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CHAPTER 35

Oxytocin and experimental therapeutics in autism spectrum disorders

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Abstract: Autism is a developmental disorder characterized by three core symptom domains: speech and communication abnormalities, social functioning impairments and repetitive behaviours and restricted interests. Oxytocin (OXT) is a nine-amino-acid peptide that is synthesized in the paraventricular and supraoptic nucleus of the hypothalamus and released into the bloodstream by axon terminals in the posterior pituitary where it plays an important role in facilitating uterine contractions during parturition and in milk let-down. In addition, OXT and the structurally similar peptide arginine vasopressin (AVP) are released within the brain where they play a key role in regulating affiliative behaviours, including sexual behaviour, mother–infant and adult–adult pair-bond formation and social memory/recognition. Finally, OXT has been implicated in repetitive behaviours and stress reactivity. Given that OXT is involved in the regulation of repetitive and affiliative behaviours, and that these are key features of autism, it is believed that OXT may play a role in autism and that OXT may be an effective treatment for these two core symptom domains. In this chapter we review evidence to date supporting a relationship between OXT and autism; we then discuss research looking at the functional role of OXT in autism, as well as a pilot study investigating the therapeutic efficacy of OXT in treating core autism symptom domains. Finally, we conclude with a discussion of directions for future research.

Keywords: autism spectrum disorders; oxytocin; vasopressin; experimental therapeutics; treatment; social functioning; social cognition; repetitive behaviours

Introduction

Over the years, a number of researchers have observed that the peptide hormone oxytocin (OXT) may be implicated in autism and related autism spectrum disorders (ASD) given that repetitive behaviours and social deficits are core ASD symptom domains, and that OXT is involved in the regulation of repetitive and affiliative behaviours (Modahl et al., 1992; Panksepp, 1992; Waterhouse et al., 1996; McCarthy and Altemus, 1997; Insel et al., 1999; Hollander et al., 2003; Lim et al., 2005; Bartz and Hollander, 2006; Carter, 2007). In this chapter, we discuss the idea that OXT may be implicated in ASD and review recent efforts to target the repetitive behaviours and social cognition/functioning domains in ASD using intravenous and intranasal OXT administration. Specifically, we begin by providing a brief overview of ASD and its core symptom domains and address why OXT may be relevant to ASD; we then review evidence to date supporting

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a relationship between OXT and ASD, specifically focusing on studies of altered blood plasma levels in ASD, genetic studies involving the OXT and AVP V1a receptors and ASD and our research looking at the functional role of OXT in ASD, as well as a pilot study investigating the therapeutic efficacy of OXT in treating core ASD symptom domains.

Autism spectrum disorders

Autism and ASD are characterized by abnormalities in speech and communication, impaired social functioning and repetitive behaviours and restricted interests; this review will focus on the latter two symptom domains because they are most relevant to OXT. Social interaction impairments are the most characteristic deficits in ASD. These impairments include the failure to use standard non-verbal behaviours to regulate social interactions with others (e.g., gaze aversion when interacting with others, limited range of affective expression, or not directing affective expressions to others and difficulty coordinating gesture with speech to support communication). Failure to share enjoyment, interests and achievements with others is also characteristic, as is a lack of social and/or emotional reciprocity. More generally, individuals with ASD have difficulty engaging in two-way interactions, and interaction partners are often left with the impression that they are aloof, passive or somewhat odd. Finally, awareness of and/or interest in others are often impaired, which can undermine the individual's ability to be empathic. In addition to these general social deficits, individuals with ASD show specific social cognitive deficits, in particular difficulties recognizing faces (Szatmari et al., 1990; Davies et al., 1994; Barton, 2003), and difficulties processing the affective states of others, through both facial displays (Hobson et al., 1988; Tantam et al., 1989) and tone of voice (Hobson et al., 1988; Rutherford et al., 2002).

Repetitive behaviours and narrow, restricted interests define the third symptom domain. These include intense preoccupations that can be abnormal in their intensity, or content. In addition, preoccupation with parts of objects and repetitive behaviour directed at objects are also characteristic, as is rigid adherence to routines and rituals and a desire for sameness. Some individuals also exhibit stereotyped and repetitive motor mannerisms, typically involving the hands (e.g., clapping and finger flipping) or the whole body (e.g., rocking).

Oxytocin and autism spectrum disorders

Oxytocin

As described in detail elsewhere in this volume, OXT is a nine-amino-acid peptide, or nonapeptide. It is synthesized in magnocellular neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus and secreted into systemic circulation (via the posterior pituitary) where it acts as a hormone, facilitating uterine contractions during parturition and milk let-down (Burbach et al., 2006). However, OXT and the structurally similar peptide arginine vasopressin (AVP) are also released within the brain where they act as neuromodulators. In the brain, these neuropeptides are released from multiple sites of the neuronal membrane, but especially dendrites, and can act on relatively distant targets (Landgraf and Neumann, 2004), including the hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens and nuclei in the mid- and hindbrain (Sofroniew, 1983). Importantly, it is through its neuromodulatory role that OXT (and AVP) influences sexual and social behaviour (e.g., mother–infant and adult–adult pair-bonding, social memory/recognition), and other processes including stress–response, emotionality, and learning and memory (Argiolas and Gessa, 1991; Insel, 1992; Engelmann et al., 1996; McCarthy and Altemus, 1997; Insel et al., 1999; Landgraf and Neumann, 2004). As we discuss later, specific OXT receptors that are localized in different brain regions play an important role in the regulation of social behaviour (Breton and Zingg, 1997). OXT receptors are profuse in the limbic system and in the autonomic regions of the brain stem; however, their expression in different brain regions can vary, even in closely

related species, and it is believed that differences in social behaviour can be accounted for, in part, by differences in the distribution of OXT and AVP receptors in the brain.

Oxytocin and repetitive behaviours

Research suggests that OXT is involved in repetitive behaviours. Intracerebroventricular (ICV) administration of OXT has been found to induce such stereotyped behaviours as stretching, repetitive grooming, startle and squeaking in mice (Meisenberg and Simmons, 1983; Drago et al., 1986; Insel and Winslow, 1991; Nelson and Alberts, 1997), grooming in rats (Drago et al., 1986; Van Wimersma Greidanus et al., 1990) and wing-flapping in chicks (Panksepp, 1992). Moreover, OXT has been linked to obsessive-compulsive disorder (OCD) — which is marked by obsessional thinking and/or repetitive behaviours. As McDougle et al. (1999) summarize, in addition to the animal findings just described, reports indicate that pregnancy or the puerperium (periods when OXT levels may fluctuate) is associated with OCD onset or a worsening of symptoms in women. Moreover, adults with non-tic-related OCD were found to have increased cerebrospinal fluid OXT. Finally, as McDougle et al. (1999) note, the OXT system has extensive interactions with the serotonin and dopamine systems, both of which are implicated in OCD.

Oxytocin and social behaviour

As noted, two and a half decades of research suggest that OXT and AVP play a critical role in regulating social behaviour. Most of this research is based on animal studies investigating selective and enduring adult–adult pair bonds and maternal behaviour. In particular, prairie voles are well suited to study the neurobiology of affiliation because they typically form enduring pair-bonds (i.e., are socially monogamous) and display biparental care, and because the closely related montane vole, which tends to be more asocial, allows for comparative investigations (Carter et al., 1995; Insel, 1997; Insel and Young, 2001). OXT — and AVP — have been implicated in the social behaviour displayed by prairie voles. For example, researchers have been able to establish a partner preference in female prairie voles in the absence of mating (mating is typically required for partner preference formation) by centrally administering OXT (Williams et al., 1994; Insel and Hulihan, 1995), and have been able to block the formation of a partner preference in female prairie voles by administering an OXT antagonist prior to mating (Insel and Hulihan, 1995). Interestingly, although differences in the expression of OXT in prairie and montane vole have not been found (Wang et al., 1996); as alluded to earlier, differences in OXT receptor distribution have been reported (Insel and Shapiro, 1992; Insel et al., 1994; Young et al., 1996, 1997). It is thought that these differences in receptor distribution likely underlie differences in social behaviour displayed by these two vole species because these peptides are acting on different brain regions. In prairie voles, OXT receptors are abundant in regions associated with reward processing, reinforcement and conditioning like the prelimbic cortex and nucleus accumbens; by contrast, in montane voles, OXT receptors are less prevalent in these regions, and are more prevalent in other regions like the lateral septum.

Studies of maternal behaviour also support the role of OXT in social affiliation. Although virgin female rats typically find pups to be aversive and actively avoid them (see Fleming and Anderson, 1987), maternal behaviour can be induced by centrally administering OXT (Pedersen et al., 1982), whereas the onset (but not maintenance) of maternal behaviour can be inhibited by centrally administering OXT antagonists (Insel, 1992). In addition, ICV injection of OXT has been found to facilitate maternal behaviour (i.e., acceptance of a foreign lamb) in sheep (Kendrick et al., 1987; Keverne and Kendrick, 1992), one of the few species to display selective maternal care (Insel and Young, 2001). Finally, Olazabal and Young (2006b) observed a positive correlation between maternal behaviour (i.e., time spent crouching over pups) and the density of OXT receptor binding in the nucleus accumbens in juvenile prairie voles, suggesting that OXT influences individual differences in maternal behaviour

within a species; moreover, these researchers found that maternal behaviour could be blocked by administering an OXT antagonist in the nucleus accumbens in adult female prairie voles (Olazabal and Young, 2006a).

Of particular interest to autism and the present chapter is research on the role that OXT and AVP play in social cognition. Rodents primarily rely on olfaction for social recognition; as such, the duration of olfactory investigation is a standard procedure for measuring social recognition in rodents. Using duration of olfactory investigation to measure social recognition, Popik et al. (1992) found that low (but not high) doses of OXT facilitated social recognition in rodents; other researchers have shown that centrally administered OXT antagonists disrupt social memory in female rats (Engelmann et al., 1998). Moreover, studies have found that genetically modified mice that do not produce OXT fail to recognize a novel mouse over repeated exposures (Ferguson et al., 2000; Choleris et al., 2003), but that this deficit can be rescued by a single ICV injection of OXT prior to the initial encounter (Ferguson et al., 2001). Interestingly, social memory deficits have also been observed in mice with a null mutation in the AVP receptor (V1a) gene (*Avpr V1a*) (Bielsky et al., 2004); as with the OXT knockout mice, this social memory deficit can be rescued through site-specific treatment with a vasopressin receptor (AVPR) (V1a) viral vector in the lateral septum, which renews AVPR (V1a) binding in the targeted area (Bielsky et al., 2005).

Although research examining the effects of OXT on human social behaviour has been limited — mainly because of the methodological difficulties involved — a few recent studies suggest that OXT may be involved in aspects of trust, social cognition and regulating responses to social stimuli. Kosfeld et al. (2005) administered intranasal OXT or placebo to male volunteers who then played the "trust game" in which they were given a sum of money and were given the opportunity to invest portions of that money with an anonymous partner; investing in the other player could lead to higher payoffs for both players, but the investor always ran the risk that the trustee may violate that trust. Intranasal OXT significantly increased trust among participants compared to placebo. Another study used functional magnetic resonance imaging (fMRI) to investigate changes in amygdala activity in male participants who received intranasal OXT or placebo and then viewed fear-inducing stimuli of a social (angry and fearful faces) and non-social (threatening scenes) nature; reduced amygdala activity in response to the fearful stimuli was observed following OXT compared to placebo (Kirsch et al., 2005). Finally, Domes et al. (2007) found that OXT facilitated performance on the Reading the Mind in the Eyes test, which assess the ability to infer the mental states of others — this finding is of particular relevance to ASD because individuals with ASD often show deficits in Theory of Mind, and on this task in particular (Baron-Cohen et al., 2001).

The oxytocin–autism link

In light of the findings described above implicating OXT in repetitive behaviours and aspects of social functioning, researchers have speculated that OXT may be implicated in autism given that these are two core symptom domains of the disorder (Modahl et al., 1992; Panksepp, 1992; Waterhouse et al., 1996; McCarthy and Altemus, 1997; Insel et al., 1999; Hollander et al., 2003, 2007; Lim et al., 2005; Bartz and Hollander, 2006; Lim and Young, 2006; Carter, 2007). In support of this notion, lower blood plasma OXT levels have been observed in children with autism compared to age-matched controls (Modahl et al., 1998); moreover, the plasma samples obtained from the autistic children were associated with higher OXT precursor levels, as well as an increased ratio of OXT precursor to OXT, suggesting that OXT may be processed differently in the brains of children with autism (Green et al., 2001). Another study, however, found higher OXT plasma levels in adults with ASD compared to controls (Jansen et al., 2006); the reason for this discrepancy is unclear, however, as the authors suggest, developmental factors may contribute to the observed increased basal OXT levels in adulthood.

Genetic studies also support a role of OXT in ASD. Ylisaukko-Oja et al. (2006) conducted a

combined analysis of primary genome scanned data to identify potential susceptibility loci for autism; findings from this study implicate the region of chromosome 3 — in which the OXT receptor gene (*Oxtr*) is located — as a susceptibility loci for ASD. Wu et al. (2005) found an association between two single nucleotide polymorphisms in the *Oxtr* and ASD in a sample of Han Chinese family trios. Finally, Jacob et al. (2007) also found an association between the *Oxtr* and autism in a small Caucasian sample; specifically, a significant association was detected at rs2254298 but, in contrast to Wu et al., not at rs53576. Interestingly, polymorphisms in the AVP receptor gene (*Avpr*) have also been linked to autism. Kim et al. (2002) found evidence for disequilibrium between autism and one microsatellite polymorphism of the *Avpr (V1a)* gene; Wassink et al. (2004) also found evidence for linkage disequilibrium in the *Avpr (V1a)*; and Yirmiya et al. (2006) demonstrated a link between the *Avpr (V1a)* gene and autism.

Targeting the repetitive behaviours and social cognition symptom domains

Drawing upon the large animal literature implicating OXT in repetitive behaviours and affiliation, as well as research by Modahl et al. (1998), Hollander and colleagues have been interested in investigating the functional role of OXT in ASD, as well as the potential therapeutic value of OXT in treating core ASD symptom domains.

Intravenous OXT challenge and repetitive behaviours

To investigate the role of OXT with respect to repetitive behaviours in ASD, Hollander and colleagues conducted a double-blind, placebo controlled, cross-over study in which synthetic OXT (Pitocin) was administered to 15 adults with ASD via intravenous infusion in a randomized, counter-balanced fashion (Hollander et al., 2003). Each subject served as his or her own control and completed both OXT and placebo challenges on separate days; synthetic OXT or placebo was continuously infused over a 4-h period following an overnight fast (see Hollander et al., 2003, for a complete description of the methodology).

Frequency of repetitive behaviours were assessed using a four-point ordinal scale ranging from 0 (*never*) to 3 (*constantly*) at baseline (0), 60, 120, 180 and 240 min over the course of the laboratory challenge. A repeated measures analysis of variance revealed that the frequency of repetitive behaviours was reduced over time following OXT administration compared to placebo. In addition, a decrease in the total number of different repetitive behaviours was observed following OXT administration compared to placebo. Reported side effects from OXT infusion were mild and included drowsiness, anxiety, depression, headache, tingling, backache, trembling, restlessness, stomach cramps and enuresis.

This study suggests that OXT may have value in treating repetitive behaviours in ASD; however, it also raises some interesting questions. As noted, OXT administration in animals actually increases stereotyped behaviours. Moreover, two early studies investigating the therapeutic efficacy of OXT in treating obsessive-compulsive symptomatology in patients with OCD found no support for the therapeutic efficacy of OXT (den Boer and Westenberg, 1992; Epperson et al., 1996). Given these observations, why would OXT reduce repetitive behaviours in ASD? We believe it is important to keep in mind that the animal studies examined the relationship between OXT and repetitive behaviours in a normal, intact animal model, not in an altered system as is believed to be the case in autism. With respect to the negative findings regarding OXT treatment of OCD, it may be that too much OXT or an increased sensitivity to OXT is implicated in OCD, whereas a deficit of OXT is implicated in ASD (as suggested by Modahl et al.'s research). Moreover, recent research suggests that repetitive behaviours in autism may differ from those in OCD, not only phenomenologically, but also in terms of underlying neurobiology and, possibly, genetics (Anagnostou et al., 2005). Thus, OXT may have different effects in the treatment of repetitive behaviours in autism compared to repetitive behaviours characteristic of OCD.

Intravenous OXT challenge and social cognition

We also have preliminary data demonstrating the beneficial effects of intravenous OXT on the aspects of social cognition in ASD; in particular, ability to assign affective significance to speech (Hollander et al., 2007), a deficit that is present in many individuals with ASD and that is thought to be central to the social and speech deficits in ASD (Gervais et al., 2004; Kuhl et al., 2005). Specifically, comprehension of affective speech (Heilman et al., 1975) was tested at baseline (just prior to the OXT infusion), and at 30, 60, 120, 180 and 240 min over the course of the infusion (see above study for methods description). In this task, participants were presented with four pre-recorded sentences of neutral content (e.g., "The boy went to the store"); each sentence was presented with one of four emotional intonations (*happy*, *indifferent*, *angry* and *sad*), with the pairing of emotional expression and sentences in 1 of 6 counterbalanced orders. Participants indicated the emotional mood of the speaker by pointing to the word that corresponded to the emotion that they believed matched the one they heard on the tape.

Data were first transformed and scored dichotomously as 1 (*all items correct*) and 0 (*not all items correct*) to account for negative skew and to better balance task difficulty. Mixed regression analysis was used to estimate linear trends in speech comprehension performance for each subject; these individual linear trends were used as the dependent variables. As depicted in Fig. 1, subjects who received OXT first showed increased levels of retention on the task, and did not show a tendency to revert to baseline when retested after a delay of approximately 2 weeks, whereas subjects who received placebo first tended to revert to baseline after the delay. Although this study did not observe a direct effect of OXT on the comprehension of affective speech task (possibly because ceiling effects obscured our ability to detect such effects), these findings are nonetheless consistent with the aforementioned study by Domes et al. (2007) in which intranasal OXT facilitated participants' ability to identify emotion through facial stimuli.

Pilot treatment study of intranasal OXT in autism spectrum disorders

In sum, these data support the potential role of OXT in ASD and suggest that OXT may have therapeutic benefits for the treatment of repetitive behaviours and social deficits; however, research is needed to determine the feasibility and long-term therapeutic effects of OXT for the treatment of ASD. To this end, our group has a pilot study underway investigating the effects of intranasal OXT on core ASD symptoms (i.e. repetitive behaviours, social functioning and social cognition) and global functioning in adults with ASD.

This pilot study is on-going, but preliminary data are promising. Eight high functioning patients meeting criteria for an ASD based on DSM-IV diagnoses and the Autism Diagnostic Interview were randomized to intranasal OXT (IN-OXT) or placebo conditions. Beginning and average endpoint dosing was 24 IU bid (i.e. three puffs/nostril twice daily, morning and noon). Reported side effects were minimal per treating clinician adverse events record forms. One patient, randomized to IN-OXT, reported side effects which included increased fatigue and sneezing, which were mild in nature. Analyses indicate that IN-OXT treatment vs. placebo resulted in improvements in repetitive behaviours in this small preliminary data set (E. Anagnostou, personal communication, May 2, 2007). In addition, analysis of responders and non-responders based on the Clinician's Global Impressions-Improvement (CGI-I) scale ratings suggest that more IN-OXT subjects were categorized as responders than placebo subjects; similarly, responders analysis of CGI-I, (Social) ratings suggest that more IN-OXT subjects were categorized as responders than placebo subjects (Bartz et al., 2006; Anagnostou et al., 2007; Bartz et al., 2007).

In addition to these primary outcome measures, preliminary analyses revealed intriguing findings on the Diagnostic Analysis of Non-Verbal Accuracy (DANVA2), which measures emotion recognition across multiple modalities (facial expression, paralanguage or tone of voice and posture). Specifically, improvements from baseline for the IN-OXT group are emerging on some DANVA2

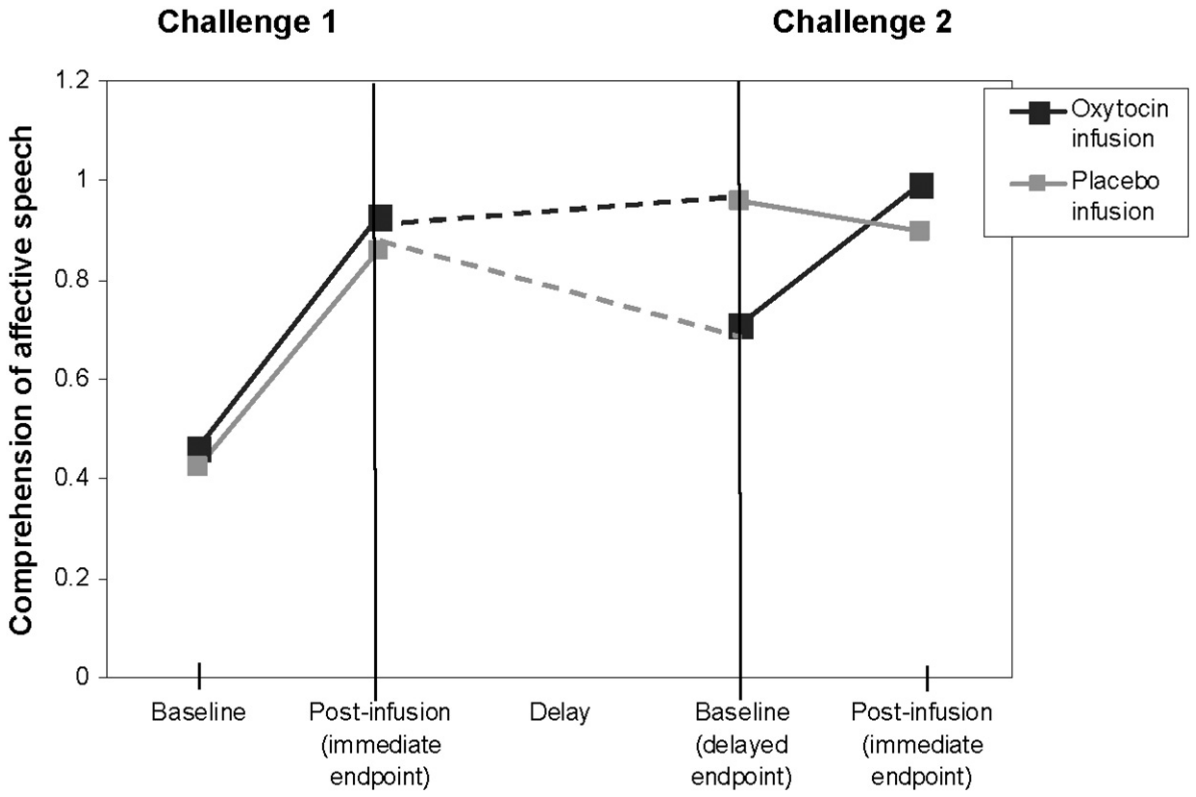

Fig. 1. Mixed regression analysis of predicted linear trends across time of affective speech comprehension as a function of condition (oxytocin vs. placebo) and order of administration (oxytocin 1st vs. placebo 1st). Adapted with permission from Elsevier; Hollander et al., 2007.

subscales (those using child stimuli which may be more challenging for the adults in this study to interpret) (Anagnostou et al., 2007; Bartz et al., 2007) and (E. Anagnostou, personal communication, May 2, 2007). These findings — if they continue to hold — replicate and extend our findings from the challenge study (Hollander et al., 2007) in that they show that IN-OXT has a direct effect on social information processing; these findings are also consistent with the aforementioned findings observed by Domes et al. (2007).

Finally, Event Contingent Records (ECR), a diary methodology that allows participants to report on symptoms, affect, thoughts and behaviour close in time to experience, was included as an exploratory measure to track changes in participants' social functioning in the real world. A subset of participants in this pilot study completed ECR forms for a 4-day period at baseline and a similar period at week 6. Preliminary analyses indicate that fewer cold/aloof behaviours (e.g., "I ignored the other's comments") were indorsed in social interactions in the IN-OXT compared to placebo group (Bartz et al., 2007), suggesting that OXT has the potential to influence participants' behaviour and affective experience in their real life social interactions.

Functional magnetic resonance imaging study of the effects of intravenous OXT in adults with ASD

In addition to looking at the behavioural effects of OXT in ASD, it will also be important to investigate the neural correlates of OXT in ASD. Animal studies indicate that differences in social behaviour appear to be due, at least in part, to differences in the distribution of OXT and AVP receptors in the brain, both within and across

species. To date, no one has yet been successful in developing ligands for OXT and AVP that could be used to identify the distribution of OXT and AVP receptors in the human brain. Although unable to detect specific receptor location, fMRI can be used to identify the neural correlates of OXT in ASD, which can shed light on how OXT is exerting its effects on behaviour, and can be used as a biomarker of treatment response. Hollander and Anagnostou are currently using fMRI to study the effects of intravenous OXT on response inhibition (a proxy for repetitive behaviours) and face processing in adults with ASD. Very preliminary data suggest greater prefrontal cortex and fusiform face area activation post-OXT infusion compared to pre-infusion for the subject that received OXT.

One question arising from this research concerns the issue of exogenous administration and brain penetration. As noted, the effect of OXT on social behaviour is due to its role as a neuromodulator in the brain. Moreover, endogenous OXT in the plasma cannot cross the blood brain barrier (BBB) (Landgraf and Neumann, 2004). So how does OXT, administered via intravenous infusion, exert its effects on repetitive behaviours and social cognition as Hollander et al. (2003, 2007) observed? Most likely, a small amount of exogenous OXT crosses the BBB following intravenous infusion. This is consistent with the notion proposed by Landgraf and Neumann (2004) that transport across the BBB of exogenously administered OXT can result in functionally significant effects if plasma concentrations of exogenous OXT exceed a certain threshold. Indeed, supporting this idea, Jin et al. (2007) showed that peripherally administered OXT could rescue maternal nurturing and social memory deficits in *CD38* mutant mice. Similarly, Ring et al. (2006) showed that peripherally administered OXT could produce anxiolytic effects in male mice that were comparable to the effects achieved by central administration (although substantially larger doses were required for peripheral administration to achieve such effects). Moreover, Ring et al. (2006) showed that a centrally administered OXT antagonist (that does not cross the BBB) can fully reverse the anxiolytic effects of peripherally administered OXT, providing further support for the claim that peripherally administered OXT can penetrate the brain. Intranasally administered OXT, by comparison, is likely directly transported from nasal mucosa to the cerebrospinal fluid, which acts as a mechanism to transport exogenous neuropeptides across the ependyma into the brain parenchyma (Bittencourt and Sawchenko, 2000).

Future directions

In conclusion, tremendous progress has been made over the years in identifying the neurobiology of attachment and social behaviour, and this research has implications for understanding and treating disorders marked by deficits in social functioning like ASD. In particular, OXT and the structurally similar peptide hormone AVP have been implicated in social motivation, pair-bond formation and other aspects of attachment. Drawing upon this literature, our program of research embraces a translational approach to understand core ASD symptom domains and to identify novel treatments for core ASD symptoms. We have found that OXT plays a role in repetitive behaviours and aspects of social cognition in ASD, and preliminary findings suggest that OXT may have value in treating these core ASD symptom domains. Research investigating the effects of OXT in humans, however, is in its infancy and more research is needed in this area. Below we outline some unresolved questions and directions for future research.

Research by Hollander et al. (2007) and by Domes et al. (2007) suggests that OXT facilitates social information processing through two different sensory modalities — that is, through auditory and visual modalities, respectively. This raises questions about mechanism of action. In particular, *how* does OXT facilitate social cognition? Previous research indicates that OXT plays a role in regulating stress and fear reactivity. Thus OXT may facilitate the ability to process social information by reducing anxiety that is inherent in many social encounters. This explanation, in fact, is particularly relevant to ASD because individuals with ASD often report experiencing anxiety when processing social information. Alternately, OXT may increase peoples' motivation to attend to

social cues in their environment by reinforcing social information processing. This hypothesis is supported by research showing that differences in social behaviour in prairie and montane voles can be explained in part by where OXT and AVP are acting in the brain. Future research will most certainly want to investigate this question in humans as it may shed light on the pathophysiology of ASD, as well as possible targets for intervention.

In addition, although genetic studies point to alterations in the *Avpr (V1a)* and risk for ASD, no one has looked at the functional role of AVP in ASD, or the potential therapeutic value of AVP in treating core ASD symptoms. Given the functional overlap between OXT and AVP, and that they are able to influence each other's receptors and functions (Engelmann et al., 1996; Cho et al., 1999; Bales et al., 2004; Landgraf and Neumann, 2004; Ragnauth et al., 2004; Pedersen and Boccia, 2006), it will be important for future researchers to systematically assess the role of both OXT and AVP in ASD. Finally, more research is needed to investigate the OXT and AVP systems in humans across development, especially in the context of ASD. Given that ASD is a developmental disorder, with onset occurring prior to three years of age, it is likely that abnormalities in these systems arise relatively early in development. Along these lines, Carter (2007) proposed the intriguing theory that the male vulnerability to ASD (ratio of males to females with ASD is approximately 4:1) may be due to disruptions in the AVP system, and possibly an excess of AVP, during development because AVP is androgen dependent and AVP plays a key role in male behaviour. If disruptions occur in the AVP system during development (possibly due to increased exposure to androgens), males may be more sensitive to these disruptions, leading to developmental traits associated with ASD (i.e., reduced social behaviour, repetitive behaviours and anxiety). By contrast, Carter (2007) argues, females may be protected from ASD because of their independence and/or insensitivity to the AVP system (many of the processes controlled by AVP in males rely on OXT in females), and/or because of potential protective factors associated with OXT and/or oestrogen.

Finally, it may be useful to consider other factors that influence the functioning of the OXT and/or AVP systems. Recently, Jin et al. (2007) showed that *CD38*, a transmembrane receptor with ADP-ribosyl cyclase activity, plays a key role in regulating complex social behaviour (social recognition and maternal nurturing) by regulating OXT secretion. Thus, variations in *CD38* activity may be associated with individual differences in social cognition and social functioning that characterize individuals with ASD (Bartz and McInnes, 2007; Young, 2007).

Abbreviations

ASD	autism spectrum disorders
AVP	arginine vasopressin
Avpr (V1a)	vasopressin receptor 1a gene
AVPR	arginine vasopressin receptor
CD38	CD38 gene
CGI-I	clinician's global impressions-improvement scale
DANVA2	diagnostic analysis of non-verbal accuracy
ECR	event contingent records
fMRI	functional magnetic resonance imaging
ICV	intracerebroventricular
IN-OXT	intranasal OXT
OCD	obsessive-compulsive disorder
OXT	oxytocin
Oxtr	oxytocin receptor gene
PVN	paraventricular nucleus
SON	supraoptic nucleus

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