MeA seems to be crucial for social recognition memory. Indeed, MeA-specific OTR disruption by antisense injection caused impairment in social recognition memory [102]. OT infusion to other brain areas, such as the OB and LS, was also found to enhance social memory [103]. Therefore, it seems that OT may act in several brain regions to modulate the effect of social stimuli [104, 105].

AVP also plays an important role in social recognition memory. For example, Brattleboro rats, which carry a spontaneous null mutation in the *AVP* gene, are impaired in social recognition memory [106], similar to *AVPR1a*-knockout mice [107]. In the case of AVP, it seems that the LS is the most important brain area for social recognition: infusion of AVP into the LS of Brattleboro rats [106] restores social recognition memory, as does viral-mediated delivery of a functional *AVPR1a* gene into the LS of *AVPR1a*-knockout mice [108] (fig. 4b). However, the LS may not be the only brain area involved: a recently discovered population of AVP-expressing neurons in the OB of rats may also be instrumental for social recognition memory [109].

Overall, animal studies that have investigated the role of OT and AVP in social behavior point to a concerted action of these peptides in specific brain areas that modulate a neuronal network responsible for certain aspects of mammalian social behavior [59, 70].

Oxytocin, Vasopressin and Human Social Behavior

When summarizing the data regarding the role of OT and AVP in human social behavior, it is important to note that most human studies correlate various parameters with peptide concentrations in either the blood, saliva or urine, fluids that can be collected with no or minimal invasion. However, it is the cerebrospinal fluid concentration that is the truly relevant measure. In addition, many studies that deal with the human response to the peptides deliver them via intravenous infusion. In these cases, only a small fraction of the peptides penetrates the blood-brain barrier and arrive at the brain. Recently, more studies are beginning to use intranasal application of peptides to deliver them efficiently to the CNS [110]. This relatively new method may also be used in the near future for therapeutic applications.

Anxiety

In humans, AVP seems to play an anxiogenic role [33]. Elevated expression of AVP in the PVN is associated with an increased level of anxiety and arousal. In contrast, OT causes relaxation and a decrease in anxiety levels. This effect of OT is at least partially caused by the inhibition of the hypothalamic-pituitary-adrenal axis. Endogenous OT release in lactating women is associated with decreased levels of plasma ACTH and cortisol as well as reduced stress responses [111–113]. Similar results were obtained with women receiving positive physical contact [114]. Moreover, exogenous application of OT was shown to act synergistically with social support to reduce endocrine and psychological stress responses [115]. Furthermore, intranasal delivery of OT was shown to increase positive communication and reduce cortisol levels during couple conflict [116].

Another mechanism by which OT may reduce anxiety is via modulation of amygdala-mediated autonomic fear responses through amygdala OT receptors. fMRI studies have shown that exogenous OT infusion reduces fear responses in the amygdala [117–120].

Trust

In humans, trust is necessary for social approach and affiliation. In a landmark study, Fehr and his colleagues [121] used a monetary game to assess the effect of OT on

trust in humans. In the experiment, male volunteers were given a sum of money and were presented with the opportunity to invest a portion of it in the hands of an unknown partner. Investing in the other partner could lead to higher payoffs for both players, but the investor always ran the risk of losing the invested money in the hands of the trustee. The researchers found that intranasally-delivered OT caused a significant increase, as compared to the placebo, in the individual's willingness to accept risks that arose through interpersonal interactions. Later, they showed that the same treatment prevented people from losing trust in others who had breached it [122]. Using fMRI, they found that this effect of OT was associated with a reduction of activity in several brain regions linked to fear processing, including the amygdala.

Social Cognition

Intranasal OT administration enhanced the ability of humans to recognize the affective state of other individuals from facial cues [123]. It also increased the duration of their gazes towards the eye region of faces [124]. Recently, it was found that intranasally administered OT increased the ratings of facial trustworthiness and attractiveness [125] and enhanced processing and memory of positively-expressing faces [126, 127]. Additionally, several studies have shown that OT plays a role in human parenting [128–130]. Altogether, these results suggest that OT plays a role in facial processing and human interpersonal communication.

Interestingly, a study by Shamay-Tsoory et al. [131] demonstrated that OT administration facilitated envy (when the subject believed that he/she earned less money in a monetary game than the other participant) and enhanced gloating over the other's misfortune (when the subject believed that he/she earned more than the other participant). These results suggest that OT is not merely a prosocial neurohormone, but also plays a complicated role in a wide range of social behaviors [132, 133]. Moreover, De Dreu et al. [134] recently used an intergroup monetary game (intergroup prisoners' dilemma-maximizing differences game) to investigate the role of OT in parochial altruism in the context of intergroup conflict in humans. Their results clearly show that OT administration (compared with placebo) drives a 'tend and defend' response which enhances in-group trust and cooperation, and at the same time promotes defensive, but not offensive, aggression toward competing out-groups. These results support the hypothesis that the oxytocinergic system in the human brain is part of evolutionary adaptation that contributes to individual survival by promoting and maintaining social life, hence enhancing group protection against eminent threats, including competing out-groups.

Human AVPR1a and OTR Genes

The human *OTR* and *AVPR1a* genes each contain a distinct type of polymorphism in noncoding sequences that were shown to be associated with changes in social behavior [135, 136]. In the case of *AVPR1a*, the main polymorphism is in 4 microsatellite elements that are located in the promoter and intronic regions (fig. 3b). Of these elements, the most well-studied is the *RS3*, whose length varies between distinct alleles of the *AVPR1a* gene. Using the monetary 'dictator' game, Knafo et al. [137] demonstrated a positive correlation between the length of the *RS3* element and the level of altruistic behavior displayed by males. A genetic association was also found between the *RS3* polymorphism and several aspects of male marital bonding in a sample of 552 Swedish twin pairs [138]. In addition, *RS3* length was associated with the age of first sexual intercourse in males and females [139]. Moreover, an fMRI study revealed a correlation between *RS3* length and activity in the amygdala of male subjects in response to fearful faces [140].

These studies, taken together, suggest an association between polymorphism in microsatellite elements in the human *AVPR1a* gene promoter and male social behavior [135]. This association is similar to the one found in voles between the microsatellite element of the *AVPR1a* gene and male social behavior [66]. However, as long as the mechanism by which the polymorphism in the untranscribed microsatellite element exerts its action on receptor function remains unknown, the linkage between it and social behavior remains tentative. The requested mechanism may involve influence of the microsatellite element on the regulation of the *AVPR1a* gene transcription. Such an effect is supported by a correlation found between the receptor mRNA level in human postmortem hippocampus and the *RS3* length [137].

The human *OTR* gene spans roughly 19 kb and comprises 4 exons and 3 introns, harboring more than 30 mostly intronic single nucleotide polymorphisms (SNPs; fig. 3a). In a polymorphic region of the 3rd exon, which was found to regulate the gene expression [67], a single SNP *(rs53576)* was shown to be genetically associated with empathy and response to stress in male and female college students [141]. In a different study, the same SNP was found to be genetically associated with parental sensitivity [142, 143]. In both studies the *GG* allele was more prosocial than the *AA* and *AG* alleles.

A significant association was also observed between 3 single-tagging SNPs across the *OTR* gene region and human social behavior [144]. This behavior was modeled by the dictator game and another related paradigm, the social values orientation task. Both paradigms measure altruism and prosocial decisions.

Overall, genetic studies of the human *OTR* and *AVPR1a* genes suggest a strong but complicated association of polymorphisms in noncoding sequences of the receptor genes with various aspects of human social activity [135, 136, 145]. Nevertheless, the genetic mechanisms by which these polymorphisms exert their effects on behavior remain unclear. In vitro studies examining the direct impact of these polymorphisms on gene expression might close this gap.

OT, AVP and ASD

Because of their central role in mammalian social behavior, it is tempting to suspect that these neuropeptides are involved in the etiology of ASD [146], a disorder that is characterized by impaired social behavior and cognition. Indeed, several indications do point in that direction: first, dysfunction of the amygdala has been hypothesized to play a role in the development of ASD [147, 148]. This brain area shows a particularly strong expression of OT and AVP receptors [32, 33]. Moreover, OT administration and polymorphisms in the *AVPR1a* gene were found to affect amygdala responses in humans [119, 140, 149]. Second, individuals with ASD show a specific deficit in face recognition [1], which may be related to the specific deficits of *OT*-knockout and *OTR*-knockout mice in social recognition memory [95, 150]. Third, OT administration to humans was found to enhance the ability of inferring the mental states of others [123], an ability which is specifically impaired in ASD patients [1].

Fourth, ASD is well known to be sexually biased, with a rate of occurrence that is 3–5 times higher in males. The influence of OT and AVP on animal behavior is also known to be sexually biased, with stronger effects of OT on females and of AVP in males [61]. Furthermore, both the oxytocynergic and vasopressinergic systems in the mammalian brain are known to be sexually-dimorphic [151, 152]. Specifically, the expression of AVP in the MeA and BNST, 2 brain regions that were shown to play a central role in social and reproductive mammalian behavior, is much higher in males [36]. Thus, the sex-biased OT and AVP activity in the brain may be related to the sex-biased occurrence of ASD.

The connection between OT and ASD is also supported by several lines of direct evidence, which is discussed below: (1) plasma OT levels were shown to be lower in children with ASD relative to controls, (2) genetic associations between polymorphisms in the OT and AVP receptors and ASD, (3) hypermethylation of the OTR promoter in ASD patients, and (4) OT administration was found to improve social cognition and reduce stereotypic movements in people with ASD.

(1) Modahl et al. [153] reported a significantly lower level of plasma OT in children with low-functioning autism relative to age-matched controls. Later, these same researchers [154] reported that the low plasma OT levels in autistic individuals were correlated with higher levels of unprocessed OT precursor (OT-X) that may be explained by impaired processing of OT. Recently, Andari et al. [155] published similar observations of high-functioning autistic patients. On the other hand, Jansen et al. [156] found higher plasma OT levels than controls in adult individuals with ASD. This discrepancy could be explained by the different developmental stages of the subjects tested in the distinct studies (children vs. adults).

(2) Two genome-wide studies have identified the genomic region of the *OTR* (3p25.3) as a promising linkage site for ASD [157, 158]. Explorations of copy number variations associated with ASD identified several cases with deletions in chromosome 3 which abolished the *OTR* [69, 159]. Four independent genetic linkage and linkage disequilibrium studies in different populations, including a family-based study, have shown a genetic association between several SNPs of the human *OTR* and ASD [160–163]. One of these SNPs, *rs2254298*, was found to be associated with ASD in all 4 studies. A 5th study showed an association not only with the *OTR*, but also with the *OT* gene and ASD [164]. On the other hand, a study using 3 independent Caucasian populations found no genetic association between ASD with 18 SNPs of the *OTR* [165]. Nevertheless, this study did show a correlation between intronic SNPs in the *OTR* gene and mRNA levels in peripheral lymphocytes and postmortem amygdala tissue, hinting to a possible effect of these SNPs on the receptor expression. The *AVPR1a* gene was also shown to be genetically linked with ASD by 3 independent linkage and linkage disequilibrium studies [166–168] which found a genetic association between ASD and polymorphism in the microsatellite elements of the *AVPR1a* promoter. Overall, these studies support a weak genetic linkage between ASD and the *OTR* and *AVPR1a* genes.

(3) Recently, Gregory et al. [69] used genome-wide microarrays to identify copy-number variants in 119 individuals with ASD from multiplex autism families. They found a family in which one affected member had a heterozygotic deletion in the *OTR* gene, which he inherited from his mother. An affected sibling did not possess the deletion allele, but had a hypermethylated promoter of the *OTR* gene. The researchers hypothesized that such hypermethylation of the OTR promoter may cause downregulation of its expression, hence a similar phenotype to the deletion of the gene. To challenge this hypothesis, they examined DNA methylation at this region in 20 autistic individuals and 20 controls. Their results showed that individuals with ASD had a significantly higher methylation in 3 *CpG* sites in the *OTR* promoter as compared to controls. In addition, an examination of postmortem temporal cortex tissue from autistic individuals revealed the sites to be hypermethylated as compared to age-matched controls. This hypermethylation was correlated with a 20% reduction in OTR mRNA levels in the tissue of autistic individuals as compared to controls. The results of this study implicate, for the first time, the epigenetic regulation of *OTR* in the development of the disorder.

(4) In 2003, Hollander et al. [169] published the results of the first study exploring the effect of OT administration on subjects with ASD. They have conducted a double-blind placebo experiment in which OT was intravenously administered to 15 adults with ASD, each completing both OT and placebo challenges, hence serving as his or her own control. The OT/placebo was continuously infused during a 4-hour period during which repetitive behavior, one of the core symptoms of ASD, was assessed at 5 time points. Results showed that the frequency of repetitive behaviors decreased during the OT periods as compared to the placebo periods.

In a 2nd study, Hollander et al. [170] found that similar treatment induced long-term (2 weeks) improvement in the comprehension of affective speech by individuals with ASD, whereas the placebo had only a short-term effect. Preliminary data from the same group [171] show similar improvements using intranasal delivery of OT.

Recently, Andari et al. [155] investigated the behavioral effect of OT inhalation on 13 individuals with ASD. They found that OT enhanced interactions with the partner as well as feelings of trust and preference, and selectively increased the duration of gaze in the eye region of the face in pictures presented to the participants, an effect that is considered to be prosocial. In another recent study, Guastella et al. [172] showed improvement in the ability of subjects with ASD to recognize emotional states of others following intranasal OT administration. Altogether, these results suggest a therapeutic potential of OT through its action on the core dimensions of ASD.

Conclusions and Future Directions

It is clear that OT and AVP activities in the brain play an important role in mammalian social behavior [59]. However, their direct effects on neuronal activity, as well as their underlying mechanisms, remain unknown. Recent studies in humans have shown that social cognition and behavior are significantly modulated by these 2 peptides [173]. Do these peptides play a role in the etiology of ASD? Despite several sets of data supporting such a claim, it is still difficult to answer this question, as the biology underlying ASD is not well-understood. Nevertheless, the ability to efficiently deliver the peptides to the CNS via intranasal application and the resulting influence on human social behavior suggest that even if the brain oxytocinergic and vasopressinergic systems are not involved in ASD etiology, these peptides may be used to reduce ASD symptoms [171]. They can also be combined with other interventions, such as psychological and behavioral treatments, to improve the condition of individuals with ASD.

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