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REVIEW ARTICLE

Brain Oxytocin: A Key Regulator of Emotional and Social Behaviours in Both Females and Males

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In addition to various reproductive stimuli, the neuropeptide oxytocin (OXT) is released both from the neurohypophysial terminal into the blood stream and within distinct brain regions in response to stressful or social stimuli. Brain OXT receptor-mediated actions were shown to be significantly involved in the regulation of a variety of behaviours. Here, complementary methodological approaches are discussed which were utilised to reveal, for example, anxiolytic and anti-stress effects of OXT, both in females and in males, effects that were localised within the central amygdala and the hypothalamic paraventricular nucleus. Also, in male rats, activation of the brain OXT system is essential for the regulation of sexual behaviour, and increased OXT system activity during mating is directly linked to an attenuated anxiety-related behaviour. Moreover, in late pregnancy and during lactation, central OXT is involved in the establishment and fine-tuned maintenance of maternal care and maternal aggression. In monogamous prairie voles, brain OXT is important for mating-induced pair bonding, especially in females. Another example of behavioural actions of intracerebral OXT is the promotion of social memory processes and recognition of con-specifics, as revealed in rats, mice, sheep and voles. Experimental evidence suggests that, in humans, brain OXT exerts similar behavioural effects. Thus, the brain OXT system seems to be a potential target for the development of therapeutics to treat anxiety- and depression-related diseases or abnormal social behaviours including autism.

Key words: anxiety, maternal care, aggression, sexual behaviour, cognition, stress coping.

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The neuropeptide oxytocin (OXT) is currently attracting considerable attention as a result of the discovery of the amazing behavioural functions it regulates, especially in the context of social interactions. A broad variety of behaviours, including maternal care and aggression, pair bonding, sexual behaviour, and social memory and support, as well as anxiety-related behaviour and stress coping, are modulated by brain OXT. These discoveries make this neuromodulator/neurotransmitter system of the brain a promising target for psychotherapeutic intervention and treatment of numerous psychiatric illnesses, for example, anxiety disorders, social phobia, autism and postpartum depression.

Together with the related nonapeptide arginine vasopressin (AVP), OXT is an essential part of the hypothalamo-neurohypophysial system. Since the original description of this system in fish by the German biologist Ernst Scharrer in 1928 (1), this well-defined arrangement of magnocellular neurones at the base of the brain has been one of the most valuable model systems in neuroendocrinology and neuroscience. Outstanding discoveries have been made through studying the OXT and AVP systems. These include the very first characterisation of a neuropeptide by DuVigneaud and, independently, by Acher in the 1950s, important insights into the bursting pacemaker activity of neurosecretory neurones (2), the discovery of neuropeptidergic pathways within the brain (3), novel views of neuronal-glial interactive plasticity (4, 5), and the development of neuropeptide receptor antagonists (6). Furthermore, the OXT system served as a suitable model arrangement for discovering important molecular and cellular mechanisms of neuropeptide synthesis, precursor processing, and cellular trafficking (7, 8), as well as the stimuli and neuronal mechanisms of intracerebral neuropeptide release within distinct brain regions (9–11). These important findings have, in parallel, raised the question of the behavioural consequences of local OXT release and subsequent OXT receptor-mediated actions within brain target regions (12, 13).

Methodological approaches to reveal behavioural consequences of OXT release

Several complementary methodological approaches are possible and necessary in order to characterise specific behavioural functions of a given neuropeptide, such as OXT, within the brain. Results obtained using different approaches are often controversial and inconsistent, and the behavioural effects vary depending on the species, strain, gender, behavioural test conditions, mode of drug administration and other experimental manipulations. Clearly, the pharmacological manipulation of the OXT system and subsequent examination of behavioural consequences is the major methodological approach. This includes central [intracerebroventricular (icv), local] administration of synthetic OXT at varying doses, or of selective OXT receptor antagonists in order to acutely block receptor-mediated actions and to reveal behavioural effects of *endogenous* OXT. However, OXT shows structural similarities with AVP, and cross-interactions between these neuropeptides and their receptors are likely (14). Therefore, more selective techniques can be used in order to sequence-specifically manipulate either OXT or OXT receptor synthesis, including antisense oligodeoxynucleotides targeting the OXT or OXT receptor gene (15–18). Recently, virally mediated gene transfer has been introduced for selective overexpression of AVP (19–21) or OXT (22) receptor synthesis within specific brain regions and associated with relevant behavioural alteration(s). Another important approach is the use of knockout and transgenic animals, and both OXT and OXT receptor knockout animals have been extensively characterised with respect to a variety of behaviours (23–25; for reviews, see 26, 27). All of these techniques have their own advantages and limitations, but each of them makes a valid contribution to the completion of the puzzle of the complex behavioural functions of neuropeptides such as OXT. However, it seems essential to keep in mind that manipulation of a single brain component is likely to co-affect multiple related systems. This holds true, in particular, if chronic treatments or transgenic animals are used, or if the approach adopted has long-term neuronal consequences, making the unambiguous interpretation of data more difficult.

In our laboratory, we also employ an alternative approach to manipulation of the OXT system, and monitor patterns of OXT release into the extracellular fluid within a brain area of interest during the display of a particular behaviour. Both intracerebral microdialysis and push-pull perfusions are suitable for quantifying the dynamics of local release of OXT or other neuropeptides (e.g. AVP and prolactin) and neurotransmitters in a freely behaving animal. Usually, these intracerebral microperfusions are performed prior to, during and after exposure to a behavioural challenge, for example during exposure to a conspecific intruder, either during maternal defence or in the resident-intruder test. Monitoring of local release patterns of a given neuropeptide during ongoing behavioural performance in rodents is challenging, but possible using microdialysis. Thus, even during the display of aggressive (28) or sexual (29) behaviour, dialysates can be sampled without interference with the behaviour of interest. In order to reveal the behavioural consequences of the local release patterns of OXT, we can then administer either a receptor ligand or a receptor antagonist locally via inverse microdialysis (retrodialysis) over the entire observation period. Importantly, microdialysis/retrodialysis can also be performed in conscious mice (30).

Monitoring the release patterns within the brain is especially important, as changes in OXT concentrations in blood plasma occur independently of those in the extracellular fluid of an intracerebral target region. Thus, plasma OXT does not necessarily reflect the dynamics of intracerebral, locally restricted release (31). Further, OXT cannot cross the blood–brain barrier in physiologically relevant concentrations and, therefore, stimulus-dependent alterations in plasma OXT should not be behaviourally relevant. However, in humans, plasma OXT is frequently taken as an indication of general OXT system activity, including intracerebral OXT release, an interpretation that is clearly limited, but at least partly useful.

Stimuli and mechanisms of OXT release within the brain have been extensively reviewed elsewhere (9, 11, 32). Here, I will focus instead on the involvement of brain OXT in complex stress-related and social behaviours.

Oxytocin, emotional behaviours and stress coping

Brain OXT has generally been described as an important regulator of the stress response, with both physiological and behavioural aspects (for reviews, see 27, 33, 34). In this context, the regulation of anxiety-related behaviour has attracted particular attention. Acute or chronic central administration of synthetic OXT was found to exert an anxiolytic effect both in female and in male rats, and in mice (35–37). In order to reveal the role of *endogenous* brain OXT in the regulation of anxiety-related behaviour in more detail, brain OXT receptors were blocked using an OXT receptor antagonist (38), specifically within the central amygdala (33). However, the effects of antagonist treatment on anxiety were only visible in pregnant or lactating, but not in virgin female or male, rats. Thus, it appears likely that activation of the brain OXT system, as seen in the peripartum period in females, is a prerequisite for an anxiolytic effect of this system (38, 39). In support of this, up-regulation of OXT receptor expression within the central amygdala of virgin female rats, using an adenoviral vector to simulate activity levels in the peripartum period, significantly reduced anxiety levels compared with respective control virgin females (22).

Moreover, important, although controversial, evidence for an involvement of the endogenous OXT system in regulating anxiety behaviour comes from studies with OXT knockout mice, with females showing an increased level of anxiety (27, 40). In contrast, the social anxiety of female OXT knockout mice, as indicated by stretched approaches towards the intruder, was lower than in respective controls, indicating that OXT may also be differentially involved in anxiety-related behaviours in social versus nonsocial contexts (41).

To date, the anxiolytic effects of OXT in rats have been localised within the central amygdala (33, 42, 43) and within the hypothalamic paraventricular nucleus (PVN) (36). Within the latter, we could show that OXT receptor-mediated anxiolytic effects involve the activation of the extracellular signal-regulated kinase (ERK1/2) signalling cascade. Local blockade of the OXT-induced

ERK1/2 phosphorylation by local pre-infusion with a MAP kinase kinase (MEK) inhibitor prevented the anxiolytic effect of OXT (36).

In addition to the regulation of anxiety levels, OXT also modulates other aspects of behavioural stress coping. For example, released within the central amygdala during forced swimming, OXT promotes a passive coping style and increases the time spent floating, which might be mediated via an inhibitory influence on the local release of excitatory amino acids (44). Interestingly, within the central amygdala, OXT actions on the electrophysiological activity of distinct neuronal populations have been described (45).

Brain OXT also plays a major role in the regulation of complex physiological stress responses including stress-induced neuronal activation (46, 47) and activity of the hypothalamo–pituitary–adrenal (HPA) axis (35, 38, 47, 48), which have been reviewed elsewhere (27, 33, 34). Specifically, OXT was found to inhibit HPA axis responses to a wide variety of physical, emotional and pharmacological stressors, and may thus make an important contribution to the attenuated stress responsiveness found in pregnancy and during lactation. These neuroendocrine adaptations, which have been described in both rodents and humans, are mainly reflected by lower peak levels of corticosterone/cortisol and corticotrophin in response to acute stressor exposure.

The fine-tuned modulation of both emotional and neuroendocrine stress responses by OXT, i.e. inducing a state of reduced anxiety and increased calmness accompanied by blunted plasma glucocorticoid responses, is likely to play an important role in the peripartum period. In pregnancy and during lactation, the activity of the brain OXT system is significantly elevated, and this should be beneficial both for the offspring and for the mother. The offspring clearly benefit from OXT-induced promotion of maternal behaviour and reproduction-related physiological adaptations, including the prevention of excessive circulating glucocorticoid levels. Importantly, high brain OXT activity might also be beneficial for the maternal brain to prevent emotional maladaptations caused by the dramatic changes in circulating sexual steroids (for reviews, see 49, 50).

Oxytocin and maternal care and aggression

As a circulating hormone, OXT controls important reproductive functions such as labour and milk ejection in the peripartum period. Simultaneously, central release of OXT during parturition and suckling (51) suggests that synergistic effects of OXT released both into maternal blood and within the maternal brain are important for offspring survival. Indeed, since the first discovery that central OXT can induce maternal behaviour in virgin rats (13), growing evidence has revealed a significant contribution of brain OXT to both the establishment and maintenance of fine-tuned maternal care in several species. These effects of OXT have been recently reviewed by several experts of the field (52–56).

In addition to maternal care, most lactating mammals show a remarkable level of aggression, thus protecting their offspring against potential social threats. Thus far, controversial results exist as to the involvement of OXT in maternal aggression (for reviews, see 57).

In order to reveal a possible role of OXT in the regulation of maternal aggression, we monitored OXT release within the central amygdala and the hypothalamic PVN in lactating residents during the maternal defence test (58, 59). An increased release of OXT was found in rats, which displayed a particularly high level of maternal aggression, whereas it was unaltered (PVN) or even decreased (amygdala) in dams, which were less aggressive. Importantly, the amount of locally released OXT was correlated with the aggressive behaviour displayed by the dam (59). Blockade of local OXT receptor-mediated actions by local administration of an OXT receptor antagonist [des-Gly-NH_2,d$(CH_2)_5$[Tyr(Me)^2,Thr^4]OVT, kindly provided by Dr Maurice Manning, Toledo, OH, USA] via retrodialysis lowered the level of aggression, further supporting a functional involvement of OXT in the regulation of maternal aggression (Fig. 1).

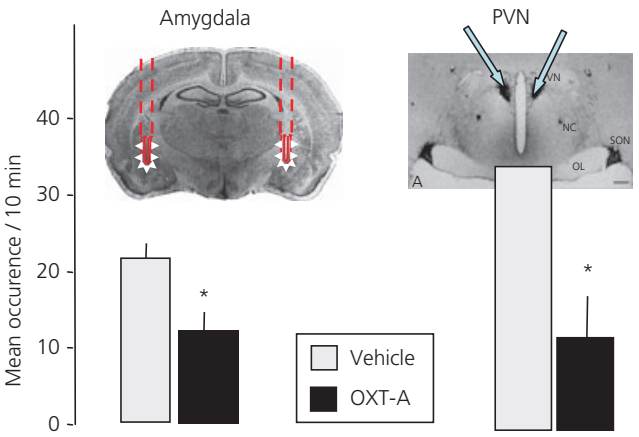

Fig. 1. Local retrodialysis of an oxytocin (OXT) receptor antagonist (OXT-A) bilateral into the central amygdala (left) and the paraventricular nucleus (PVN) during the maternal defence test reduces maternal aggressive behaviour of lactating rat dam. *P < 0.05 versus vehicle. Adapted from Ref. 59.

In contrast to these findings providing robust evidence for OXT as an important regulator of maternal aggression, very little is known about OXT actions on male aggression (but see 60, 61). However, OXT effects on various other aspects of social behaviour have also been reported in males.

Oxytocin and sexual behaviour

Brain OXT plays an important role in the regulation of male and female sexual behaviour. In both males and females, a significant stimulus for OXT secretion into peripheral blood is sexual activity and, in humans, orgasm (62–64). Given the importance of brain OXT in social interactions (24, 65) and the fact that sexual interaction is the most intense social contact found, mating behaviour is also likely to be a relevant stimulus for the intracerebral OXT system. In support of this suggestion, increased Fos expression was found in OXT neurones within the PVN in response to mating, suggesting an increased activity of OXT neurones (66, 67). Further, using micro-dialysis, we recently showed an elevated OXT release within the PVN of male rats during successful mating (29). The fact that local OXT release already started to rise as a result of the presence of the primed female behind a perforated wall, which allowed olfactory and visual contact, but not physical contact or mating,

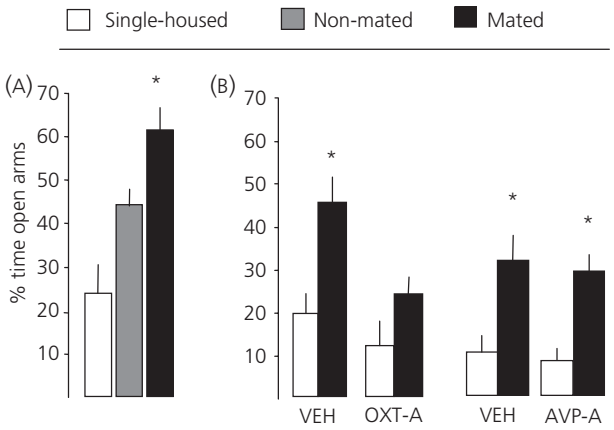

Fig. 2. Anxiolytic effect of sexual activity and mating in male rats (A) and involvement of brain oxytocin (OXT), but not vasopressin (AVP) (B). (A) Male rats were mated with a primed female, housed with a non-primed female or single-housed for 30 min in the light phase. (B) Immediately after sexual activity, mated males were treated with icv vehicle (VEH), an OXT receptor antagonist (OXT-A) or an AVP receptor antagonist, before their anxiety level was scored as percentage of time spent in the open arms of the plus-maze. Data are means + standard error of the mean. *P < 0.05 versus single-housed and non-mated males after analysis of variance. Adapted from Ref. 29.

indicates that the presence of a receptive female, even without mating, partially activates the OXT system.

Several lines of experimental evidence suggest that brain OXT facilitates erectile function and male sexual behaviour in mice, rats, rabbits and monkeys (for reviews, see 68, 69), The PVN seems to be a major target of OXT actions possibly involving autoexcitatory neuropeptide actions (70). In support of this theory, electrolytic or chemical excitotoxic lesions of the PVN abolish the pro-erectile effect of OXT (71, 72). The brain OXT system is also involved to a significant extent in female sexual behaviour, at least in rats, specifically promoting lordosis behaviour in an oestrogen-dependent manner (15, 73, 74).

In an attempt to reveal the behavioural consequences of sexual activity and mating-induced central OXT release, we tested the anxiety-related behaviour of male rats on the elevated plus-maze and in the light-dark box. In comparison with single-housed males, and males that were housed with a non-primed female for 30 min, mated males showed a reduced anxiety-related behaviour 30 and 360 min after mating (29; Fig. 2A). This anxiolytic effect of sexual activity could be blocked by an OXT receptor antagonist administered icv immediately after mating (Fig. 2B).

Together these results provide evidence that activation of the endogenous brain OXT system, seen both in females at the end of pregnancy and during lactation and in males during sexual activity, exerts beneficial effects, in particular inhibiting stress-induced behavioural and/or neuroendocrine responses (Fig. 3).

Oxytocin and pair bonding

The best experimental model with which to study pair bonding and its neuropeptidergic regulation is the monogamous prairie vole

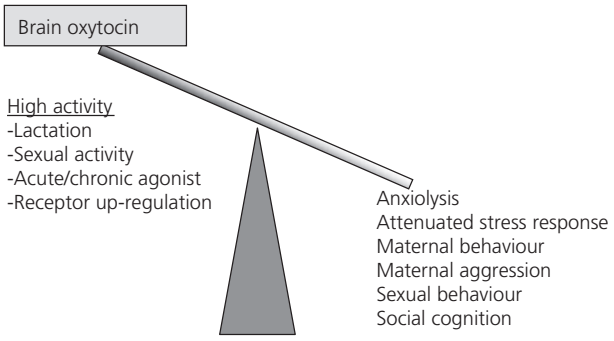

Fig. 3. Examples of behavioural consequences of high brain oxytocin activity induced by physiological stimulation or external manipulation.

(*Microtus ochrogaster*). Like humans, these voles display a remarkable diversity in social organisation including, for example, the formation of enduring pair bonds and biparental behaviour (for reviews, see 75, 76). Initially, comparison of OXT and AVP receptor distribution in distinct brain regions of monogamous and non-monogamous vole species revealed a higher density of OXT (caudate putamen and nucleus accumbens) and AVP receptors (ventral pallidum, medial amygdala and mediodorsal thalamus) in monogamous prarie voles (77, 78). Both OXT and AVP were demonstrated to play a major role in pair bonding in a gender-specific fashion. Although both peptides may facilitate pair-bond formation in either sex (79), AVP seems to be more important in males, whereas OXT is more critical in females. The mechanism underlying this sex difference in behavioural response to OXT and AVP is unclear, because receptor densities in the brain are similar in males and females. Acute administration of OXT into the cerebral ventricles of female prairie voles accelerated pair bonding (80), whereas application of an OXT receptor antagonist blocked mating-induced pair bonding in females. Combined, these results suggest that central release of OXT also occurs during mating in females (81). Possible target regions of OXT include the nucleus accumbens and the prefrontal cortex (for a review, see 76), both being involved in reward, emotional evaluation of stimuli and fear expression.

Oxytocin and social cognition

Given the importance of OXT in a variety of complex social behaviours, as discussed above, it seems logical to hypothesise an involvement of OXT in social memory processes and recognition of conspecifics. Indeed, central administration of OXT exerted dose-dependent effects on social memory in male rats (82). Further, OXT in the olfactory bulb can facilitate and prolong social recognition in male rats (83, 84), an effect that is likely to involve a critical interaction with local norepinephrine (for a review, see 9).

In support of an involvement of brain OXT in social memory, OXT knockout mice show deficits in social recognition, but normal non-social learning and memory abilities (23, 24, 41, 85). These deficits are reversible by OXT administration specifically into the central amygdala (86). Interestingly, male mice lacking the gene for CD38, a transmembrane protein essential for neuronal OXT release, show substantial impairment of social memory and recognition of con-

specific females (87). This is in further agreement with the importance of central OXT release for social memory.

Also, in female rats and mice, OXT is an important factor in social cognition. In female rats, icv administration of an OXT antagonist interfered with the animals' ability to establish normal social memory (88) (for a review, see 89). In female OXT knockout mice, the essential role of OXT 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 remain pregnant) and a novel mate (with the consequence of interrupted pregnancy). OXT 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 (90). This inability to distinguish between the mate and a novel male in females with deficits in the OXT systems further demonstrates the importance of OXT in long-term social memory as well as short-term social recognition. Recently, a conditional OXT receptor knockout mouse has been created which lacks the OXT receptor in distinct forebrain regions and shows comparable deficits in social recognition (91).

Additional examples demonstrating the essential role of OXT in social memory and recognition come from experiments performed in ewes and in monogamous prairie voles, respectively. In ewes, lamb recognition and bonding after birth could clearly be related to the release of OXT, for example within the olfactory bulb (92). Thus, OXT seems to be the common signal for the development of selective offspring recognition. 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, OXT plays a critical role in social bonding, especially in female prairie voles, as discussed above in more detail (76, 81). Thus, parturition- and mating-induced stimulation of OXT release within distinct brain regions seems to be a promoting factor for social cognition, i.e. lamb recognition and pair-bond formation, respectively.

There is also evidence for an OXT-mediated facilitation of spatial memory, especially in lactation. In multiparous mice, an improved spatial memory has recently been found in comparison with virgin control mice which might importantly improve the search for additional food resources (93) and the rapid and safe return of the mother to the offspring. Blockade of brain OXT receptors in lactating mice inhibited their improved spatial memory abilities, hippocampal long-term potentiaton and CREB phosphorylation (93). Thus, the specific sequence of events, including up-regulation of brain OXT receptors, central OXT release within distinct brain regions during reproduction and the subsequent OXT-induced increase in hippocampal CREB phosphorylation and plasticity, is likely to underlie the improvement of long-term spatial memory found in motherhood.

Behavioural actions of OXT in humans

Although detailed experimental data is limited, there is evidence to support similar behavioural effects of brain OXT in humans. For example, indirect evidence for anxiolytic and anti-stress effects of OXT comes from nursing mothers, who are more likely to describe positive mood states, reduced anxiety levels and increased calmness [(94); for reviews see 95, 96]. Moreover, breast-feeding shortly before exposure to a psychological stressor reduced the emotional response compared with bottle-feeding lactating mothers (94). As suckling triggers OXT release within various brain regions in sheep and rodents (51, 92, 97, 98), an activated brain OXT system, in addition to other factors (for a review, see 49), is likely to contribute to these behavioural consequences of nursing.

In men, a comparable physiological stimulation, which is likely to trigger a high level of activity of the endogenous brain OXT system, is sexual activity (see above, Fig. 3). Increased plasma OXT levels were found during warm social contact with the partner (e.g. hugging) (99) and during orgasm (63, 100, 101). There is convincing anecdotal and experimental evidence of a link between sexual activity and sedation, increased relaxation and calmness in the post-coital period (102, 103). Therefore, given the involvement of OXT in stress regulation, as discussed above, it is likely that OXT contributes to these positive effects (29) also in humans. Additionally, OXT was shown to exert reinforcing and rewarding actions in rodents (104). Therefore, the possibility also exists that enforced and reinforced trust in the sexual partner also involves brain OXT.

This hypothesis is substantiated by the finding that intranasal OXT makes humans more trusting (105). Moreover, reduced levels of anxiety to psychosocial stress were described in subjects treated with intranasal OXT and receiving social support (106). Consistent with this, intranasal OXT reduced neuronal responses within the amygdala to fearful social stimulation in healthy men, as revealed by magnet resonance imaging studies (107). Thus, OXT receptor-mediated actions are involved to a significant extent in processing social stimuli and in modulating pro-social responses also in humans. Importantly, OXT seems to increase the ability to read the mental state of others using social cues from facial expressions (108). In contrast, intranasal AVP decreased perception of friendly faces and increased perception of anger and threat in neutral human facial expressions (109, 110). Thus, AVP and OXT play important, although different, roles in social communication. In this context it is interesting to note that a link between autism spectrum disorders and polymorphisms in the OXT receptor gene and changes in OXT availability have been described (111–113).

In summary, receptor-mediated effects of OXT within the brain may have far-reaching implications for the complex regulation of emotionality, stress coping and social behaviours in both sexes. Consequently, the brain OXT system is a promising target for the development of novel therapeutic strategies to treat anxiety- and depression-related diseases or abnormal social behaviours.

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