Brain Oxytocin Mediates Beneficial Consequences of Close Social Interactions: From Maternal Love and Sex

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Summary

There is growing interest directed toward understanding positive emotions, and maternal and romantic love are among the most desired and positive social experiences encountered. It is only now that we are beginning to understand not only their neurobiological and neurochemical regulation but also their beneficial health consequences. For example, around parturition, profound adaptations of the maternal brain take place with significant behavioural consequences that ensure the healthy development of the child, or the offspring, including nutrition, protection and maternal emotional care. There is an activation of several neuroendocrine systems, including oxytocin and prolactin, that play important roles as classical hormones in the regulation of parturition, lactogenesis and milk ejection, respectively. Importantly, as signalling molecules of the brain, they were shown to be important promoters of maternal behaviour. Moreover, oxytocin released within the rat brain is correlated with the protection of the offspring, i.e., with the display of maternal aggression. Thus, oxytocin and prolactin are important for meeting the physiological demands of the offspring, but also to satisfy their emotional demands, including protection and close affiliation with the mother. In turn, the maternal brain profits from these adaptations: oxytocin and prolactin exert anxiolytic effects at various brain sites and have been shown to reduce stress responsiveness at neuronal, neuroendocrine and behavioural levels. As a consequence, increased calmness, reduced anxiety levels and blunted hypothalamo-pituitary-adrenal axis and sympathetic responses to numerous stressors have been described in pregnancy and/or lactation, both in human and animal studies. These complex brain adaptations are clearly beneficial for the mother. However, they are vulnerable to stressful life experiences and maladaptations, e.g., lack of adaptive activation of the brain oxytocin and prolactin systems may result in postpartum mood disorders with negative consequences for both maternal health and child development.

Is there a comparable physiological and behavioural situation in males? There is scientific and anecdotal evidence for sedation and calmness after sexual activity. Oxytocin is released within the hypothalamus during mating, where it is crucially involved in the regulation of male sexual behaviour. Evidence will be provided that activation of brain oxytocin, as seen during sexual activity, also mediates beneficial effects in males.

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Introduction

For many decades, neurobiologists have focussed on uncovering the neurochemical brain circuitries underlying emotions, in particular of anxiety, fear and aggression. However, there has also been growing interest in understanding positive emotions. In this context, maternal and romantic love are among the most desired and positive experiences encountered in our lives, and we are beginning to understand not only their neurobiological and neurochemical regulation, but also their beneficial health consequences. In this chapter, I will focus on brain neuropeptide systems, in particular on brain oxytocin (OXT) and prolactin (PRL), which are activated, for example, in the maternal brain peripartum and which may mediate the positive effects on various health parameters, including reduced stress vulnerability. Additionally, I will provide initial evidence that, in males, sexual activity and mating represent comparable physiological stimuli activating these neuropeptide circuitries that, in turn, exert long-lasting beneficial effects.

Complex Adaptations of the Maternal Brain Peripartum

Remarkable physiological and behavioural changes have been extensively described in the mammalian maternal brain in the peripartum period. These profound adaptations start during pregnancy as complex and direct consequences of mainly hormonal signals arising from the fetus. They continue around birth and in lactation as a result of close social interactions between mother and offspring, for example during suckling, maternal care and protection. Pup-derived stimuli, for example during the suckling stimulus, in turn, are essential for these neuroendocrine and complex emotional adaptations to continue in the mother until weaning. Several of these maternal physiological adaptations are a primary prerequisite for offspring survival and development, i.e. the provision of sufficient nutrients both in utero and during lactation, and of a stable hormonal and biochemical environment during pregnancy, and a safe birth.

Tellingly however, profound alterations in systems that are not directly linked to reproductive functions, but that may play a supportive role, have also been described. For example, pregnancy- and lactation-associated alterations have been repeatedly demonstrated in several species with respect to maternal stress-coping style. There is a severely attenuated responsiveness of the hypothalamo-pituitary-adrenal (HPA) axis to a broad variety of stressors, with the consequence of lower stress-induced plasma concentrations of glucocorticoids, i.e., cortisol in humans and corticosterone in rodents (de Weerth and Buitelaar 2005; Kammerer et al. 2002; Lightman et al. 2001; Neumann et al. 1998c; Russell et al. 1999; Stattery and Neumann 2007; Stern et al. 1973). Such alterations seem to be essential for the healthy development of the offspring to prevent excessive circulating stress hormone levels, which have been shown to have adverse effects on prenatal development (Weinstock 2001; Welberg and Seckl 2001). Moreover, there is a growing body of evidence suggesting that mechanisms underlying the attenuated stress responses are also important for the mental health of the mother. In this context, several neurobiological mechanisms have been discussed, including the activation of the brain OXT and PRL systems (Fig. 1).

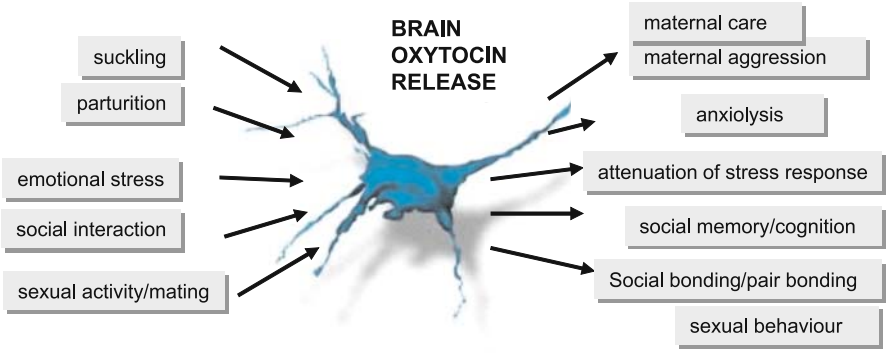

Fig. 1. Stimuli that trigger the release of oxytocin (OXT) within the brain, e.g., within the hypothalamic paraventricular nucleus, include suckling and parturition in females and emotional stress, social interactions and mating also in males. On the right side, consequences of oxytocin actions within the brain in a behavioural context are listed

Activation of Brain OXT and PRL Systems Around Birth

In the context of peripartum adaptations of stress systems, two brain neuropeptides are likely to play a prominent role: OXT and PRL. Whereas the existence of a brain OXT system is well established, there is emerging evidence for a brain PRL system with PRL synthesis in hypothalamic neurons, specifically within the hypothalamic paraventricular nucleus (PVN), and an abundant presence of PRL receptors throughout the brain. As neurohormones, both OXT and PRL are directly related to reproductive functions and become activated before birth, i.e., there is increased hormone storage in the neurohypophysis and in the lactotrophe cell of the adenohypophysis, respectively. When released into the blood stream, they are importantly involved in the delivery process (OXT), lactogenesis (PRL) and milk ejection (OXT).

Importantly, there is also activation of the OXT and PRL systems within the brain in the peripartum period, as witnessed by an increased OXT and PRL gene expression and synthesis within distinct brain regions and an increased expression and binding of their respective receptors. Moreover, OXT is released within the hypothalamic PVN and supraoptic nucleus (SON) and the olfactory bulb during parturition (Kendrick et al. 1988a; Neumann et al. 1993b) and also within the hippocampus and the medio-lateral septum in response to the suckling stimulus (Moos et al. 1984; Neumann et al. 1993b; Neumann and Landgraf 1989; Fig. 1). Recently, using the rather old-fashioned, but more sensitive, push-pull perfusion technique, we have shown that close social contact with the pups and the suckling stimulus also triggers neuronal release of PRL within the PVN (Torner et al. 2004).

Functions of Locally Released OXT and PRL in the Maternal Brain

Several functions of brain OXT have been suggested in a physiological or behavioural context (summarized in Fig. 1). For example, it has been postulated that locally released

OXT within the hypothalamus is involved in the auto-regulation of OXT neuronal activity during the phase of pulsatile release patterns into blood, as seen during the milk ejection reflex or during birth (Kombian et al. 1997; Moos et al. 1984; Neumann et al. 1994, 1996). Moreover, brain OXT seems to play a major role in the neuronal plasticity observed within the hypothalamic SON in the peripartum period (Theodosis 2002). Importantly, various changes in social behaviour have also been attributed to the action of brain OXT in the context of reproductive behaviour. For example, the onset and fine-tuned maintenance of maternal behaviour has been directly linked to the action of OXT (Lonstein and Morrell 2006; Numan and Insel 2003; Pedersen and Boccia 2003; Pedersen and Prange 1979). Moreover, there is compelling evidence of changes in social cognitive functions, including offspring recognition, which have been related to the action of locally released OXT (Dluzen et al. 2000; Kendrick et al. 1988b, 1987, 1997; see below). Therefore, these multiple effects of local OXT provide an excellent example of the synergistic action of a neuropeptide in dependence on the site of release.

Although far less is known about the functions of brain PRL, there is good evidence of a significant involvement of PRL in the regulation of maternal behaviour (Bridges et al. 1984, 1990; Torner et al. 2002). Thus, as seen for OXT, there are also synergistic actions of PRL secreted from lactotroph cells into the bloodstream to promote lactogenesis and of PRL released within distinct brain regions to regulate a respective behavioural profile of the mother. In general, maternal behaviour is regulated in a complex manner, with many neuronal circuits and neurotransmitter systems involved (for review see Lonstein and Morrell 2006; Numan and Insel 2003), and centrally released OXT and PRL seem to be key players in these neuronal systems. Interestingly, breastfeeding women interact more positively with their babies, directing more touching and smiling toward their infants, than do bottle-feeding mothers (Dunn and Richards 1977; for review, see Carter et al. 2001). Therefore, it is likely that the suckling-induced, site-specific release of OXT and PRL contributes to this behavioural effect. As the quality of maternal care is a key component for the healthy emotional development of the offspring, as seen in rodents, primates and also in humans, the central actions of maternal OXT and PRL have far-reaching implications for the future health of the baby and its social competence, as well as the competence of future generations (Francis et al. 1999; Liu et al. 2000).

Brain OXT and Maternal Aggression

Protection of the offspring and enhanced aggressive behaviour toward potential conspecific encounters are features of the complex pattern of maternal behaviour in mammals (Erskine et al. 1978; for review, see Numan and Insel 2003), and there is strong evidence demonstrating a contribution of brain OXT in the display of maternal aggression (Consiglio and Lucion 1996; Elliott et al. 2001; Lubin et al. 2003). Recently, we demonstrated increased OXT release within the central amygdala and within the hypothalamic PVN in rat dams showing a high level of maternal aggression towards a virgin intruder. In both of these regions of the limbic system, local OXT release was found to be directly correlated with the intensity of aggressive behaviour (Bosch et al. 2005). Furthermore, if local OXT actions were blocked by local

administration of the selective receptor antagonist, highly aggressive rats showed a reduced number of attacks. In contrast, when synthetic OXT was slowly infused into the PVN of low aggressive dams, they displayed more attacks and lateral threats toward the intruder. These results clearly show that, in the peripartum period, brain OXT mediates, at least in part, the behavioural response to potentially threatening social stimuli, like a conspecific rat placed into the dam's home cage. Thus, locally released OXT promotes the display of relevant aggressive behaviours necessary for the protection of the offspring. Intra-individual differences in the activation of the brain OXT system seem to determine the differences seen in these complex social behaviours.

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 Winslow et al. 2000). However, OXT is importantly involved in various aspects of social behaviour in males as well (Crawley et al. 2007; Domes et al. 2007; Kirsch et al. 2005; Kosfeld et al. 2005; Winslow et al. 2000).

Beneficial Consequences of Being a Mother

The above-described adaptations of the maternal brain, including activation of the brain OXT and PRL system, are clearly directed towards and beneficial for the offspring, or for the baby, to ensure their survival and healthy development. According to our hypothesis, these adaptations should also be beneficial for the mother, and brain OXT and PRL are importantly involved. For example, lactating dams were reported to show a reduced level of anxiety and emotional stress response (Neumann et al. 2001; Walker et al. 1995; Windle et al. 1997a). The anxiolytic effect of lactation can even be seen in rat dams with a high innate level of anxiety-related behaviour; therefore, being a mother seems to be beneficial for these animals with respect to state anxiety (Neumann 2001). Similarly, in humans, nursing mothers are more likely to describe positive mood states, reduced anxiety levels and increased calmness (Heinrichs et al. 2001; for review, see Carter and Altemus 1997; Carter et al. 2001). It would be interesting to speculate to what extent these emotional adaptations and positive mood effects are prerequisites for mothers to manage the highly demanding multi-tasking of their lives while keeping a balanced and healthy mood.

The peripartum alterations in emotionality, which are dependent upon social stimuli from the offspring, are likely to be related to the changes seen in the neuronal and hormonal responsiveness of the HPA axis. A blunted response to a broad variety of psychological and physical stressors has been found in rats and mice at the end of pregnancy and in lactation (Brunton and Russell 2003; Douglas et al. 2003; Johnstone et al. 2000; Lightman et al. 2001; Neumann 2001; Neumann et al. 1998c; Shanks et al. 1999; Stern et al. 1973; Walker et al. 1995; Windle et al. 1997b). This blunted response is reflected by an attenuated rise in plasma corticotrophin (ACTH) and corticosterone following stressor exposure, despite the elevated plasma glucocorticoid levels found at this time under basal conditions (Neumann et al. 1998a; Russell et al. 2001). Similarly, in pregnant and lactating women, lower cortisol responses to various stressors (Amico et al. 1994; de Weerth and Buitelaar 2005), including treadmill exercise (Altemus et al. 1995), cold stress (Kammerer et al. 2002) and psychological stress (Heinrichs et al.

2001), have been described, indicating similar adaptive mechanisms in the human maternal brain.

Although there is experimental evidence that hypo-responsiveness of the HPA axis in pregnancy prevents excessive levels of circulating glucocorticoids and, thus, negative effects on the fetus in utero (Weinstock 2001; Welberg and Seckl 2001), the positive effects of these adaptations for the offspring are less clear in lactation. In contrast, there are indications for beneficial effects for the mother, which becomes evident if we discuss in more detail the neurobiological mechanisms involved in stress hypo-responsiveness peripartum.

Mechanisms of Blunted Stress Responses Peripartum

Several brain mechanisms contribute to the blunted emotional and neuroendocrine response seen peripartum, as studied in rodent models. These include, for example, a lower level of stress-induced neuronal activation within several forebrain and limbic brain regions (da Costa et al. 2001), which might reflect the process of perception of a given stressor. Moreover, there is a loss of excitatory inputs to the hypothalamic PVN, the main regulatory centre of the HPA axis, in pregnancy and during lactation. For example, the noradrenergic excitatory tone of the PVN is reduced, and there is a lower expression of noradrenergic alpha$_{1A}$-adrenoceptors in the parvo- and magnocellular PVN (Douglas et al. 2005; Toufexis et al. 1998). Also, the excitatory input of the HPA axis exerted by endogenous opioids is reduced at the end of pregnancy (Douglas et al. 1998; Kammerer et al. 2002; Kofman 2002) and is further reversed into a highly significant inhibition during parturition (Wigger et al. 1999). Further, endogenous opioid inhibition of the OXT system disappears at the time of birth and is not seen in virgins (Douglas et al. 1995), which may contribute to differences in regulating stress adaptations peripartum (Wigger and Neumann 2002).

As a consequence of (or in parallel to) these changes, the expression of corticotropin releasing factor (CRF) within the PVN is reduced both in pregnancy (da Costa et al. 2001; Douglas and Russell 1994; Johnstone et al. 2000) and in lactation (Lightman et al. 2001; Walker et al. 2001). Similarly, reduced CRF expression has been described in the central nucleus of the amygdala, a region important for regulating HPA axis activity and emotionality (Davis and Whalen 2001). Moreover, the pituitary sensitivity to CRF is diminished due to reduced CRF receptor binding at pituitary corticotrophs (Neumann et al. 1998b). A potential intracellular mechanism underlying the attenuated CRF system is via the immediate-early gene *nur77* (NGFI-B), which controls CRF gene expression under conditions of stress (Kirschbaum et al. 1999), but hypothalamic NGFI-B expression is lower in pregnancy (Douglas et al. 2003). A generally lowered activity of the CRF system may contribute to the attenuated ACTH and corticosterone responses observed during pregnancy and in lactation. Moreover, a low brain CRF system activity is likely to be related to the reduced anxiety of the dam (Hard and Hansen 1985; Neumann 2003; Toufexis et al. 1998; Windle et al. 1997b) and to the promotion of social behaviours, including maternal behaviour (Pedersen et al. 1991) and maternal aggression (Gammie et al. 2004). CRF has been shown to inhibit both maternal behaviour and aggression. For example, rhesus monkeys that abuse their infants were shown to have higher plasma levels of CRF (Maestripieri et al. 2005).

OXT and PRL Mediate the Beneficial Effects for the Mother

There is substantial evidence that peripartum activation of the brain OXT and PRL systems mediates the beneficial effects of these stress adaptations for the mother in concert with the factors described above. In general, an anxiolytic effect of OXT administered peripherally (McCarthy and Altemus 1997) or centrally (Bale et al. 2001; Ring et al. 2006) has been established. Also, chronic infusion of OXT in virgin rats results in an attenuation of the emotional, neuroendocrine and neuronal responses to an acute stressor (Windle et al. 1997a, 2004). Mice lacking the OXT gene show an increased emotional responsiveness (Amico et al. 2004). Central infusion of a selective OXT receptor antagonist before testing on the elevated plus-maze revealed an anxiolytic effect of endogenous brain OXT in both pregnant and lactating rats (Neumann et al. 2000a), an effect that could be localized within the central amygdala (Neumann 2002). These findings indicate that up-regulation of the activity of the brain OXT system at the end of pregnancy and throughout lactation mediates the lower level of emotionality, including reduced anxiety.

Brain PRL is another important anxiolytic regulator of the brain that, as described above, is up-regulated in the maternal brain. Both female and, to a lesser extent, male rats show a reduced anxiety-related behaviour on the elevated plus-maze following icv PRL treatment (Torner et al. 2001). Also, down-regulation of brain PRL receptors by use of antisense oligodesoxynucleotides directed against the short form of PRL receptors (see Torner and Neumann 2002 for review of the physiology of PRL receptors) in the brain of lactating rats resulted in elevated emotionality, indicating the involvement of brain PRL receptors in the anxiolytic effect (Torner et al. 2001).

In addition to the attenuation of emotional stress responses, both OXT and PRL show common actions in the reduction of hormonal and neuronal stress responses. Thus, chronic intracerebral infusion of OXT (Windle et al. 1997a, 2004) or PRL (Donner et al. 2007) reduced the stress-induced increase in neuronal activity in several brain regions, as revealed using c-fos as a marker, hypothalamic CRF mRNA expression, and hormonal stress responses in virgin rats. Inhibition of brain PRL receptor expression (see above) enhanced HPA axis stress responses in lactating dams.

Indirect evidence suggests that these results can be translated into humans. In lactating mothers, breast-feeding shortly before exposure to a psychological stressor reduced the emotional response and salivary cortisol levels compared with bottle-feeding lactating mothers. As mentioned above, both OXT and PRL are released in several brain regions, including the hypothalamic PVN, in response to the suckling stimulus (Moos et al. 1984; Neumann et al. 1993a; Torner et al. 2004). Therefore, it is likely that such locally released neuropeptides exert inhibitory effects on HPA axis reactivity and state anxiety, possibly via direct or indirect actions on CRF neurons. In conclusion, the high activity of the brain OXT and PRL systems contributes to the blunted stress vulnerability of the mother.

If these physiological adaptations are partially prevented, we believe that mood disorders like postpartum blues or depression are more likely to occur. The dramatic reproduction-related fluctuation in sexual steroid concentration around birth is likely to contribute to an increased vulnerability to mood disturbances and psychopathologies in susceptible individuals, depending on their genetic predisposition and stressful life events. Therefore, attenuation of complex stress circuitries by a high activation of

brain OXT and PRL represents a necessary mechanism to protect the maternal brain. Interestingly, postpartum depression is associated (or goes hand in hand) with impaired maternal bonding and sometimes even rejection of the child and with impaired stress management, parameters that are mediated by OXT and PRL.

OXT Effects on Stress Coping in the Male Brain

In comparison to females, relatively little is known about brain OXT actions in males. However, in male rats and mice, comparable effects of OXT on HPA axis responsiveness (Neumann et al. 2000b) and anxiety (Blume et al. 2008; Ring et al. 2006) have been described (Fig. 1). For example, blocking central OXT receptors by infusion of an OXT receptor antagonist increased basal HPA axis activity and responses to swim stress, indicating an inhibitory influence of endogenous OXT also in males (Neumann et al. 2000b). As in females (Bosch et al. 2005; Wigger and Neumann 1998), OXT is released within several regions of the male brain, including the amygdala and the hypothalamic PVN, in response to social stimuli (Ebner et al. 2000; Wotjak et al. 1996) and various non-social stressors (Ebner et al. 2005; Hattori et al. 1992; Wotjak et al. 2001; for review, see Landgraf and Neumann 2004). In addition, locally released OXT regulates the behavioural and neuroendocrine stress response in the male rat (Ebner et al. 2005; Engelmann et al. 2004; Neumann et al. 2006). Furthermore, within the central amygdala, OXT released during stressor exposure promotes a passive stress-coping strategy (Ebner et al. 2005), and effects of OXT on local neuronal activity patterns were also described in males (Huber et al. 2005). Moreover, central manipulation of the OXT system by application of an antagonist or agonist revealed that OXT modulates wakefulness and sleep patterns: under basal, undisturbed conditions, OXT promotes sleep whereas at higher doses OXT delays sleep onset, indicating an acute arousal effect (Lancel et al. 2003). Taken together, these results provide substantial evidence that, also in male rats, brain OXT is significantly involved in the regulation of behavioural and hormonal stress responses.

In humans, intranasal OXT, which has been shown to cross the blood-brain barrier (Born et al. 2002), reduced neuronal responses within the amygdala to threatening, non-social cues and to fearful social stimulation, as revealed by magnetic resonance imaging studies (Kirsch et al. 2005). Thus, OXT seems to be an important modulator of processing social stimuli also in humans, which is further substantiated by the finding of a suppressed anxiety to psychosocial stress (Heinrichs et al. 2003) and of a substantial increase in social trust (Kosfeld et al. 2005) in subjects treated with intranasal OXT.

Positive Effects of Social Interactions in the Male: Involvement of OXT?

Given such effects of OXT in males and since they do not undergo birth or lactation as do females, is there a clearly defined physiological stimulation that triggers a high level of activity of the endogenous brain OXT system in males? In other words, under which physiological circumstances can males benefit from the positive effects of OXT on various aspects of stress coping?

Social support is the most intensively investigated social factor in humans, and there is a growing body of evidence that the intensity of social support is associated with positive effects on various stress-related diseases, including hypertension, cardiovascular diseases, depression (House et al. 1988; Knox and Uvnas-Moberg 1998; Paykel 2001; Rozanski et al. 1999) and stroke outcome (DeVries et al. 2001). In particular, social support in humans can provide a buffer against stress-induced responses of the HPA axis in humans (for review, see DeVries et al. 2003; Kikusui et al. 2006). For example, the salivary free cortisol response of healthy young men to the Trier Social Stress Test, a psychosocial stressor, was reduced by social support provided by their best friend during the preparation period prior to stressor exposure (Heinrichs et al. 2003; Kirschbaum et al. 1995). Moreover, diseases that respond to cortisol concentrations, like asthma (Buske-Kirschbaum et al. 2003), heal better in socially supported patients.

In animals that show a distinct level of social bonding, like mice, rats, guinea pigs and marmosets, social support by conspecifics was demonstrated to lower plasma glucocorticoid levels, although this has mainly been studied in females (Gonzalez et al. 1982; Sachser et al. 1998; Smith and French 1997).

Furthermore, promoting social interactions of laboratory rodents by group housing lowers their plasma corticosterone concentrations (for review, see DeVries et al. 2007; Kikusui et al. 2006). On the other hand, social stress, an unstable social environment or a subordinate position in the hierarchy results in HPA axis hyper-activity, paralleled by adrenal insufficiency after prolonged stressor exposure (Reber et al. 2006), thymus-atrophy, an increase in pro-inflammatory cytokines, and in impaired recovery from injuries or diseases, such as wounds, stroke, and cardiac arrest (Reber et al. 2007; for review, see DeVries et al. 2007). Moreover, chronic social stress in male laboratory mice, mediated by subordinate colony housing, was shown to induce colonic inflammation and to increase the severity of a pharmacologically induced colitis in mice (Reber et al. 2007). Thus, depending on the circumstances, social factors can buffer the stress response or impair the healthy state of the individual.

Interestingly, effects of social buffering were directly found within the hypothalamic PVN. The stress-induced increase in the immediate early gene product Fos within the PVN was attenuated in rats that were accompanied by a partner rat (Kiyokawa et al. 2004). Similarly, in sheep, the visual presentation of pictures of sheep faces was sufficient to induce social buffering in terms of neuronal responses to stress within the PVN (da Costa et al. 2004). These findings give some indications to presume that social stimuli, either visual, tactile or olfactory, activate the brain OT system, which in turn attenuates stress responsiveness.

Activation of OXT in the Male Brain During Social Stimuli: Effects of Sexual Activity

Although limited, there is evidence of stimulation of the brain OXT system during social interaction in males. For example, OXT release within the septum is triggered in stressful social situations, i.e., defeat by a conspecific male (Ebner et al. 2000). Also, OXT secretion into blood is induced by massage and stroking (Uvnas-Moberg 1997). Moreover, the most intense social behaviour found in males, i.e., sexual behaviour and mating, is accompanied by increased OXT secretion into blood (Carmichael et al. 1987;

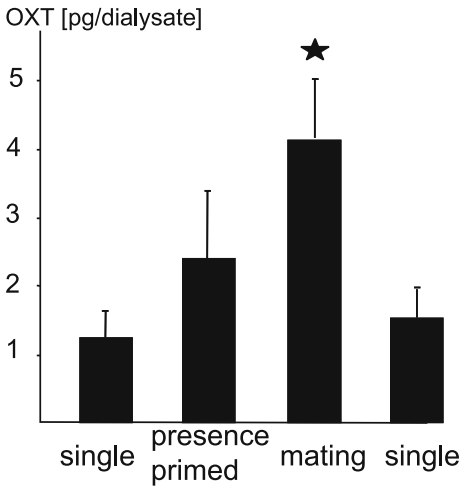

Fig. 2. Oxytocin release within the paraventricular nucleus of the hypothalamus in male Wistar rats, under basal conditions, in the presence of an estrogen-primed female behind a wall and during mating, as revealed by 30-min microdialysis periods. Data from Waldherr and Neumann 2007

Stoneham et al. 1985). Moreover, brain OXT plays an important role in the regulation of male (and female) sexual behaviour (Argiolas and Gessa 1991; Flanagan et al. 1993; McCarthy et al. 1994), and increased Fos-expression was found in OXT neurons within the PVN in response to mating (Witt and Insel 1994). In monogamous species, i.e prairie voles, a mouse-like rodent that forms a lasting pair bond with its mate (Young et al. 1998), release of OXT within relevant brain regions during mating has repeatedly been hypothesized to underlie their monogamous nature, at least in females. OXT actions were found to facilitate pair bonding in female voles whereas vasopressin seemed to play the dominant role in establishing pair bonds in males.

However, central OXT release during mating does not seem to be limited to monogamous species, where mating is a prerequisite for pair bonding. Recently, we demonstrated that the presence of a receptive female rat and successful mating triggered the release of OXT within the hypothalamic PVN, as quantified by microdialysis performed during ongoing behavioural monitoring (Waldherr and Neumann 2007; Fig. 2). Interestingly, local OXT release began to rise in the presence of the primed female behind a perforated wall that allowed olfactory and visual contact but not physical contact and mating (Fig. 2). Because males clearly displayed signs of behavioural arousal under these conditions, it can be concluded that OXT activation is induced by the presence of a receptive female in anticipation of, but without, mating, although this effect was not found to be significant.

OXT Mediates the Anxiolytic Effect of Sexual Activity in Males

Without any doubt, a high level of social interaction is a prerequisite for successful mating. Is there evidence that males benefit from the activation of the central OXT

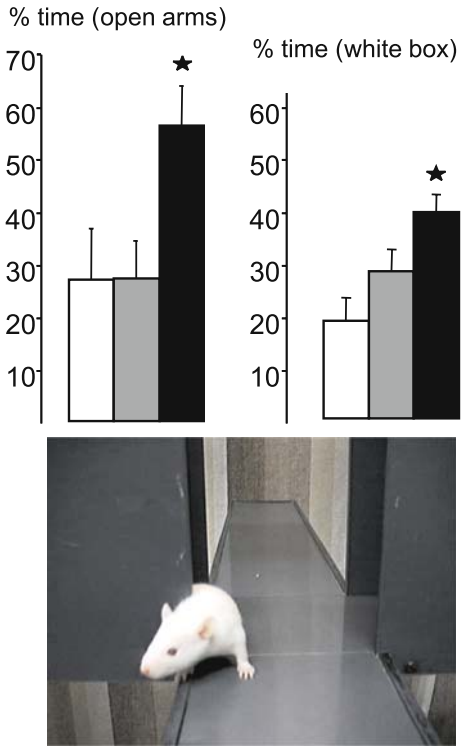

Fig. 3. Effects of sexual activity and mating on anxiety behaviour on the elevated plus-maze, as indicated by the percentage of time spent in the open arms and the percentage of entries performed into the open arms of the maze. Male rats were either single-housed (*white columns*), housed with a non-primed female (*grey columns*) or allowed to mate with a primed female (*black columns*). Behavioural testing was performed four hours after a 30-min mating period as shown in the photograph below. Data from Waldherr and Neumann 2007

system in response to sexual activity? In general, anecdotal and experimental evidence has given rise to the commonly held perception that sedation and calmness are consequences of sexual activity in humans, contributing to a general feeling of well-being. Therefore, it is not surprising that positive consequences of sexual activity have been described in several mammalian species, including humans. For example, greater rates of sexual intercourse have been associated longitudinally with lower risk of mortality (Smith and Ruiz 2002) and lower blood pressure responses (Brody 2006).

We have demonstrated that male rats show a reduced level of anxiety-related behaviour up to four hours after mating with a receptive female but not following olfactory and visual cues (Fig. 3). The anxiolytic effect of sexual activity was already evident after 30 min and could be confirmed both on the elevated plus-maze and in the light-dark box. Importantly, if brain OXT receptors were blocked by icv infusion of a selective OXT receptor antagonist immediately after the 30-min mating period, the anxiolytic effect was abolished. Therefore, it is tempting to conclude that activation of the brain OXT system during sexual activity, i.e., increased release of OXT within the brain and

subsequent neuropeptide-receptor interactions in relevant brain regions including the hypothalamus, mediates the anxiolytic effect of mating in males.

In support of our findings, Edinger and Frye (2007) demonstrated reduced anxiety levels in male rats that have experienced a lifetime of sexual stimuli, indicating long-term positive mood effects of repeated sexual activity. These anxiolytic effects were linked to the rise in basal plasma testosterone found in sexually experienced males. Androgens were recently found to have positive effects on mood (Haren et al. 2002), and lower testosterone levels were correlated with the occurrence of anxiety and depression (Aikey et al. 2002; Granger et al. 2003; van Honk et al. 1999).

As discussed above, social support and social bonding exert a variety of positive effects on health and stress susceptibility. As social interactions activate the brain OXT system in males, it is very likely that OXT also mediates positive effects of close social interaction. As mentioned above, social support by the best friend reduced stress-induced HPA axis responses and anxiety levels (Heinrichs et al. 2003). Interestingly, volunteers who were socially supported and also received an intranasal OXT administration showed the lowest hormone levels, whereas OXT alone had little effect. Moreover, the common action of both social support and OXT further increased their calmness and reduced the level of anxiety experienced during the stress test. These results provide further evidence for our hypothesis that endogenous OXT stimulated during social interactions mediates the positive and buffering effects of social support.

Thus, mating and sexual activity represents a physiological stimulus activating OXT release within the brain in males, which could be an important neurobiological mechanism contributing to the positive health effects of sexual activity. In this context, it would be of interest to study whether infant contact regulates the OXT system in paternal circumstances – in parallel with those described above for the mother – and if differences can be found between paternal and non-paternal species.

OXT Mediates the Rewarding Nature of Close Social Interactions: Maternal and Romantic Love

Clearly, social affiliation and sexual behaviour have rewarding effects. Social animals seek affiliation and sexual activity, and these experiences enhance the motivation for seeking it. Thomas Insel (Insel et al. 1997) described the rewarding property of affiliation as "love is addiction," and this statement holds clearly true for both maternal and romantic love. It has been reported in the monogamous prairie vole that establishing social bonds involves neural reward systems, including dopamine and opioid circuitry (Nelson and Panksepp 1998; Young and Wang 2004). Importantly, OXT significantly modulates the activity of these systems and vice versa, e.g., OXT amplifies the mesolimbic dopamine system (Wang and Aragona 2004; Young and Wang 2004) and increases preproenkephaline in the nucleus accumbens, thus activating neural reward systems (Lim et al. 2004). Recently, the existence of a neural circuit has been suggested that integrates OXT and dopamine actions on the consummatory, motivational and rewarding aspects of sexual behaviour (Melis et al. 2007; Succu et al. 2007).

Moreover, evidence exists that endogenous opioids regulate not only stress responsiveness (Douglas et al. 1998) but also OXT neuronal activity, in particular peripartum (Douglas et al. 1995; Wigger and Neumann 2002). Additional support has recently been

shown using imaging techniques that the suckling stimulus triggers high activity in mesolimbic reward systems (Febo et al. 2005; Ferris et al. 2005). As suckling activates the OXT system, and given the above-mentioned interactions between OXT, dopamine and endogenous opioids, it is likely that activation of central OXT release both during close maternal-offspring interactions and interactions with the bonding/mating partner, e.g., during sexual behaviour, mediates the rewarding effects of these complex affiliative behaviours.

Another positive effect of a stimulated brain OXT system by close social interactions that necessitates discussion relates to social cognition. Initial studies on OXT in social cognition showed strong dose-dependent effects after peripheral or icv administration of OXT (Popik and van Ree 1991). In females, administration of an OXT antagonist interfered with the animals' ability to establish normal social memory (Engelmann et al. 1998; for review, see Bielsky et al. 2004; Bielsky and Young 2004). Additional support for an involvement of OXT in social cognitive abilities comes from studies using OXT knockout mice, which show clear deficits in social recognition but normal non-social learning and memory abilities (Choleris et al. 2003; Ferguson et al. 2000; Kavaliers et al. 2003; Nishimori et al. 1996). The deficit in social recognition was reversible with OXT administration, clearly demonstrating the importance of this peptide in the processing of social cues and subsequent social recognition. In female OXT knockout mice, the essential role of OXT in social memory has also been demonstrated in the context of the Bruce effect. 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 (Temple et al. 2003). 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.

Other examples of OXT being essential for social memory and recognition come from experiments performed in ewes and in monogamous prairie voles. In ewes, lamb recognition and bonding immediately after birth could clearly be related to the intracerebral release of OXT, for example within the olfactory bulb, during parturition (Kendrick et al. 1988b), where OXT modulates GABA, noradrenaline and acetylcholine neurotransmission, and, consequently, mitral cell activity (Levy et al. 1995). 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 clearly 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 the social bonding in female prairie voles, as does vasopressin in the male prairie voles (Insel and Hulihan 1995). Thus, mating-induced stimulation of OXT release within distinct brain regions seems to be a promoting factor for social cognition and pair-bond formation. Importantly, the distribution of OXT receptors differs greatly between the monogamous and promiscuous species (the montane vole), with a high OXT receptor density found in the nucleus accumbens of female and a high vasopressin receptor density found in the ventral pallidum of male prairie voles (Insel and Shapiro 1992). These brain regions are important components of the reward system, further indicating a functional and behaviourally relevant relation between close social interactions, as seen during mating or during suckling, intracerebral OXT release and activation of reward systems beneficial for mental health.

In related studies, OXT has been shown to increase social skills in humans. As described above, OXT makes humans more trusting (Kosfeld et al. 2005), which is clearly a necessary emotion to have when forming and maintaining social bonds. Furthermore, OXT has been shown to increase the ability to gauge the mental state of others using social cues from facial expressions (Domes et al. 2007), which provides further indication of the likelihood of a similar role of OXT in social recognition in humans.

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