Chapter 8
The Role of the Oxytocin/Arginine Vasopressin System in Animal Models of Autism Spectrum Disorder

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8.1 Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition primarily characterised by impairments in social interaction and communication as well as repetitive/stereotypic patterns of behaviour. The exact aetiology of ASD is unknown, but there are good indications that both genetic and environmental risk factors contribute to its pathogenesis (Hallmayer et al. 2011). Among all methods currently available for the treatment of ASD, rehabilitation training is the only method that has been proven effective. Although some drugs can relieve some of the co-morbid symptoms while also causing adverse reactions, they don't improve the social interactions or language abilities in most cases. Therefore, it is important to better understand the aetiology and pathophysiology of ASD in more detail to find better therapies. Several lines of evidence suggest that the central oxytocin (OXT) and arginine vasopressin (AVP) system might be involved in the development of ASD since both neuropeptides play important roles in regulating social behaviours.

8.2 OXT/AVP Systems and ASD

In mammals, OXT and AVP are nonapeptides with a six-member disulfide ring between Cys residues on positions one and six. There are high levels of sequence homology between OXT and AVP with only two amino acids difference between them (Harony and Wagner 2010). Through evolution, the two neuropeptides might have arisen from a gene duplication event, making OXT and AVP known as "twin" neuropeptides (Donaldson and Young 2008). Both are mainly synthesised in the hypothalamic supraoptic and paraventricular nuclei (SON and PVN, respectively). CD38, an ADP-ribosyl cyclase, was recently found to mediate OXT release in the brain (Jin et al. 2007), and oxytocinase (human leucyl/cystinyl aminopeptidase, LNPEP) is the enzyme that metabolises OXT and AVP (Tsujimoto and Hattori 2005). The oxytocin receptor (OXTR) is widely distributed in the brain including the hippocampus, amygdala, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brainstem. In the periphery, the OXTR is mainly found in the uterus, mammary gland and the heart. The receptors for AVP are classified into three subtypes named AVPR1A, AVPR1B and AVPR2 (Thibonnier et al. 2002). AVPR1A is highly expressed in the brain and plays important roles in the modulation of mammalian social behaviour and cardiovascular functions; AVPR1B is expressed in the brain and pituitary gland, and several studies revealed that AVPR1B is involved in the regulation of stress. AVPR2 is mainly expressed in the kidneys and is associated with water retention (Carter 2007; Harony and Wagner 2010; Meyer-Lindenberg et al. 2011).

After being synthesised in magnocellular neurons of hypothalamic nuclei, OXT and AVP are transported and processed along axonal projections to the posterior

lobe of the pituitary gland. Here they are stored and released into the blood stream to mediate uterine contractions and milk ejection (OXT) or fluid homeostasis and blood pressure control (AVP) (Aoyagi et al. 2009; Hew-Butler 2010). Moreover, OXT- and AVP-expressing magnocellular neurons were also found to project to the amygdala. OXT and AVP are further synthesised in parvocellular neurons of hypothalamic nuclei that project to the hippocampus, amygdala, striatum, suprachiasmatic nucleus, bed nucleus of stria terminalis and brainstem to regulate glucose metabolism (Cai and Purkayastha 2013), feeding behaviour (Chaves et al. 2013), sexual behaviour (Veening et al. 2015), learning and memory (Chini et al. 2014) and pain perception (Tracy et al. 2015). AVP also participates in the modulation of feeding, pain perception and aggression behaviour (Ray et al. 2015). In addition, there is accumulating evidence suggesting that both OXT and AVP play important roles in the regulation of complex social behaviours, such as social cognition and attachment (Insel and Young 2001), social exploration and recognition (Winslow and Insel 2004), social approach (Pagani et al. 2011; Eskandarian et al. 2013), social preference and avoidance (Lukas and Neumann 2014), maternal aggression (Eskandarian et al. 2013), affinitive behaviour [i.e. pair-bonding (Scheele et al. 2012)] and maternal behaviour (Rich et al. 2014). Importantly, some of these behaviours are also impaired in ASD.

Data have been obtained showing that plasma levels of OXT (Modahl et al. 1998; Jacobson et al. 2014) and AVP (Al Ayadhi 2005) were lower in autistic children compared to typically developing children. Moreover, plasma levels of OXT are positively correlated with the degree of core symptoms in ASD patients using the Childhood Autism Rating Scale (CARS) (Alabdali et al. 2014). Lower levels of OXT and AVP were also found in mothers of autistic children, showing a negative correlation with their children's autistic behaviour scores (Xu et al. 2013). However, in a mixed child and adolescent population, ASD was associated with higher levels of OXT (Taurines et al. 2014) and AVP (Momeni et al. 2005) indicating that there are multiple factors determining the plasma levels of these peptides including age (Miller et al. 2013), gender (Jacobson et al. 2014) and methodological issues (Szeto et al. 2011).

Genetic variants have also been described for the *OXTR* gene in ASD populations from different ethnical backgrounds (Wu et al. 2005; Jacob et al. 2007; Liu et al. 2010; Campbell et al. 2011). The current largest and most comprehensive meta-analysis included 3941 individuals with ASD and showed significant associations between ASD and the single nucleotide polymorphisms (SNPs) rs7632287, rs237887, rs2268491 and rs2254298 in the *OXTR* gene (LoParo and Waldman 2015). For the *AVPR1A gene*, a weak association with ASD was reported in some ethnical groups (Yirmiya et al. 2006; Tansey et al. 2011).

In order to gain a better understanding of the roles of OXT and AVP in the pathophysiology of ASD, various animal models have been established. In this respect, two main strategies have been followed: one is to inactivate rodent Oxt and Avp system-related genes and analyse putative ASD-like phenotypes; the other is to find out whether there are changes in the rodent Oxt and Avp systems in existing ASD animal models. Assays to test for ASD-like symptoms in animal models are,

for example, the three-chamber test to measure social interaction, the analysis of ultrasonic vocalisations (USVs) to evaluate vocal communication, the documentation of increased self-grooming, jumping or repeated circling to analyse stereotypic repetitive behaviours and the measurement of prepulse inhibition (PPI) of the startle reflex to screen for abnormal sensory perception.

8.3 Oxt and Avp System-Related Animal Models of ASD

8.3.1 Genotype-Based Models: Oxt System

There are three critical genes of the Oxt system that have been identified so far: *Oxt*, *Oxtr* and *Cd38*. Accordingly, these genes have all been manipulated in mice to study Oxt system-related phenotypes (Modi and Young 2012).

The first two *Oxt* germline knockout (KO) mouse lines were created independently in 1996 focusing on peripheral phenotypes, i.e. female KO of both lines showed normal parturition but no postpartal milk ejection (Nishimori et al. 1996; Young et al. 1996). The following studies found that *Oxt* KO mice were responding to psychogenic stress with overexpression of c-fos and CRH (Nomura et al. 2003; Amico et al. 2008). Moreover, maternal behaviour was impaired (Pedersen et al. 2006), and *Oxt* KO females were not able to discriminate parasitised male odour (Kavaliers et al. 2003). In addition, *Oxt* KO mice were more aggressive, anxiety was exaggerated and they failed to develop social memory (Ferguson et al. 2000, 2001; Winslow et al. 2000; Amico et al. 2004; Ragnauth et al. 2005). However, olfactory detection, spatial memory capabilities and sexual behaviour seemed to be unaltered (Ferguson et al. 2000; Winslow and Insel 2002; Becker et al. 2013). Interestingly, the amygdala was found to be involved in the described alterations of social behaviour (Becker et al. 2013; Mantella et al. 2004). *Oxt* KO mice further showed signs of metabolic impairments affecting glucose homeostasis (Amico et al. 2004; Camerino 2009), hydration status (Rinaman et al. 2005) and thermoregulation (Kasahara et al. 2007).

Germline *Oxtr* KO lines were more specifically characterised regarding ASD-like phenotypes and showed impaired cognitive flexibility, social deficits, increased aggression and increased seizure susceptibility (Sala et al. 2011). Importantly, other studies confirmed the social deficits (Pobbe et al. 2012a, b). *Oxtr* KO females were fertile and showed normal reproductive behaviour, but a high level of pup abandonment was seen (Rich et al. 2014). Compared with the *Oxtr* null genotype, heterozygous *Oxtr* mutants showed normal cognitive flexibility and aggression but impaired social interaction (Sala et al. 2013). A selective ablation of the Oxtr in the forebrain using conditional *CamkIIα-Cre-Oxtr* mutants resulted in a prominent reduction of the target gene in the lateral septum, hippocampus and ventral pallidum but not in the medial amygdala. Interestingly, males from this

Table 8.1 Summary of the main behavioural phenotypes relevant to ASD in genotype-based models of the OXT/AVP system

Model	Gender	Main behavioural phenotypes relevant to ASD	References
Oxt$^{-/-}$	♂ and ♀	Social memory ↓ Maternal behaviour ↓ (♀) Response to psychogenic stress ↑ Aggressive behaviour ↑	Ferguson et al. (2000), (2001) Pedersen et al. (2006) Nomura et al. (2003), Amico et al. (2008) Winslow et al. (2000), Ragnauth et al. (2005)
Oxtr$^{-/-}$	♂ and ♀	Social interaction ↓ USV number during infancy ↓ (♂) Pup abandonment ↑ (♀) Cognitive flexibility ↓ Aggressive behaviour ↑	Sala et al. (2011), Pobbe et al. (2012a, b) Sala et al. (2011) Rich et al. (2014) Sala et al. (2011) Sala et al. (2011)
Cd38$^{-/-}$	♂ and ♀	Social recognition ↓ (♂) USV number during infancy ↓ (♂) Maternal behaviour ↓ (♀) Paternal behaviour ↓ (♂) Locomotor activity ↑	Higashida et al. (2011) Liu et al. (2008) Lopatina et al. (2011) Akther et al. (2013) Liu et al. (2008)
BB rat	♂ and ♀	Social recognition ↓ Emotional reactivity ↓ PPI deficits	Engelmann and Landgraf (1994) Williams et al. (1985) Birkett and Pickering (1988)
Avpr1a$^{-/-}$	♂	Social interaction ↓ Social recognition ↓ Spatial memory ↓	Egashira et al. (2007) Bielsky et al. (2004) Egashira et al. (2007)
Avpr1b$^{-/-}$	♂ and ♀	Social recognition ↓ Social memory ↓ (♀) Social motivation ↓ USV modulation ↓ Maternal behaviour ↓ (♀) Aggressive behaviour ↑ Locomotor activity ↑ PPI deficits	Wersinger et al. (2002) Wersinger et al. (2008) Wersinger et al. (2004) Scattoni et al. (2008) Wersinger et al. (2007a, b) Wersinger et al. (2002), Caldwell and Young (2009) Daikoku et al. (2007) Egashira et al. (2005)

conditional mutant line failed to recognise individual mice implicating a specific deficit of social recognition behaviour (Lee et al. 2008).

Cd38 is a transmembrane glycoprotein with ADP-ribosyl cyclase activity, which regulates the Ca^{2+}-dependent secretion of Oxt in the hypothalamus. It was shown that *Cd38* KO mice exhibited markedly lower ADP-ribosyl cyclase activity in both the hypothalamus and pituitary gland. The plasma level of Oxt, but not Avp, was significantly decreased in *Cd38* KO mice, and depolarisation-induced Oxt secretion and Ca^{2+} elevation in oxytocinergic neurohypophysial axon terminals were disrupted (Jin et al. 2007). Further analysis of these mice revealed a significant impairment of maternal behaviour in females (Lopatina et al. 2011) and paternal

Table 8.2 Stimuli of Oxt/Avp release within defined brain regions

Stimulus	Species	Brain regions	Neuropeptides	References
Physiological stimuli				
Parturition	Sheep	SN, OB, CSF	Oxt↑	Kendrick et al. (1988) Kendrick et al. (1991)
	Rats	PVN, SON	Oxt↑, Avp-	Neumann et al. (1993b) Neumann et al. (1996)
Suckling	Rats	SON, septum, hippocampus	Oxt↑, Avp-	Neumann et al. (1994a) Landgraf et al. (1992) Neumann and Landgraf (1989) Moos et al. (1989)
	Rats	MPOA, BNST	Oxt-, Avp↑	Bosch et al. (2010)
Hyperosmotic stress	Rats	SON	Oxt↑, Avp↑	Neumann et al. (1993a) Ludwig et al. (1994) Neumann et al. (1995) Ludwig et al. (1996)
	Rats	Septum	Avp↑	Demotes-Mainard et al. (1986)
Social/emotional stimuli				
Maternal defence	Virgin rats Lactating rats	PVN	Oxt↑	Bosch et al. (2004)
Maternal aggression	Lactating rats	CeA	Avp↑	Bosch and Neumann (2010)
Mating	Rats	PVN	Oxt↑	Waldherr and Neumann (2007) Nyuyki et al. (2011)
	Voles	NAc	Oxt↑	Ross et al. (2009)
Social discrimination	Rats	LS	Avp↑	Lukas et al. (2011)
Social fear	Mice	DLS	Oxt↑	Zoicas et al. (2014)
Social defeat	Rats	LS	Oxt↑ Avp-	Ebner et al. (2000)
	Rats	SON	Oxt↑	Engelmann et al. (1999)
	Rats	PVN	Oxt- Avp↑	Wotjak et al. (1996)
Physical stimuli				
Electrical stimulation	Rats, in vitro	Isolated neurohypophyses	Oxt↑ Avp↑	Han (2003)
Restraint stress	Rats, voles	PVN	Oxt↑	Babygirija et al. (2012a, b) Smith and Wang (2014)
Shaker stress	Rats	PVN	Oxt↑ Avp-	Nishioka et al. (1998)
Forced swimming	Rats	PVN, SON	Oxt↑ Avp↑	Wotjak et al. (1998)
	Rats	SCN, septum, CeA	Avp↑	Ebner et al. (1999) Ebner et al. (2002) Engelmann et al. (1998)
Haemorrhage	Rats	PVN	Avp↑	Ota et al. (1994)

(continued)

Table 8.2 (continued)

Agents	Species and administration	Brain regions	Neuropeptides	References
Mc4r agonists	Voles, i.p.	NAc	Oxt↑	Modi et al. (2015)
alpha-MSH	Rats, in vitro	Isolated SON	Oxt↑	Sabatier et al. (2003)
5-HT	Rats, i.c.v.	PVN	Oxt↑	Jorgensen et al. (2003a) Jorgensen et al. (2003b)
CCK-8	Rats, i.v.	SON	Oxt↑ Avp↑	Neumann et al. (1994b)
Interleukin-1β	Rats, i.c.v	SON	Oxt↑ Avp↑	Landgraf et al. (1995)
Neurosteroid	Rats, in vitro	Isolated SON	Oxt↑ Avp↑	Widmer et al. (2003) Wang et al. (1995)
$GABA_A$ receptor agonist (muscimol)	Rats, in vitro	Isolated SON	Oxt↑	Widmer et al. (2003)
Angiotensin	Rats, i.c.v.	SON, PVN	Avp↑	Moriguchi et al. (1994)
OXT agonist	Rats, in vitro	Isolated SON	Oxt↑	Moos et al. (1984)
AVP analogue	Rats, local administration	SON	Avp↑	Wotjak et al. (1994)
Naloxone	Rats, s.c., i.p.	SON, hippocampus	Oxt↑ Avp-	Neumann et al. (1991) Douglas et al. (1995)
Histamine $H_{1/2}$	Rats, local administration	PVN	Oxt↑	Bealer and Crowley (1999)

SN substantia nigra, *OB* olfactory bulb, *CSF* cerebrospinal fluid, *MPOA* medial preoptic area, *BNST* bed nucleus of stria terminalis, *CeA* central amygdala nucleus, *NAc* nucleus accumbens, *LS* lateral septum, *DLS* dorsolateral septum, *SCN* suprachiasmatic nucleus, *MC4R* melanocortin receptor 4, *5-HT* serotonin, *CCK-8* cholecystokinin, *s.c.* subcutaneous, *i.c.v.* intracerebroventricular, *i.v.* intravenous, *i.p.* intraperitoneal

behaviour and social recognition in males (Higashida et al. 2011; Akther et al. 2013). The animals also showed increased levels of locomotor activity and less frequent USVs in male pups (Liu et al. 2008), while no deficits in lactation or milk ejection were found in *Cd38* female KO mice. Overall, the social deficits of *Cd38* KO were less severe than that in *Oxt* or *Oxtr* KO mice (Liu et al. 2008). For a summary of phenotypes, see Table 8.1 and Table 8.2.

8.3.2 Genotype-Based Models: Avp System

Within the Avp system, three genes have been under focus in animal model studies: *Avp*, *Avpr1a* and *Avpr1b*.

The Brattleboro (BB) rat is the most extensively studied Avp-deficient animal model, which lacks the ability to synthesise Avp because of a single-base-pair deletion in the coding region of the *Avp* gene (Birkett and Pickering 1988; Feifel and Priebe 2001). These rats exhibit a series of behavioural deficits including decreased emotional reactivity (Williams et al. 1985), altered motivation and attention (Williams et al. 1983), impaired social recognition (Engelmann and Landgraf 1994) and PPI deficits (Birkett and Pickering 1988).

The *Avpr1a* germline KO mouse exhibits profound impairments in social recognition and social interaction (Bielsky et al. 2004; Egashira et al. 2007), subtle olfactory deficits (Wersinger et al. 2007a, b) and impaired spatial memory (Egashira et al. 2004).

Avpr1b germline KO mice also exhibited reduced social motivation and impaired social recognition with no change in olfactory discrimination (Wersinger et al. 2002, 2004). It has also been suggested that female *Avpr1b* KO mice may have some social memory deficits since they failed to terminate pregnancy in the presence of an unfamiliar male (this pregnancy block is also referred to as the Bruce effect) (Bruce 1959; Wersinger et al. 2008). The ability to modulate USVs within different social contexts was also impaired in *Avpr1b* KO mice, and maternal potentiation of USVs was absent in *Avpr1b* KO pups. Adult female *Avpr1b* KO mice further emitted fewer USVs during the resident-intruder test (Scattoni et al. 2008). Additionally, *Avpr1b* KO mice displayed markedly reduced social forms of aggression, including intermale aggression and maternal aggression (Wersinger et al. 2002, 2004, 2007a, b; Caldwell and Young 2009). Besides these behavioural alterations, *Avpr1b* KO mice also exhibited deficits of PPI of the startle reflex (Egashira et al. 2005) and a higher locomotor activity (Daikoku et al. 2007). For a summary of phenotypes, see Table 8.1.

8.3.3 The Oxt/Avp System in Monogenic Mouse Models of ASD

Importantly, the Oxt/Avp system has also been under investigation in some monogenic mouse models of ASD. For example, the number of Oxt-positive cells was decreased in the PVN of *Fmr1* (Francis et al. 2014), *Cntnap2* (Penagarikano et al. 2015) and *Magel2* KO mice (Meziane et al. 2015). Oxtr expression was also altered in several ASD mutant mice including *Fmr1*, *Dhcr7*, *Ube3a*, *Oprm1* and *Mecp2* mutants (Kotulska and Jozwiak 2011; Gigliucci et al. 2014). These findings indicate that an altered Oxt/Avp system may be common feature of monogenic ASD models.

8.3.4 Phenotype-Based Models

In contrast to the comparative exploration of inbred mouse strains, there are animals with natural variations in social behaviour, which may result from changes in Oxt/Avp system.

Microtine rodents (voles), for example, show a natural diversity in social behaviour. Therefore, these animals have become an important model to study the neurobiology of social behaviour in general, but also the specific role of hormones like Oxt can be analysed. Prairie voles (*Microtus (M.) ochrogaster*) are a highly partner-oriented rodent species characterised by a socially monogamous mating strategy and high levels of alloparental care. The analysis of the Oxt system in these animals showed that Oxtr density was highest in the prelimbic cortex, bed nucleus of the stria terminalis, nucleus accumbens (NAc), midline nuclei of the thalamus and the lateral aspects of the amygdala. In contrast, low levels of Oxtr binding in the NAc have been demonstrated in nonmonogamous rodent species, including meadow voles (*M. montanus* and *M. pennsylvanicus*), mice and rats (Insel and Shapiro 1992; Insel and Young 2001). The dense distribution of Oxt-immunoreactive fibres in the NAc is conserved in voles, mice and rats, and it is speculated that the differences of social performance might be due to remarkable species differences in Oxtr binding in this specific region (Ross et al. 2009).

The application of various chemical compounds has also been used to develop animal models of ASD. For example, valproic acid (VPA) was given to pregnant rats. The offspring of these rats showed decreased social interactions and fewer social contacts with both familiar and unknown animals (Schneider and Przewlocki 2005; Dufour-Rainfray et al. 2010). We found that the levels of *Oxt* and *Avp* mRNA and Oxt and Avp peptide were significantly lower in the PVN and SON of the hypothalamus in a VPA-induced rat model of ASD (unpublished data). However, opposite observations have also been reported indicating that adult VPA rats had an increased expression of Oxt in the SON and PVN and an increased expression of Oxtr in some brain regions including the basolateral and basomedial amygdala (Stefanik et al. 2015).

The Oxt/Avp system is also involved in some other animal models that exhibit social behavioural deficits. Results from our research group suggested that sex hormone levels during pregnancy might play a role in the susceptibility of the foetus to ASD (Xu et al. 2013, 2015). Rats or mice prenatally exposed to higher levels of testosterone or bisphenol A (BPA) displayed fewer social interactions as compared to controls. The analysis of gene expression revealed that *Avp* mRNA levels were fourfold diminished in F1 embryonic brains exposed to BPA (Wolstenholme et al. 2012; Xu et al. 2015). Phencyclidine (PCP) also induces a dose-dependent disruption of social behaviour and an increase of stereotyped behaviour in rats. Interestingly, subchronic PCP administration significantly reduced the density of Avpr1a binding sites in several brain regions in rats (Sams-Dodd 1995; Tanaka et al. 2003). Mutations in the *MECP2* (methyl-CpG-binding protein 2) gene are causative for Rett syndrome (Amir et al. 1999). It has

been suggested that this gene can also regulate Avp expression within the hypothalamus (Murgatroyd et al. 2009; Forbes-Lorman et al. 2012).

8.4 Therapeutic Strategies for Targeting the OXT/AVP System

8.4.1 Acute Administration

Clear improvements in ASD-like symptoms following acute administration of OXT or AVP have been reported in multiple animal models. For example, single intraventricular injections of OXT but not AVP could rescue social memory in *Oxt* KO mice (Ferguson et al. 2000), while injection of both OXT and AVP could lower aggression and fully reverse ASD-like behaviour in *Oxtr* KO mice. A subcutaneous injection of OXT could further rescue social memory and maternal care in *Cd38* KO mice (Jin et al. 2007). From these experiments it has been suggested that OXT can also bind to the Avp receptor in the *Oxtr* KO model (Sala et al. 2011). Moreover, administration of AVP by microdialysis into the septum could significantly improve social recognition in BB rats (Engelmann and Landgraf 1994). In monogenic ASD models such as *Oprm1* KO mice, single intranasal administration of OXT could rescue social impairments (Gigliucci et al. 2014). It has further been demonstrated that AVP could increase partner-oriented behaviour in male prairie voles, an effect that was not seen in male montane voles (Young et al. 1999).

The re-expression of the *Avpr1a* gene in the lateral septum of *Avpr1a* KO mice using a viral vector system resulted in a complete rescue of social recognition (Bielsky et al. 2005). The introduction of the entire human *AVPR1A* locus (with all the surrounding regulatory elements) could also rescue the PPI impairments in *Avpr1a* KO mice that were showing increased reciprocal social interactions (Charles et al. 2014).

8.4.2 Chronic Administration

Regarding chronic treatment, it was reported that daily administration of OXT in the first postnatal week was sufficient to prevent deficits in social behaviour and led to a more lasting behavioural recovery in adult *Cntnap2* mutant mice (Penagarikano et al. 2015). Other labs reported that chronic administration of OXT has no therapeutic effects, and sometimes it can even cause impairments in social behaviour. In the BTBR mouse model of autism, for example, intranasal administration of OXT for 30 days starting on P21 did not lead to any improvements in ASD-like phenotypes including social interaction, repetitive behaviour and fear-conditioned

learning and memory except for female sniffing in the three-chamber social interaction test (Bales et al. 2014). Moreover, intranasal administration of OXT in prairie voles given from P21 (weaning) to P42 (sexual maturity) with low (0.08 IU/kg), medium (0.8 IU/kg) and high (8.0 IU/kg) dosages resulted in dosage-dependent deficits in partner preference behaviour (Bales et al. 2013). These results indicate that the effects of chronic OXT administration may vary with dosage, age, duration and course of treatment.

8.4.3 Stimuli Enhancing Synthesis or Release of Oxt and Avp in Animals

Although direct administration of OXT or AVP is potentially beneficial for ASD patients, there are several hurdles preventing both from being used as therapeutic agents: (1) short half-life of both peptides (about 20 min in the brain and 5 min in the periphery, Mens et al. 1983), (2) poor penetration of the blood-brain barrier because of the size and charge (Landgraf and Neumann 2004) and (3) the receptors are desensitised after chronic administration. Therefore, the enhancement of the physiological synthesis or release of endogenous OXT and/or AVP by various stimuli may provide an alternative and possibly even more effective therapeutic strategy.

In rodents, several push-pull perfusion and microdialysis studies have proved that there is a local release of Oxt and Avp within the hypothalamus and other limbic brain regions in response to physiological stimuli [suckling, (Moos et al. 1989; Neumann and Landgraf 1989; Landgraf et al. 1992; Neumann et al. 1994a), parturition (Neumann et al. 1993b; 1996), hyperosmotic challenge (Neumann et al. 1993a, b, 1995; Ludwig et al. 1994)], social or emotional experience (maternal defence, Bosch et al. 2004, and social defeat, Engelmann et al. 1999) and physical stimuli (such as chronic homotypic stress, Babygirija et al. 2012a, b, and forced swimming, Wotjak et al. 1998). Some pharmacological agents also stimulate release of neuropeptides by activating hypothalamic Oxt and/or Avp neurons. For example, the exogenous administration of melanocortin receptor (Mcr) agonists to mice selectively activated Oxt neurons in the hypothalamus (Kublaoui et al. 2008) and enhanced the central release of Oxt. This can further be blocked by a melanocortin-4 receptor (Mc4r) antagonist (Sabatier 2006). In addition, the stimulation of Mc4r facilitated Oxt-dependent partner preference formation in the prairie vole (Modi et al. 2015) and improved social interaction in the *Cntnap2* mutant mouse model of autism (Penagarikano et al. 2015). The serotonin system is also involved in the regulation of Oxt secretion. Serotonergic fibres and 5-HT receptors are found in PVN and SON. Both animal and human studies demonstrated that 5-HT agonists elevated peripheral OXT/Oxt (Van der Kar et al. 2001; Lee et al. 2003) and AVP/Avp levels (Jorgensen et al. 2003a, b). The central administration

of 5-HT increased the excitability of PVN magnocellular neurons (Ho et al. 2007) and promoted the synthesis and release of Oxt and Avp (Jorgensen et al. 2003a, b).

OXT and AVP are mainly synthesised and stored in the PVN and SON of the hypothalamus. Several stressors, including forced swimming, immobilisation and long-term dehydration, increased *Oxt* and/or *Avp* mRNA concentrations in the rodent hypothalamus (Wotjak et al. 2001; Babygirija et al. 2012a, b). Interestingly, both single and repeated exposure to restraint stress resulted in the upregulation of *Oxt* (Zheng et al. 2010) and *Avp* (Jezova et al. 1995) mRNA expression in the rat PVN. A recent study in our lab also reported increased number of Oxt-immunoreactive cells in the PVN in response to stress (unpublished observation), whereas Avp-immunoreactive cells in PVN or SON were not affected. During the development of the OXT/AVP system, the production of these neuropeptides might be especially vulnerable to early-life manipulations. Both environmental (such as sensory experience, Zheng et al. 2014) and pharmacological (Bales and Carter 2003; Yamamoto et al. 2004; Penagarikano et al. 2015) manipulations during early postnatal life enhanced Oxt production as well as social behaviours during adult life.

Acupuncture, an important component of traditional Chinese medicine, is also used as a therapeutic option for a wide range of clinical conditions. It has been suggested that acupuncture or electroacupuncture (EA) stimulation with unique frequencies facilitates the release of frequency-specific neurochemicals in the central nervous system (CNS) eliciting profound physiological effects (Han 2003). Rats exposed to 30 min of EA treatment showed increased Oxt levels both in cerebrospinal fluid (CSF) and in the plasma (Uvnas-Moberg et al. 1993). This increase also occurred in certain brain regions, including the hypothalamic suprachiasmatic nucleus, the hypothalamic ventromedial nucleus and periaqueductal grey (Yang et al. 2007). A study in our lab showed that single EA intervention potentiated Oxt and Avp gene expression in the SON, but not in the PVN of adult rats. Repeated sessions of EA resulted in the upregulation of *Avp* mRNA levels and increased Oxt and Avp content in the SON. Interestingly, the EA-induced elevation of neuropeptide levels was accompanied with a social behavioural improvement of rats (Zhang et al. 2015). Despite these encouraging findings on EA in rats, several critical questions still need to be clarified in future studies including the optimal parameters of EA stimulation.

8.5 Translational Medicine of OXT and AVP

Since OXT and AVP are strongly involved in the modulation of social behaviours, these neuropeptides have been considered as potential therapeutic agents (Bartz and Hollander 2008; Macdonald and Macdonald 2010; Meyer-Lindenberg et al. 2011; Anagnostou et al. 2014; Gumley et al. 2014; Guastella et al. 2015; Neumann and Slattery 2016).

8.5.1 *Effects of Single-Dose Administration of OXT on Social Cognition in Humans*

A large body of research suggested the benefit of OXT nasal spray or intranasal administration for improving social behaviours including attachment (Buchheim et al. 2009), social memory (Guastella et al. 2008; Rimmele et al. 2009), facial expressions (Evans et al. 2010; Marsh et al. 2010), emotion recognition (Di Simplicio et al. 2009), empathic accuracy (Bartz et al. 2010) and trusting (Kosfeld et al. 2005; Mikolajczak et al. 2010). Neuroimaging studies in this context focused on the activity of the amygdala and the functional coupling between the amygdala and other brainstem regions that mediate autonomic and behavioural aspects of fear (Kirsch et al. 2005; Domes et al. 2007).

8.5.2 *Effects of Acute OXT Administration in Adult Patients with ASD*

Hollander et al. (2003) were the first to report on the effects of intravenous (i.v.) administration of OXT on facilitating the retention of social cognition in adult participants with Asperger syndrome. They found a significant reduction of repetitive behaviour and an enhanced ability to accurately assign emotional significance to speech intonation on the speech comprehension task (Hollander et al. 2007). Subsequent studies from other labs demonstrated that i.v. (Andari et al. 2010; Hall et al. 2012) or intranasal administration (Guastella et al. 2010) of OXT improved the symptoms in adolescents or children with Asperger or Fragile X syndrome (Tachibana et al. 2013).

8.5.3 *Multiple-Dose Studies of Intranasal OXT in Patients with ASD*

Most OXT interventions were studied in adult patients with ASD carefully considering ethical and safety factors. Open-label case studies and uncontrolled cohort studies imply potential benefits of repeated nasal OXT to treat ASD symptoms (Kosaka et al. 2012). However, later pilot trials showed controversial results with either positive (Watanabe et al. 2015) or negative (Dadds et al. 2014; Guastella et al. 2015) outcomes. Recently, a clinical trial in children raised the hope of a successful OXT treatment in ASD. In this study, 32 children with ASD received a 5-week OXT or placebo nasal spray. This resulted in significant improvements of caregiver-rated social responsiveness in the OXT-treated group with mild adverse events (thirst, urination and constipation). In summary, the human studies are quite similar to the animal studies showing that the benefit of single dosing could not yet

been translated to repeated OXT treatment. Further studies are needed to determine the optimised regimen and route of application for OXT.

For the therapeutic potential of AVP in ASD, data on experimental studies with patients are still missing. The prominent feature of peripheral AVP is to maintain blood pressure by its antidiuretic and vasopressor activity (Thompson et al. 2004). Therefore, the safety of this neuropeptide has to be carefully considered, especially when it is applied to children.

8.5.4 Endogenous Release of OXT/AVP in Humans

Due to ethical and methodological restriction, it is difficult to obtain local peptide concentrations in peptide-producing nuclei or CSF from human brains. Up to now, there are no studies on the central release of OXT or AVP in humans in response to exogenous stimuli. The reviewed literature is therefore mainly focusing on alterations of peripheral (plasma, saliva and urine) peptide concentrations.

Birth and suckling, two classical physiological stimuli, are known to induce the release of OXT from the neurohypophysis into the peripheral circulation. Dehydration leads to an increased osmotic pressure, which triggers AVP secretion into the blood stream. Social stimulation such as social vocalisations (Seltzer et al. 2010), parent-child contact (Feldman et al. 2014), spouse/partner support (Grewen et al. 2005; Light et al. 2005), empathy towards strangers (Barraza and Zak 2009) and interpersonal touch (Scheele et al. 2014) triggers peripheral OXT release. Recent studies in our lab indicated that transcutaneous electrical acupoint stimulation (TEAS) is also potent to increase plasma AVP levels in children with ASD and alleviate their social interaction impairments (Zhang et al. 2012). However, there is no direct evidence that OXT and AVP levels in the periphery reflect the levels and functions of these neuropeptides in the CNS. Therefore, the interpretation of peripheral neuropeptide levels with respect to CNS availability of these neuropeptides needs more experimental evidence (Horvat-Gordon et al. 2005; Henricson et al. 2008).

8.6 Conclusions

The OXT/AVP system plays a critical role in social cognition in mammals. Alterations of OXT/AVP, their receptors or upstream mediators lead to severe impairments of social behaviour that are reminiscent of clinical symptoms seen in ASD. Rodent animal models for ASD oftentimes show a clear dysfunction of their Oxt/Avp system, suggesting an involvement in the formation of social behaviour. Based on the findings in several animal models, OXT or AVP have been acutely administered to experimental cohorts. These studies revealed obvious positive effects on social memory or interaction both in animals and humans. Chronic

treatment, however, thus far resulted in contradictory results that might be explained by the complex pharmacological properties and pathway modulation of OXT and AVP. Stimulating endogenous synthesis and release of OXT and AVP may therefore be a more promising therapeutic strategy for the treatment of patients with ASD.

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