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Brain Oxytocin is a Main Regulator of Prosocial Behaviour - Link to Psychopathology

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1. Introduction

The neuropeptide oxytocin (OT) becomes increasingly attractive not only for neurobiologists, psychologists and psychiatrists, but also for sociologists and economists promoted by the discovery of amazing behavioural functions it regulates, especially in the context of social interactions. The discovery of multiple pro-social as well as anti-stress effects of OT, which have been discovered in recent years, makes the OT system of the brain a promising target for psychotherapeutic intervention and treatment of numerous psychiatric illnesses, for example, anxiety disorders, social phobia, depression or autism (Slattery & Neumann, 2010). The endogenous OT system of the brain can be found in different activity forms. Consequently, neuronal OT synthesis, OT release within distinct regions of the brain, OT receptor binding and the intensity of OT behavioural effects can vary in dependence on the physiological (or pathophysiological) activity state, which will be outlined in more detail below. It is generally assumed that psychopathologies associated with impaired social interactions, such as autism, are accompanied by an impaired activity of the brain OT system, which may affect at least one of the above mentioned parameters.

1.1 The oxytocin system

Chemically, OT consists of nine amino acids. Two cystein residues form a disulfid bridge creating the circular structure of the nonapeptide discovered almost 60 years ago (Du Vigneaud et al., 1953). OT and the structural related neuropeptide arginine vasopressin (AVP) belong to the arginine vasotocin family (Acher et al., 1972). Neuropeptides of this family are ubiquitous within vertebrates and evolutionary highly conserved, both in structure and functions (Hoyle, 1999).

Together with AVP, OT is an essential part of the hypothalamo-neurohypophysial system. OT and AVP are mainly synthesized in a well-defined arrangement of magnocellular neurons located within the hypothalamic supraoptic (SON) and paraventriular nuclei (PVN) of the hypothalamus at the base of the brain. Via axonal projections OT and AVP reach the neurohypophysis where they are released into the blood stream.

Originally, OT has been reported as a hormonal key regulator of female reproductive functions in all mammalian species when secreted into blood. Thus, OT accelerates the delivery process as it promotes uterine contractions, and is essential for milk ejection during

lactation. However, starting with the fundamental discoveries of David DeWied and Cort Pedersen (De Wied, 1965, Pedersen & Prange, 1979), OT (and also AVP) emerged as a neuromodulator of the brain regulating a broad variety of behaviours. Among the various behavioural effects of OT are prosocial actions such as the promotion of maternal care and aggression, pair-bonding, sexual behaviour in males and females, social cognition, social memory and social support (for review see Bielsky & Young, 2004, Donaldson & Young, 2008, Neumann, 2009). Moreover, OT has the potential to reduce anxiety and to inhibit physiological stress responses which is likely to accompany these prosocial actions (Neumann, 2002, 2009).

In the context of these multiple behavioural effects, neuronal release of OT within the brain is of main relevance and has recently attracted the attention of many neurobiologists. The locally restricted intracerebral release of OT or AVP can be monitored using microdialysis in combination with sensitive radioimmunoassays, even in freely behaving animals (for review see Landgraf & Neumann, 2004, Veenema & Neumann, 2008). Monitoring of central release patterns of OT during ongoing behavioural performance is challenging, but possible. Thus, even during mating, mother-offspring interactions and suckling, or the display of aggressive or defensive behaviours, dialysates can be sampled without interference with the behaviour of the animal. Moreover, using this technique, the dynamic changes in the concentration of OT in the extracellular fluid surrounding oxytocinergic neuronal structures can be correlated with ongoing behavioural performance.

The release of OT and AVP within the brain should occur from dendrites or perikarya of magnocellular neurons described within the hypothalamus (Ludwig & Leng, 2006), but also from axonal or collateral projections of parvo- or magnocellular neurons targeting, for example, regions of the limbic brain (Buijs et al., 1983). OT and AVP systems served as a suitable model arrangement not only for the discovery of important molecular and cellular mechanisms of neuropeptide synthesis, precursor processing, and cellular trafficking, but also for the stimuli and neuronal mechanisms of intracerebral neuropeptide release within distinct brain regions (Landgraf & Neumann, 2004, Ludwig & Leng, 2006, Ludwig & Pittman, 2003, Neumann, 2007). In the context of this chapter it is important to mention that a variety of social stimuli trigger the activation of OT neurons and, thus, local OT release within the brain (see below), in some, but not all, instances accompanying peripheral secretion into blood. We hypothesize that, in humans, lack of OT activation in a social context might be associated with social dys-functions as seen in a variety of psychopathologies.

1.2 Autism and social behaviors

Various psychiatric disorders are associated not only with emotional disturbances, but also with dysfunctions and deficiencies in social interactions (Kohn & Asnis, 2003, Neumann et al., 2010). Thus, impaired social functions such as social withdrawal, social phobia, aggression and violence, or impaired social cognition are core symptoms for, for example, major depression, anxiety disorder, posttraumatic stress disorder (PTSD), borderline syndrome, schizophrenia, and autism spectrum disorders (ASD) including the Asperger's Syndrome. Deficits in sociability seen in ASD become apparent during standard nonverbal social interactions, e.g. eye contact or affective expression. Reduced empathy the inability to share blissful and tearful emotions with others, and a lack of social and emotional reciprocity further demonstrate reduced sociability. Moreover, individuals with ASD fail to recognize faces and to integrate facial expressions of emotions caused by impaired social cognitive abilities (Harony & Wagner, 2010).

Due to its profound pro-social actions discovered in animal studies, OT effects on human social behaviour started to be in the focus of interest of psychologists and psychiatrists, among others. Consequently, a potential involvement of the brain OT system in mal-adaptations during these diseases and the potential of synthetic OT as therapeutic strategy has been suggested (Harony & Wagner, 2010).
This chapter aims at summarizing various activity states of the OT system and provides evidence from both animal and human studies for its role as a key regulator of complex social behaviors.

2. The brain OT system and rodent social behaviour

There are various physiological conditions associated with an altered activity state of the endogenous OT system. These include, for example, the peripartum period in females, sexual activity in both males and females, social interactions between conspecifics, both offensive and friendly, or pairbonding in the female monogamous prairie vole. Under these conditions of a naturally occurring high-activity state, the functional relevance of the endogenous brain OT system can be nicely investigated using various pharmacological tools such as selective receptor antagonists. Moreover, studying the dynamic release patterns of OT within a relevant brain region during such an activity state tells us a lot about the neurobiological activity of the endogenous brain OT system, which is important for the final aim to either use OT as a possible therapeutics or, alternatively, to target the brain OT system therapeutically. Most of our knowledge regarding the intracerebral release of OT during such high-activity states as well as the functional significance for pro-social behaviours arrives from rodent studies.

2.1 Intracerebral OT release in the context of female social behaviours peripartum

Physiological and behavioural changes have been extensively described in the mammalian maternal brain occurring in the peripartum period (Neumann, 2001, Slattery & Neumann, 2008). They continue in lactation as a direct result of close social interactions between mother and offspring, for example during suckling, maternal care and protection. The OT system is highly activated peripartum as it plays a predominant role in female reproduction for speeding up birth and facilitating milk ejection. The general activation of the OT system is reflected by increased OT synthesis in neurons of the hypothalamus, OT secretion into blood, and local OT release and OT receptor binding in several brain regions (for review see Neumann, 2003, Numan & Insel, 2003, Slattery & Neumann, 2008).
Using intracerebral microdialysis or push-pull perfusion techniques, local release of OT has been shown, for example, within the hypothalamic SON and PVN, the septum, hippocampus, and the olfactory bulb during parturition and suckling (Kendrick et al., 1988, Neumann et al., 1993, for review see Neumann, 2009). Such centrally released OT has been shown to be involved in several neuroendocrine and behavioural functions: both during birth and in response to suckling, brain OT regulates the pulsatile release of OT into the blood in a positive feedforward mechanism (Moos & Richard, 1989, Neumann et al., 1994). Further, centrally released OT simultaneously promotes the fine-tuned maintenance of mother-offspring interactions, such as offspring recognition (sheep), maternal care, but also maternal defence behaviour (Bosch, 2011, Bosch & Neumann, 2008, Kendrick et al., 1988, Lubin et al., 2003, Pedersen, 1997). Together these physiological functions are important prerequisites for the survivial of the offspring. In addition, OT at this high activity state

inhibits emotional, e.g. anxiety-related, and neuroendocrine responses to acute stressful stimuli (Neumann et al., 2000).

Moreover, we could monitor increased release of OT within the hypothalamic PVN and the central amygdala during the defence of the pups against a virgin intruder rat in lactating rats. Intracerebral microdialysis allowed simultaneous monitoring of locally restricted release patterns as well as of various maternal aggressive and non-aggressive aspects of social behaviour of the dam (Bosch et al., 2005). Interestingly, central OT release was found to be correlated with the intensity of maternal aggression, indicating a direct link between local neuropeptide release and behavioural performance (Bosch et al., 2005). In order to reveal the functional significance of locally released OT, we blocked local OT receptors using a specific OT receptor antagonist before behavioural testing. Within the PVN and the central amygdala, bilateral application of the OT antagonist reduced aggressive behaviour towards the virgin intruder (Bosch et al., 2005), but pup-directed maternal behaviour was not altered. Thus, in lactation, OT released within the hypothalamus and amygdala and acting at local receptors fulfils an important role in promoting maternal defence behaviour and offspring protection. Within the amygdala, OT directly regulates neuronal activity (Huber et al., 2005, Neumann, 2002). Moreover, both within the PVN and the amygdala OT exerts anxiolytic effects in female and male rats (Bale et al., 2001, Blume et al., 2008, Neumann, 2002). Therefore, it is tempting to suggest a functional link between locally released OT in response to a social challenge, i.e. exposure to the intruder, the reduction in anxiety and the display of maternal aggressive behaviour. Indeed, different levels of maternal behaviour and maternal aggression have been found in rats selectively bred for high versus low trait anxiety (Bosch, 2011, Bosch & Neumann, 2008).

In addition to the link between the high activity of the brain OT system and respective pro-social and defensive behaviours of the mother, the high activity state of the OT system peripartum has further been associated with a state of anxiolysis and general attenuation of physiological stress responses (Heinrichs et al., 2001, Neumann et al., 2000, Torner et al., 2002, Windle et al., 1997) (for review see Neumann, 2009, Slattery & Neumann, 2008).

2.2 Intracerebral OT release during the display of male sexual behaviour

OT is also released within the male brain, in response to social and non-social stimuli (for review see Engelmann et al., 2004, Landgraf & Neumann, 2004, Neumann, 2007). As sexual interaction is the most intense social interaction found in males and increased OT secretion into blood has been found during orgasm (Carmichael et al., 1987, Stoneham et al., 1985) we and others have studied the activation of the brain OT system during sexual activity and its role in the regulation of sexual behaviour.

In response to sexual stimuli, there is increased Fos-expression within the hypothalamus reflecting increased neuronal activity in OT neurons of the PVN (Witt & Insel, 1994). This is likely to reflect both increased secretion of OT into blood, but also intracerebral neuropeptide release. Indeed, we could recently demonstrate using intracerebral microdialysis in freely moving male rats that successful mating triggers local release of OT within the PVN (Waldherr & Neumann, 2007). Interestingly, OT release already started to rise during the presence of the primed female behind a perforated wall, which allowed olfactory and visual, but not physical, contact or mating. As males clearly displayed signs of behavioural arousal under these conditions, OT activation may already be induced by the presence of a receptive female even without mating (Waldherr & Neumann, 2007). Within

the hypothalamic PVN OT has been shown to play an important role in the regulation of male sexual behaviour (Argiolas & Gessa, 1991), but also of anxiety (Blume et al., 2008). Specifically, during mating, such locally released OT could be shown to exert an anxiolytic effect in male rats (Waldherr & Neumann, 2007).

We therefore conclude that the release of OT within the brain during sexual activity has far reaching behavioural consequences and beneficial effects for the male rat, i.e. reducing the level of anxiety and stress responses for several hours. In humans, there is anecdotal and experimental evidence of a link between sexual activity, and sedation, increased relaxation and calmness in the post-coital period (Brody, 2006, Krüger et al., 2002). Our data show that these effects are mediated, at least in part, by an activated brain OT system. As OT was shown to exert reinforcing and rewarding actions (Liberzon et al., 1997), the possibility further exists that enforced and reinforced trust to the sexual partner also involves brain OT (Kosfeld et al., 2005), although this is still highly speculative.

In summary, the central release of OT during close social interaction, such as suckling the offspring in lactating mammals, or sexual activity in males, is likely to be involved not only in the regulation of the associated particular social behaviours, but also in the beneficial effects of these pro-social interactions. Positive effects such as anxiolysis, attenuated stress responses, increased calmness and sedation (Carter et al., 2001, Heinrichs et al., 2003, Neumann, 2002, Waldherr & Neumann, 2007) are likely to be rewarding and to further promote social interactions (Neumann 2009).

2.3 Central OT and social cognition

Social interactions, especially long-lasting social bonds, require different forms of social memory and social recognition. As shown in both male and female rodents social recognition largely depends on an intact brain OT system (for review see Bielsky & Young, 2004)

Centrally applied OT facilitates social memory in a dose-dependent manner as shown in male rats. In contrast, infusion of the OT receptor antagonist blocked this effect but was not successful to impair their social memory per se (Benelli et al., 1995). Literatur on male mice seems more straight forward. In male mice lacking the OT gene (Ferguson et al., 2000) or in mice with deficient OT release (Jin et al., 2007) impaired social cognition and social memory skills were found. Importantly, OT bilaterally infused into the amygdala was able to restore the cognitive deficits seen in OT knockout mice, whereas OT receptor antagonist infusions impaired social memory in male wildtype mice (Ferguson et al., 2001). Other regions responsive to synthetic or endogenous OT in the context of social recognition are the lateral septum (Popik et al., 1992), the olfactory bulb (Dluzen et al., 1998, Larrazolo-Lopez et al., 2008), the medial preoptic area (Popik & van Ree, 1991), and the ventral hippocampus (van Wimersma Greidanus & Maigret, 1996).

Also, in female rats brain OT seems to be important for social discrimination of two juvenile rats (Engelmann et al., 1998). The medial amygdala (Choleris et al., 2007) and the olfactory bulb (Larrazolo-Lopez et al., 2008) could be identified as sites of action using microdialysis and local pharmacological blockade or downregulation of OT receptors.

OT seems to be an important factor in female social cognition in a more complex context thus promoting long-lasting bonds such as mother-infant bonding or pair bonding. In ewes, lamb recognition and bonding could clearly be related to the release of OT, for example within the olfactory bulb, during birth and in response to suckling (Kendrick et al., 1988, Lévy et al., 1995). Moreover, in the monogamous prairie vole, social recognition

of the mate is a prerequisite for monogamous behaviour and the ability to form a selective pair-bond. Similar to the offspring bonding in ewes, OT plays a critical role in pair-bonding (see below) (Insel & Hulihan, 1995, Young & Wang, 2004). Thus, parturition- and mating-induced stimulation of OT release within distinct brain regions seems to be a promoting factor for social cognition and a requirement for the formation of lasting social bonds.

In female OT knockout mice, the essential role of OT in social memory has also been demonstrated in the context of the Bruce effect. The Bruce effect refers to the ability of a female mouse to discriminate between her mate and a novel mate. Contact with a novel male consequently leads to an interruption of pregnancy. OT knockout females failed to remain pregnant, if re-exposed to either their mate or a novel male. Only females that were allowed to remain with their mate maintained pregnancy (Wersinger et al., 2008). This inability to distinguish between the mate and a novel male in females with deficits in the OT systems further demonstrates the importance of OT in long-term social memory as well as short-term social recognition especially in females.

2.4 Central OT and female pair-bonding

There is a large body of literature concerning the facilitating effects of the neuropeptides OT and AVP in pair-bonding of monogamous voles (for review see Young & Wang, 2004). Whereas AVP is well established to be involved in pair-bonding and partner preference in male prarie voles, OT seems to play a major role in female pair-bonding (Cho et al., 1999, Cushing & Carter, 2000). This was shown by the facilitating effect of centrally applied OT on the development of partner preference even without prior mating (Williams et al., 1994), and receptor binding studies demonstrated an increased OT receptor binding in the nucleus accumbens and caudate putamen of female monogamous prairie voles compared with non-monogamous vole species (Insel & Shapiro, 1992). The involvement of OT within several brain regions in female pair-bonding was further demonstrated by blockade of mating-induced female pair-bonding following infusion of an OT receptor antagonist into the prefrontal cortex or the nucleus accumbens, but not in the caudate putamen (Young et al., 2001). Recently, we succeeded in demonstrating OT release within the nucleus accumbens during mating in female prarie voles (Ross et al., 2009). Such locally released OT was shown to originate most likely within the hypothalamic SON and PVN. Consequently, activation of magnocellular OT neurons during mating and OT secretion into blood may, simultaneously, result in locally restricted release of OT from neuronal collaterals in dependence on gender and species.

In this context, it is important to mention that the nucleus accumbens is part of the mesolimbic dopamine reward system (Wise, 2002). As mating is a rewarding stimulus, and was shown to induce pair-bonding in female voles, endogenous OT release triggered by sexual stimuli may potentially mediate its facilitating effects on partner formation and pair-bonding via these circuitries (Neumann, 2009, Wang & Aragona, 2004).

2.5 Central OT release during social stress

The OT system is highly responsive to all kind of stressors, both being non-social and social in nature (Engelmann et al., 2004, Landgraf & Neumann, 2004, Neumann, 2007) For example, exposure to forced swimming or to a larger and aggressive conspecifics during the social defeat are both stimuli for OT release in selected brain target regions (Ebner et al., 2000, Engelmann et al., 1999, Wigger & Neumann, 2002, Wotjak et al., 1998).

Exposure of male rats to social defeat selectively stimulates OT release within the hypothalamic SON (Engelmann et al., 1999) and the septal area (Ebner et al., 2000). In contrast, OT secretion into blood remains unchanged in response to this social stressor indicating independent release patterns into blood and within the brain.
Also, in virgin female rats, social defeat is a stimulus for the brain OT system and triggers OT release within the hypothalamic PVN, but not the amygdala or the lateral septum (Bosch et al., 2004). In females, social defeat can be achieved by exposure to a lactating dam in the presence of her litter (Neumann et al., 2001). During lactation, dams are highly aggressive protecting their offspring. Maternal defence behaviour is also stressful for the lactating dam resulting in elevated stress responses and an increased release of OT within the PVN and amygdala, especially in dams displaying highly aggressive behaviour (Bosch et al., 2005, Neumann et al., 2001). Interestingly, the amount of OT locally released within these regions was found to be directly correlated with the total amount of aggression displayed by the dam during the maternal defence test (Bosch et al., 2005).
Thus, both in males and females, aversive social interactions as seen during social defeat and maternal defence, respectively, are strong stimuli for the brain OT system. In lactation, brain OT strongly promotes maternal aggression (Bosch et al., 2005), but we have to keep in mind that maternal aggression is a defensive strategy important for the protection of the offspring. The neurobiological mechanisms of maternal defensive aggression and intermale aggression, for example, are almost completely independently regulated. However, to which extend central OT regulates aggressive behaviour in males is rather unclear (Ebner et al., 2000); so far, we could not reveal a clear effect of OT on aggression in male rats (unpublished observation).

3. Behavioural effects of OT in humans

In humans, intranasal or intravenous application of OT was reported to improve a broad variety of complex social behaviours (for reviews see Heinrichs et al., 2009, MacDonald & MacDonald, 2010, Meyer-Lindenberg, 2008).
Specifically, intranasal OT increased trust in healthy men (Kosfeld et al., 2005) and even prevented betrayal-triggered decrease in trust (Baumgartner et al., 2008). In this context, OT increased ratings for trustworthiness and attractiveness of unfamiliar faces (Theodoridou et al., 2009). Moreover, OT–treated subjects were significantly more generous than placebo-treated men during a generosity game (Zak et al., 2007). In general, OT seems to improve the interpretation of social cues (Domes et al., 2007b, Kosfeld et al., 2005), especially the recognition of fear (Fischer-Shofty el al., 2010). . OT also facilitates the recognition of faces (Rimmele et al., 2009) most effectively when they express positive emotion (Guastella et al., 2008b, Savaskan et al., 2008). In the context of ASD associated with avoidance of eye contact it is important to mention that OT promotes a gaze-shift towards the eye region of presented faces (Guastella et al., 2008a) also independent of their valence as this normally occurs during presentation of fearful faces (Gamer & Buchel, 2009). In the context of OT promoting social bondings it is of interest to mention initial studies demonstrating that OT enhanced attachment security (Buchheim et al., 2009)
On a more neurophysiological level, human functional imaging studies (fMRI) indicated that OT reduces amygdala responses to threatening, non-social scenes and to angry and

fearful faces (Kirsch et al., 2005). More specifically, it could be shown that OT promotes the activity in amygdala regions involved in the processing of positive social stimuli (Gamer et al., 2010), an effect that was shown to generalize to facial expressions, irrespective of their valence (Domes et al., 2007a) .

These studies show that OT promontes trust and generosity, improves "mind-reading" and facilitates the ability to recognize faces and facial expressions of social cues. Thus, there is substantial evidence for complex behavioural effects of OT, as a result of acute intranasal application, on social competence. These prosocial effects give hope for OT as a potential treatment option under condition of social dysfunctions as seen in ASD.

4. Autism spectrum disorders - involvement of brain OT

Various animal and human studies strongly support the hypothesis of an involvement of OT in complex social interactions, both under healthy and pathological conditions associated with social dysfunctions. Therefore the following paragraph will summarize human data concerning OT actions within the amygdala in the context of ASD.

4.1 Amygdala and autism

The amygdala as part of the limbic brain has been implicated in the neurobiology of autism as seen from morphometric data (Dalton et al., 2007, Dalton et al., 2005, Dziobek et al., 2006). The subnuclei of the amygdala are key areas regulating arousal and vigilance to emotionally relevant stimuli (Davis & Whalen, 2001, Fitzgerald et al., 2006, Hsu et al., 2005, Yang et al., 2002), and spontaneous social cognition by processing the rapid evaluation of social stimuli. Thus, it is very likely that the amygdala is significantly involved in the processing of both social as well as non-social, e.g. stressful and emotional stimuli, both being of high relevance for the individual. However, the amygdala is also likely to be involved in complex emotional and cognitive processes such as empathy and affiliation.

Various neurotransmitters and neuromodulators are involved in the neuronal processing within the amygdala, among them the neuropeptides OT and AVP. OT receptors were localized within the central and medial amygdala (Lukas et al., 2010, Tribollet et al., 1988), OT is locally released (Bosch et al., 2005, Ebner et al., 2005) and exerts local neuronal effects regulating the electrophysiological activity of central amygdala neurons (Huber et al., 2005). In this way, OT might be involved in the complex regulation of social behaviour and emotional responses to various social and stressful cues both under healthy and pathological conditions also in humans.

4.2 OT system activity alterations and therapeutical implications in autism

Indeed, dysfunctions of the brain OT system have been intensively discussed to contribute to the development of social deficits in autism (Carter, 2007, Hammock & Young, 2006, Harony & Wagner, 2010). For example, plasma OT concentrations, although reflecting central OT system activity only to a certain degree, were found to be attenuated in individuals with ASD (Green et al., 2001, Lane, 2009). More and more studies indicate the potential use of OT applied intravenously or intranasally in the treatment of ASD. Thus, OT reduced repetitive behaviors in patients with Asperger or autism (Hollander et al., 2002) and promoted prosocial behaviors in high-functioning autism (Andari et al., 2010). Moreover, OT improved affective speech comprehension in adults (Hollander et al., 2007) and emotion

recognition in youths with ASD (Guastella et al., 2010). Furthermore, OT was used as an adjunct to exposure therapy (Guastella et al., 2009) and was shown to attenuate amygdala reactivity to fear (Labuschagne et al., 2010) in social anxiety, another core symptom of ASD. Association studies on several ethnic groups linked polymorphisms in the OT receptor gene with ASD (Jacob et al., 2007, Lerer et al., 2007, Wu et al., 2005). Furthermore another study was able to detect epigenetic modifications within the OT receptor promotor region of ASD patients indicating altered levels of OT receptor expression (Gregory et al., 2009).

5. Conclusion

Our chapter summarizes our knowledge about different activity states of the brain OT system in the context of varying social interactions. Increased OT system activity triggered by social interactions is linked to high levels of OT release within distinct brain regions, which, in turn, is involved in the promotion of these social interactions, as seen during maternal and sexual behavior, pair-bonding or social memory functions. Moreover, high OT activity and release of OT, for example within regions of the reward circuitry, further promote social interactions as they are experienced as being rewarding. Indeed, a high activity state of the OT system is associated with calmness, anxiolysis and attenuated stress responsiveness, as seen during lactation and after sexual activity, further contributing to feeling of wellness. In contrast, although experimental evidence is extremely limited, the present data give support to the hypothesis that social dysfunctions are associated with lack of brain OT system activation, either under basal conditions or in reposnse to social stimuli, or both. Thus, appropriate brain OT system activation seems a prerequisite for healthy and normal sociability. We also discuss that translation of these findings mainly from rodents to human studies is possible. Effects of intranasal OT could be directly related to the promotion of complex human social behaviors, also under conditions of disease like autism. Consequently, targeting the brain OT system or application of synthetic OT to compensate for deficits in endogenous OT system activity in combimnation with psychotherapy, appears to be a promising treatment option promoting pro-social behaviors in humans especially under pathological conditions of impaired sociability.

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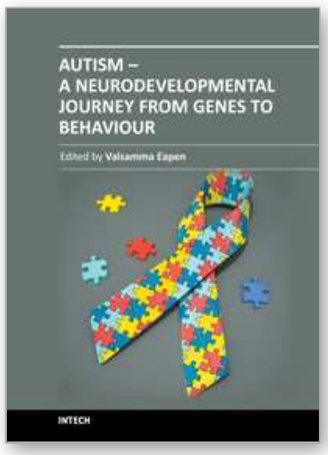

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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