Oxytocin and the social brain: between love and hate

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Abstract

Oxytocin is a peptide hormone that appears to mediate social behavior in animals and humans. Various studies have shown that oxytocin promotes love, mother-infant bonding, partner bonding and maternal care in several mammalian species. Although human social behavior depends less on hormones like oxytocin, the hormone has been found to stimulate prosocial behavior, like trust and empathy, in humans. The hormone is traditionally viewed as a “love drug” or “cuddling hormone”. Recent studies suggest, however, that oxytocin is also involved in intergroup conflicts and violence. Moreover, the hormone has been found to promote defense-motivated aggression, like maternal aggression. These findings make the view of oxytocin as a “love hormone” questionable. This thesis provides an overview of the literature concerning the effect of oxytocin on social behavior in animals and humans. Thereby, it focuses on the key question whether oxytocin can or cannot be seen as a “love hormone” and how oxytocin is capable of promoting love, bonding and aggression at the same time.

Table of contents

Introduction

This thesis will discuss the role of the hormone oxytocin in mediating social behavior. Oxytocin has been widely viewed as a “love drug” or “cuddle chemical” which promotes prosocial behavior. Conversely, the same hormone has also been associated with aggression. One of the key questions that this thesis will address is how the same hormone is capable of stimulating love, bonding and aggression at the same time.

Some recent human studies have shown the possible involvement of the hormone in intergroup conflicts. These new insights make the traditional view of oxytocin questionable. Therefore, this thesis will also focus on the key question whether oxytocin can be seen as a love hormone which makes humans prosocial.

The hormone oxytocin will be introduced in the first chapter. This chapter will be followed by a review of animal and human studies showing the involvement of oxytocin in pair bonding, maternal care and affiliation. This part will also explore how the hormone is capable of promoting both aggression and love. Furthermore, a review of human studies will provide insights into the role of oxytocin in mediating human social cognition. Finally, this thesis will discuss the view of oxytocin as the “love hormone”, by reviewing several human oxytocin administration studies.

1. Oxytocin

Structure, release and evolutionary aspects

Oxytocin (OT) is a peptide hormone that plays a well-established role in parturition and lactation. Besides its peripheral role, OT acts centrally to regulate social behavior (Argiolas & Gessa, 1991; Campbell, 2008; I. D. D. Neumann, 2008). The latter will be reviewed in the next chapter.

OT is composed of nine amino acids with a sulfur bridge between the two cysteine residues. This disulfide bond creates a cyclic six amino acid ring structure in the protein. Most of the hormone is produced in the magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus. From there, OT is transported to neuronal axon terminals in the posterior pituitary, for systemic release. A smaller amount of OT, for release

within the brain, is synthesized in the parvocellular neurons of the paraventricular nucleus and the bed nucleus of the stria terminalis, medial preoptic area and the lateral amygdala (synthesis in the latter three structures is depending on the species). OT released from these axon terminals acts as neurotransmitter in the brain to mediate different kinds of behavior (Zingg, 2002). The next chapter will be devoted to the role of OT in behavior in various species.

The hormone is cleaved from a preprohormone during transport down the axon to the place of release in the posterior pituitary. This preprohormone contains a signal peptide, the neuropeptide oxytocin and neurophysin, a carrier protein for OT (Gimpl & Fahrenholz, 2001; Lee, Macbeth, & Pagani, 2009). OT is structurally very similar to another peptide hormone called vasopressin (VP). Both differ in two amino acids only. Genes coding for the hormones are also located on the same chromosome (chromosome 20 in humans), but are transcribed in opposite direction (Lee et al., 2009). Both hormones are highly conserved across species. Almost all vertebrate species synthesize an OT or VP-like hormone (see figure 1). Bony fishes, ancestors of the land vertebrates, for example, synthesize isotocin and vasotocin (Gimpl & Fahrenholz, 2001). These homologue peptides all play a role in modulating social and reproductive behavior in different species. Although the function of OT and VP-like hormones seems to be conserved through evolution, specific behaviors regulated by the hormones are not. These are quite diverse across species (Donaldson & Young, 2008).

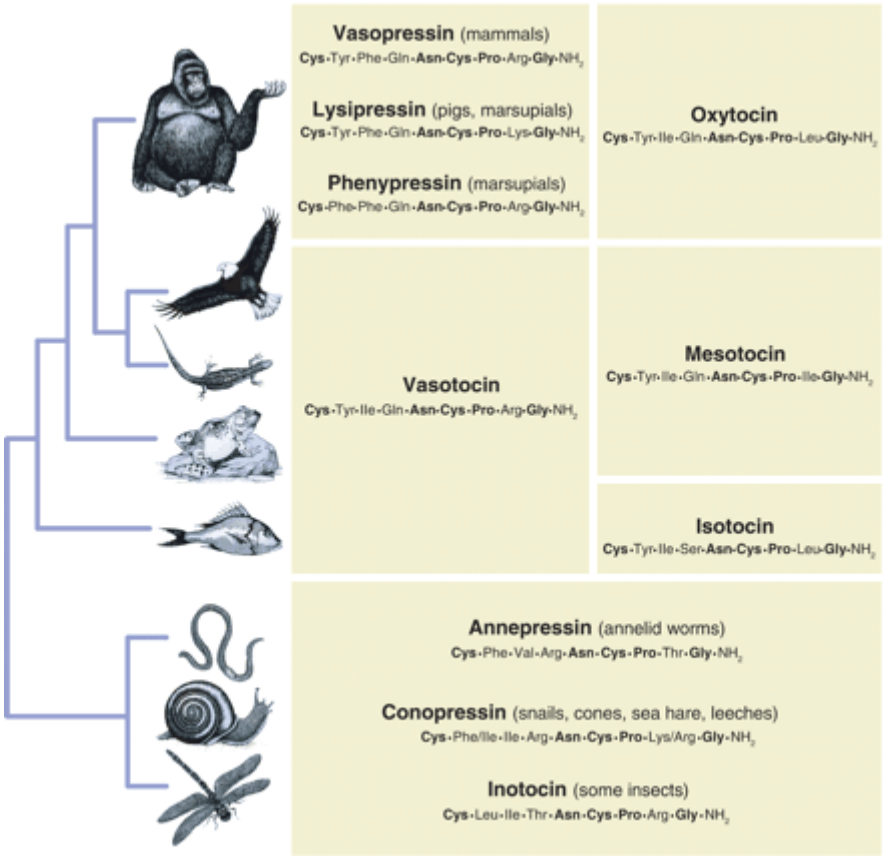

Figure 1*: *Homologs of OT and VP (Donaldson & Young, 2008)

Oxytocin receptor

Oxytocin has one known receptor (OTR). The OTR is present in peripheral tissues like the thymus, heart and reproductive organs (Carter, 2007). The OTR is also widely distributed in the central nervous system (CNS), particularly in (brain stem) regions involved in reproductive, social and adaptive behaviors and in structures involved in the regulation of the hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system (Carter, 2007). Brain structures with strong expression levels of the OTR in humans include the pars compacta of the substantia nigra, the basal nucleus of Meynert, the lateral septal nucleus, the nucleus of the solitary tract and the substantia gelatinosa of the trigeminal nucleus (Gimpl & Fahrenholz, 2001). The distribution pattern of the OTR is highly variable among species. In addition, rat studies have shown that the distribution and number of OT receptors is not constant, but rather variable during development. OT receptors are, for instance, abundantly present in some areas of the infant rat brain, whereas the receptors are not observed in these areas in the adult rat brain (Carter, 2007; Gimpl & Fahrenholz, 2001).

2. OT's role in regulating social behavior

Over the years, it has become clear that OT is not only a regulating factor in birth and lactation, but also a hormone capable of coordinating maternal behavior, behavioral changes in the mother that are essential for survival of the offspring. More recently, various studies have shown that the hormone has a lot more functions in the brain, not only in females, but also in males (Ross & Young, 2009).

The literature concerning the role of OT in regulating maternal behavior and mother-infant bonding will be reviewed in the first paragraph. Next, studies showing the involvement of OT in bonding, affiliation and aggression will be presented. Finally, the last paragraph of this chapter will present a couple of studies demonstrating the involvement of oxytocin in human social cognition.

Maternal care and mother-infant bonding

Like human females, most females of primate species find newborns attractive and their response to them is pro-nurturant. Maternal care in these species seems to be acquired mostly through learning and social experience. In lower mammals, however, nulliparous females often react hostile towards newborns. These mammals need a brain system that stimulates the induction and maintenance of mothering behavior, because newborns are helpless and depend on nutrition and their mother's body warmth. OT is thought to play a role in mediating the establishment of maternal care and bonding to the offspring (C. A. Pedersen, 2004).

Nest building, retrieving pups to the nest, crouching over pups and licking pups are examples of maternal behavior of the rat mother (C. A. Pedersen, 2004). In the rat, OTR expression has been found to increase just before parturition in specific brain regions; the supraoptic nucleus, brain stem regions, medial preoptic area, bed nucleus of the stria terminalis and the olfactory bulbs. OTR expression decreases to pre-pregnant levels within 12 hours postpartum. The prenatal increase in OTR expression is likely to contribute to the initiation of birth and maternal behavior and indicates the involvement of the OT system in maternal behavior (Meddle, Bishop, Gkoumassi, van Leeuwen, & Douglas, 2007).

In the rat, natural variations in the level of maternal care have been found. Some rat mothers show little pup licking and grooming (low LG), while others show high levels of this behavior (high LG). It has been shown that high maternally responsive females have higher levels of the OTR in the medial preoptic area, the lateral septum, the central nucleus of the amygdala, the paraventricular nucleus of the hypothalamus and the bed nucleus of the stria terminalis. This finding highlights the importance of the OT system in maternal care (F. Champagne, Diorio, Sharma, & Meaney, 2001).

Further evidence for the involvement of OT in rat maternal behavior comes from a lesion study and experiments with injections of OTR antagonists (T. R. Insel & Harbaugh, 1989; C. A. Pedersen, Caldwell, Walker, Ayers, & Mason, 1994; van Leengoed, Kerker, & Swanson, 1987). Cerebroventricular injections of OTR antagonist in female rats, after delivery of their first pup, resulted in a delay in the onset of maternal behavior in these animals, whereas control animals started to gather pups immediately. Control animals also showed all other aspects of maternal behavior within 10 minutes (van Leengoed et al., 1987). Infusions of OTR antagonist into specific brain regions in which OT is thought to activate maternal behavior, i.e. the medial preoptic area and the ventral tegmental area, also affected the onset of maternal care. Pup retrieval and assuming a nurturing posture over pups was

significantly blocked in females which had received the antagonist, in this study. Similarly, prior studies showed that OT infusions in these brain areas stimulate maternal behavior (C. A. Pedersen et al., 1994). In addition, lesions in the paraventricular nucleus of the hypothalamus (the origin of OT projections) inhibited the initiation of grouping, crouching, nest building and pup retrieval in rat mothers when lesions were made on day 15 of gestation. Lesions performed on day 4 after giving birth had less effect on maternal behavior (T. R. Insel & Harbaugh, 1989). The findings mentioned above provide clear evidence for the involvement of the OT system in maternal care. Moreover, the experiments performed by van Leengoed et al. and Insel et al. demonstrate that OT is mainly important in stimulating the onset of maternal behavior rather than maintaining this behavioral response once it has been initiated. Another experiment, however, yielded an opposite result. In this study, intracerebroventricular injections of an OTR antagonist, several days after giving birth, turned high LG females into females showing little pup licking and grooming (F. Champagne et al., 2001). This study, together with that by Pedersen and Boccia (C. A. Pedersen & Boccia, 2003), shows that OT continues to stimulate parts of rat maternal behavior after the early postpartum period.

Like rat females, ewes do not usually foster their lambs outside the peripartum period. However, the ewe actively licks the lambs and lets them suckle after giving birth. It also emits low-pitched bleats. While rat mothers care for other pups as much as for their own, the ewe creates a specific bond with her own lambs (Keverne & Kendrick, 1992; C. A. Pedersen, 2004). OT has been shown to play an important role in the induction of maternal behavior and bonding to the offspring in sheep as well (Keverne & Kendrick, 1992). This finding is in line with the previously discussed experiments in rats. Central OT administration as well as vaginocervical stimulation (VCS) in nonparturient ewes induced proceptive maternal behavior and reduced rejection of lambs. VCS also caused an increase in the level of OT in the cerebrospinal fluid (see figure 2). Both results show the critical involvement of VCS in bonding to the offspring and maternal care in sheep, probably via the associated release of OT. It seems likely that the steroid hormones progesterone and estradiol also play an important role in bonding and maternal behavior, because VCS and OT treatment had only a significant effect on bonding and maternal behavior when combined with steroid hormone priming. Both hormones act on the OT system. Estradiol has been found to induce the synthesis of OT mRNA and OTRs, whereas progesterone is thought to inhibit basal release of OT in the brain, thereby sensitizing the OTRs (Keverne & Kendrick, 1992).

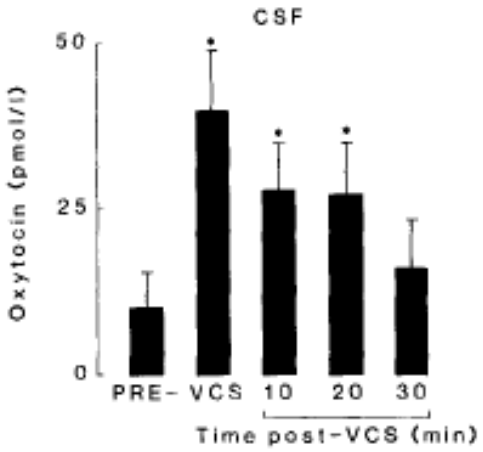

Figure 2*: *Oxytocin levels in the cerebrospinal fluid (CSF) before, during and after vaginocervical stimulation (VCS)

The figure shows a significant increase in OT during VCS and 10 or 20 minutes after VCS, compared to pretreatment OT levels. Adapted from: (Keverne & Kendrick, 1992).

The influence of estradiol on OT and maternal behavior is not exclusively present in sheep. Champagne et al. (F. A. Champagne, Weaver, Diorio, Sharma, & Meaney, 2003) demonstrated that high LG lactating female rats had an increased expression of the estrogen receptor and increased estrogen sensitivity in the medial preoptic area. Estrogen acts in this brain region to enhance OT receptor binding (F. A. Champagne et al., 2004).

In addition, a study by Keverne and colleagues demonstrates the possible involvement of opiates in the process of bonding to the offspring and maternal care in sheep. Morphine-treated ewes which also had received VCS showed increased bonding and intense maternal behavior, comparable to the situation after parturition. These animals made protesting sounds when the lambs were removed. This shows the presence of strong bonding to the lambs. Combined morphine and VCS treated ewes showed even more bonding and maternal behavior than OT and VCS treated ewes. The additional behavioral effects of morphine could be explained by its ability to potentiate the central release of OT and its ability to reduce the level of corticotropin releasing factor (CRF). Opiates are thought to inhibit CRF, thereby inhibiting a phobic reaction to the lambs (Keverne & Kendrick, 1992). The role of CRF will be more extensively discussed in a later paragraph.

The exact mechanism through which OT facilitates maternal behavior in various species, including the rat and sheep, is not precisely known. An experiment performed by DaCosta et al. (Da Costa, Guevara-Guzman, Ohkura, Goode, & Kendrick, 1996) has shown

that bilateral OT administration into the paraventricular nucleus of estrogen and progesterone primed ewes leads to the induction of maternal behavior. They hypothesized that OT in the paraventricular nucleus facilitates OT release in other brain structures, including the hypothalamus and the limbic system, via a feedback mechanism. OT released at different brain sites could lead to activation of separate aspects of maternal behavior. OT release in the olfactory bulb is, for example, thought to facilitate selective bonding to the lamb (Da Costa et al., 1996; Levy, Kendrick, Goode, Guevara-Guzman, & Keverne, 1995). In the olfactory bulb, OT might facilitate the link between the memory of the odor of the lambs with the motivational system. The latter might involve interactions with the classic neurotransmitters noradrenaline (NA) (Levy et al., 1995; C. A. Pedersen, 2004), acetylcholine (ACh) and γ-aminobutyric acid (GABA) (Levy et al., 1995). The neurotransmitter dopamine is likely to play a role in the expression of maternal behavior as well. Champagne et al. (F. A. Champagne et al., 2004) found increased levels of dopamine in the nucleus accumbens shell in high LG rat mothers as compared to low LG rat mothers. The dopamine signal was significantly increased just before and during an LG bout. The mesolimbic dopamine system could be a downstream target of OT and has also been implicated in the formation of pair bonds in monogamous species. The way OT might act together with the mesolimbic dopamine system to induce social bonding will be discussed in the paragraph “Pair bonding – the prairie vole model”.

Human maternal care

In contrast to the situation in rats and sheep, human maternal care does not critically involve OT. Humans are for example able to care for foster children. Care is also given by mothers whose babies have been carried by others. OT, however, seems to play a supplementary role in maternal care, by increasing bonding between mother and child in the first weeks after giving birth (Campbell, 2010). OT also seems to play a role in attenuation of stress reactions during lactation and pregnancy. This will be explained in the paragraph “Oxytocin and aggression”.

Pair bonding – the prairie vole model

Pair bonding has been defined as the formation of a long-term, selective social connection accompanied by biparental care of the offspring and is typically seen in monogamous mammals (T. R. Insel & Hulihan, 1995; Williams, Insel, Harbaugh, & Carter, 1994). Various studies have used the monogamous prairie vole (*Microtus ochrogaster*) as a model system for investigating the underlying factors mediating pair bond formation. Field and laboratory experiments have indicated that prairie voles form stable male-female pairs (Getz, Carter, & Gavish, 1981). Getz and colleagues (1981) have shown that aggression is rare among established male-female prairie vole breeding pairs. Additionally, they observed that pregnant females are tolerant against males with which they had mated and lived before. Moreover, females showed sexual behavior during the postpartum period, specifically during an encounter with the male with which they had mated before. In contrast, female voles often reacted aggressively during encounters with an unfamiliar male. Paired male voles also showed higher levels of aggression towards strange virgin females and females paired to another male, as compared to unpaired males. Conversely, inexperienced and sexually experienced unpaired males rarely reacted aggressively. These findings show the presence of pair bonds between male and female prairie voles, as indicated by the preference in these animals to mate and live with a familiar partner. A study conducted by Williams et al. (Williams, Catania, & Carter, 1992) provides further evidence for the presence of strong preferences for a familiar partner in female prairie voles. The experiment was carried out using an apparatus with three cages, connected by tubes. The familiar partner vole and the novel stranger were each tethered in their own cage. The subject was free to move through all cages during the test. Pair bonding was assessed by comparing contact time spent with the familiar vole with contact time spent with the stranger. Results of this study show that cohabitation of 24 hours results in a significant preference for the partner over a stranger. This preference was not further enhanced by a longer cohabitation period or mating. Six hours of cohabitation without mating did not result in a partner preference. However, estrogen-priming of the females and mating during this six-hour period did lead to a significant partner preference. Low levels of aggression were found in this study, in contrast to the study conducted by Getz et al. (1981). Both before-mentioned studies indicate the presence of pair bonding between male and female prairie voles. Furthermore, the experiment by Williams and colleagues demonstrates that events associated with sexual interaction and estrus might facilitate the onset of pair bonding.

It has been proposed that OT plays a role in mediating pair bond formation, first, because OT is also involved in mother-infant bonding (see previous paragraph) and second, because vaginal and cervical stimulation during mating has been found to release OT in the brain in several species, including the rat, sheep and humans (Williams et al., 1994). Indeed, an oxytocin administration study in female prairie voles (Williams et al., 1994) demonstrates that centrally infused OT facilitates the onset of a preference for a partner with which a female cohabits (but not mates) for 6 hours. Central infusion of OT combined with a selective OT antagonist blocked this behavioral effect. Peripheral injection of OT did not result in a selective partner preference. The latter can be explained by results of prior experiments which demonstrate that oxytocin does not normally cross the blood brain barrier. It has been found that even large amounts of peripherally injected OT do not induce behavioral effects (Williams et al., 1994).

Results of the experiment discussed above point to OT playing a role in pair bond formation. However, the behavioral effects have been demonstrated in female prairie voles. Insel and Hulihan (T. R. Insel & Hulihan, 1995) have shown that the role of OT in facilitating the onset of a partner preference might be gender-specific. OT appeared to influence pair bonding in females only in their experiment, while vasopressin (VP) seemed to be more important for pair bonding in male prairie voles. Infusion of VP in the female vole brain did not result in a partner preference and infusion of a specific VP receptor antagonist had little effect in females. In contrast, VP had a significant influence on pair bonding in male prairie voles (T. R. Insel & Hulihan, 1995; Winslow, Hastings, Carter, Harbaugh, & Insel, 1993). However, contrasting results concerning the gender-specific mechanism of inducing partner preference have also been found. Cho and colleagues conclude in their report (Cho, DeVries, Williams, & Carter, 1999) that OT and VP are both capable of regulating partner preference formation in female as well as male prairie voles. Moreover, this study and the study conducted by Liu et al. (Liu, Curtis, & Wang, 2001) show that OT receptor antagonists are capable of blocking VP-induced and mating-induced partner preferences. This finding suggests that the OT receptor is also necessary for inducing pair bond formation in males and it moreover suggests that VP requires access to OT receptors as well to exert its behavioral effect. The contrasting results concerning the regulation of pair bonding by OT and VP might be explained by differences in the experimental paradigm between the before-mentioned studies. For example, cohabitation time differed between the studies. Moreover, there were some differences in the peptide administration procedure. Liu et al. (Liu et al., 2001) infused directly into the lateral septum, whereas in the other studies, peptides were infused into the

cerebral ventricles. This might have led to peptide concentration differences between studies. In conclusion, it is not clear whether a sex difference exists regarding the involvement of OT in pair bond formation. The underlying mechanism for a potential sex difference would be difficult to explain in terms of the OT distribution in the brain, because no sex differences have been reported in the distribution of OT cell bodies and receptors. (T. R. Insel & Hulihan, 1995).

The underlying mechanisms through which OT regulates pair bonding has not been fully understood yet. A comparison between the OTR density in the prairie vole brain and the OTR density in the brain of the nonmonogamous montane vole has revealed some distributional differences between both species. A high OTR density has been identified in the prefrontal cortex (PFC) and the nucleus accumbens (NAcc) of the monogamous prairie vole, as compared to the nonmonogamous vole (see figure 3) (T. R. Insel & Shapiro, 1992; K. A. Young, Liu, & Wang, 2008). Such variation in the distribution of the OTR is thought to reflect the differences in social organization between both species, i.e. pair bonding versus promiscuity (T. R. Insel & Shapiro, 1992). This study suggests that the PFC and the NAcc are important brain structures for pair bond formation. Further evidence for the involvement of the PFC and NAcc in the creation of pair bonds has been provided by a study in which an OTR antagonist was infused into these structures in female prairie voles (L. J. Young, Lim, Gingrich, & Insel, 2001). An OTR antagonist injected into the PFC and NAcc prevented the formation of a partner preference, whereas an injection into the caudate putamen did not.

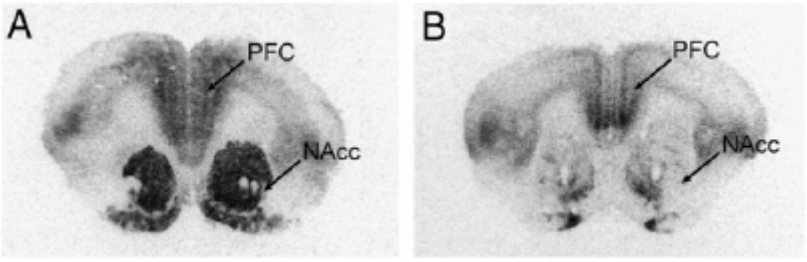

***Figure 3*: OTR density in the prairy vole and montane vole brain**

In the monogamous prairie vole (A) high OTR density has been observed within the prefrontal cortex (PFC) and the nucleus accumbens (NAcc). Low OTR density has been observed within these structures in the nonmonogamous montane vole brain (B). Adapted from: (K. A. Young et al., 2008)

Both the PFC and NAcc are part of the mesolimbic dopamine reward system, which is thought to play an important role in the reinforcing and rewarding effects of natural stimuli, such as mating and drugs. Moreover, the mesolimbic dopamine reward system has been associated with conditioned learning (L. J. Young et al., 2001). In line with the neuroanatomical evidence previously described, it has been postulated that pair bonding uses the same neural pathways as reward. OT might interact with the dopamine reward circuitry to induce pair bonding in females (L. J. Young & Wang, 2004; L. J. Young et al., 2001). Young et al. (L. J. Young & Wang, 2004) have put forward a neural circuit model for pair bonding. Prior knockout mouse studies have suggested that OT also plays a role in processing of sensory cues involved in social learning. Given this role for OT, Young and colleagues propose that pair bonding results from coupling of the reinforcing properties of the dopamine reward system and the circuits involved in social recognition. This model proposes that mating activates the ventral tegmental area (VTA). Dopaminergic projections from the VTA, in turn, release dopamine in the PFC and the NAcc. At the same time, olfactory information from the mate is processed by the olfactory bulb (OB) and conveyed to the medial amygdala. OT acts here to facilitate olfactory learning and memory. Mating also causes an increase in extracellular OT in the PFC and NAcc. OT projections to the medial amygdala, PFC and NAcc are thought to originate from cell bodies in the preoptic or hypothalamic area. Eventually, concurrent activation of dopamine D2 receptors in the nucleus accumbens and activation of the OTR in the PFC and nucleus accumbens has been thought to result in a conditioned partner preference. The description above is based on the situation in female prairie voles. A similar mechanism might underlie pair bonding in male prairie voles. However, it has been thought that the dopamine reward circuitry is coupled to the VP system in the ventral pallidium in male prairie voles (L. J. Young & Wang, 2004). The model is illustrated in figure 4.

It has been hypothesized that the mechanism leading to a specific partner preference in monogamous female species has evolved from the mechanism involved in mother-infant bonding. The cellular machinery and brain circuitry implicated in maternal behavior might have been adapted through evolution to facilitate partner preference formation. In fact, vaginocervical stimulation during birth has been found to release central OT, whereas the same stimulation during mating also releases OT in the brain.(Ross & Young, 2009)

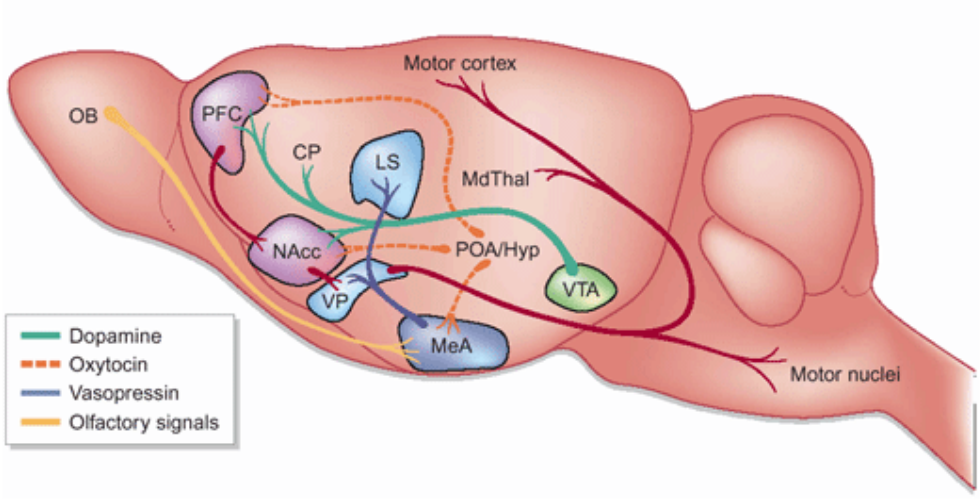

Figure 4*: *The neural circuits involved in pair bonding in the prairie vole

Pair bonding might result from coupling of the dopamine system in the nucleus accumbens and the OT system in the PFC and NAcc (or VP system in the ventral pallidium).

OB: olfactory bulb, LS: lateral septum, VP: ventral pallidium, MeA: medial nucleus of the amygdala, VTA: ventral tegmental area, MdThal: mediodorsal thalamus, POA/Hyp: preoptic and hypothalamic area (L. J. Young & Wang, 2004).

Human pair bonding

The previous paragraph focused on the involvement of oxytocin in pair bonding and discussed studies of prairie voles. Because of its monogamous social organization, the prairie vole is a useful model system for studying the effect of oxytocin on pair bonding. It is, however, not known whether oxytocin is involved in human pair bonding as well. One might speculate that this is the case. Although higher-level structures in the neocortex are most likely playing an important role in human bonding, some evidence in support of a role for oxytocin in human pair bonding has been found. For example, increased OT plasma levels have been found in women during orgasm (T. R. Insel, 1997). Increased OT plasma concentration might reflect central OT release during intercourse, which, in turn, could be present in order to strenghten bonding (L. J. Young & Wang, 2004). Moreover, some aspects of human sexuality might reflect the influence of intercourse on pair bonding. For example, human sexual activity is, in contrast to other species, not limited to the time of ovulation. It could be speculated that regular sexual activity in humans serves to activate the neural circuits underlying pair bonding (L. J. Young & Wang, 2004).

Additional evidence for the involvement of oxytocin and the reward circuitry in human pair bonding comes from functional magnetic resonance imaging (fMRI) studies. Aron et al. (Aron et al., 2005) analyzed the brain systems associated with human romantic love in an fMRI study in which participants watched photographs of beloved ones and familiar individuals. They concluded that looking at photographs of a beloved partner causes specific activation in dopamine-rich brain areas implicated in reward. This result might provide evidence for the existance of a similar neural system for pair bonding in humans and prairie voles.

Oxytocin and aggression

The previous paragraphs already discussed the involvement of OT in parental care, mother infant bonding and pair bonding between mates. However, parenting and social bonding also require control of aggression, avoidance and other responses to unfamiliar and potentially dangerous objects or individuals. Without systems that control aggression and avoidance, mothers would probably attack or eat their newborns or run away from them. Moreover, physical contact necessary for mating would not be possible without these adaptations (C. A. Pedersen, 2004). Lactating rodent females rapidly react aggressively in response to threat to the offspring and attack the intruder (Gammie, Negron, Newman, & Rhodes, 2004).

Interestingly, the hormone oxytocin seems to be capable of inducing maternal aggression against intruders to protect the offspring, while, at the same time, it seems to be capable of suppressing aggression against the newborn infants (Campbell, 2008). Ferris et al. (Ferris et al., 1992) demonstrated that OT administration into the medial amygdala has a significant effect on maternal aggression in golden hamsters. Female hamsters injected with OT displayed more bites and spent more time with a male intruder. A rat experiment performed by Bosch and colleagues (Bosch, Meddle, Beiderbeck, Douglas, & Neumann, 2005) supports this finding. They observed increased OT release within the central amygdala and paraventricular nucleus of lactating rats showing high levels of aggressive behavior, as compared to rats showing low levels of aggressive behavior, during a maternal defense test. Some other studies, however, did not find a positive link between aggression and OT (Campbell, 2008).

Assuming that there is a relationship between increased OT and maternal aggression, the question is how the same hormone is able to enhance aggression against intruders and suppress aggression against the offspring at the same time. One way by which OT might act

to increase maternal aggression is via inhibition of the corticotropin releasing factor (CRF) system (Bosch et al., 2005). Low levels of CRF have been associated with decreased fear and anxiety of the female which, in turn, could lead to increased aggression (Gammie et al., 2004).

The neuropeptide CRF can act within the brain or peripherally. Centrally released CRF mediates responses to stress and generates behavior indicative of increased fear in various fear inducing paradigms. Peripherally acting CRF, released from the paraventricular nucleus, activates the hypothalamus-pituitary-adrenal axis (HPA axis). It stimulates the anterior pituitary to release adrenocorticotropin-releasing hormone (ACTH). ACTH, in turn, stimulates the adrenal glands to release corticosterone. Corticosterone has many functions, including modulation of stress reactions (Butler, Weiss, Stout, & Nemeroff, 1990; Gammie et al., 2004). It has been widely thought that reduced centrally (extrahypothalamic) and peripherally (hypothalamic) CRF activity leads to reduced fearfulness and anxiety. Reduced fearfulness, in turn, is believed to be important for the onset of maternal care toward potentially dangerous newborns and it might allow females to defend the nest. However, not all researchers agree on this hypothesis (Lonstein, 2005).

Gammie et al. (Gammie et al., 2004) investigated maternal aggression in mice which had received an intracerebroventricular injection of CRF. They allowed intruder male mice to enter the home cage of females with the pups present in the cage. Maternal aggression was assessed by scoring latency to first attack, the number of attacks and the total attack duration. They observed that CRF injections significantly inhibits maternal aggression, but not other maternal behavior. This finding suggests that a decline in CRF is indeed needed to induce maternal aggression. Moreover, they found that injection of CRF causes brain activity in the same regions previously implicated in maternal aggression, including the lateral and medial septum, the bed nucleus of the stria terminalis, the medial and central amygdala and the periaquaductal grey (Gammie & Nelson, 2001). This could mean that CRF inhibits maternal behavior by directly altering brain activity in the maternal aggression circuitry.

To summarize, OT might have an influence on maternal aggression via inhibition of CRF neurons. It seems likely that inhibition of CRF is needed for establishing maternal aggression as well as for allowing maternal care toward potentially dangerous offspring, because CRF might reduce fearfulness in the animal.

The study by Windle et al. (Windle et al., 2004) supports this proposed mechanism. They infused OT into the ventricles of ovariectomized and estradiol treated rats. OT administration caused a significant decrease in the release of ACTH and corticosterone after

30 minutes restraint. However, more important with respect to the previously explained mechanism, OT administration also inhibited CRF mRNA expression, which would normally be evoked after restraint. Moreover, another study demonstrated that OT inhibits HPA-axis activity in general. Infusion of an OTR antagonist in rats caused increased basal and stress-induced peripheral secretion of ACTH and corticosterone in this study. Inhibition of the HPA-axis under basal conditions has been found to occur partly within the paraventricular nucleus (I. D. Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000).

A couple of human studies are in line with the discussed animal studies. These human studies also show inhibition of HPA-axis activity during late pregnancy and lactation, periods during which OT levels rise. It has been found that ACTH and cortisol are significantly decreased during breast-feeding and holding the infant (Amico, Johnston, & Vagnucci, 1994; Heinrichs et al., 2001).

Another mechanism, through which OT might act to attenuate fear and to cause increased maternal aggression, might be via inhibition of central amygdala (CeA) activity. The CeA has been thought to control autonomic fear reactions via connections to the periaquaductal grey in the midbrain, the reticular formation and the hypothalamus. OT as well as VP receptors have been found within the CeA. OTRs are located in the lateral and capsular part of the CeA, while VP receptors are located in the medial part of the CeA (Campbell, 2008; Debiec, 2005). Huber et al. (Huber, Veinante, & Stoop, 2005) have found two distinct populations of neurons. One population is exited by OTR activation and the other is inhibited by OTR activation, but stimulated by VP acting on its receptor. In this study, lateral and capsular activation of the CeA by OT have been found to inhibit the medial part of the CeA via inhibitory GABA-ergic projections. The neurons in the medial CeA, which are stimulated by VP, have been thought to enhance fear responses. Thus, OT is able to attenuate fear responses via GABA-ergic inhibition of medial CeA neurons (see figure 5) (Debiec, 2005; Huber et al., 2005). This inhibitory network in the amygdala gives more insight in the way love, care and aggression might act together during maternal care and pair bonding.

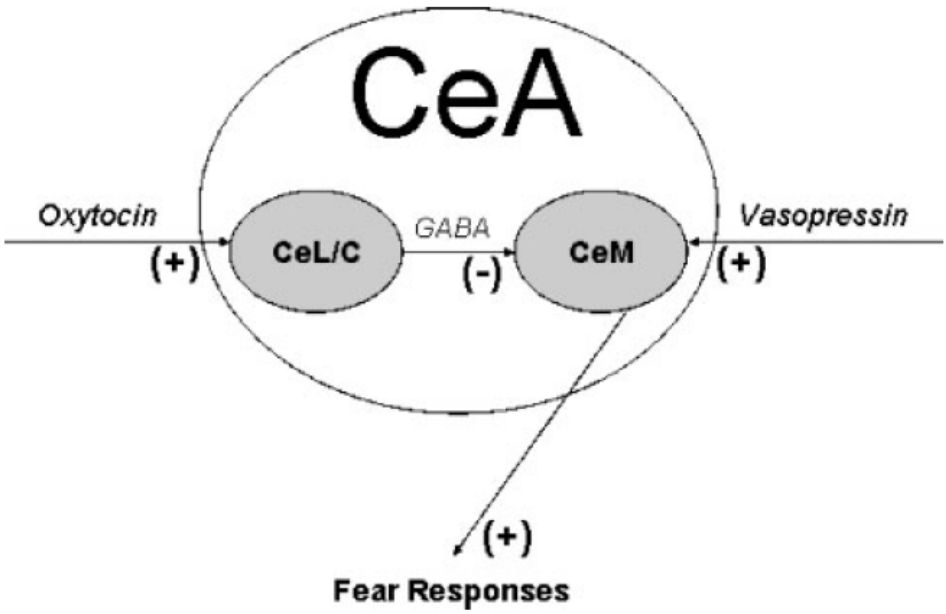

Figure 5*: *Mechanism of fear attenuation in the central amygdala (CeA)
OT input into the lateral and capsular part (CeL/C) of the CeA inhibits the medial part (CeM) of the CeA via GABA-ergic projections. VP induced fear responses in the CeM are inhibited (Debiec, 2005).

Human social cognition

It has been thought that behavioral responses like maternal care, maternal bonding and partner bonding are less hard-wired and less dependent on hormones like OT in humans than in lower species like the rat (Campbell, 2010). However, as discussed before, OT has a supplementary role in facilitating maternal behavior and bonding in humans. In addition, various experiments have revealed that OT could have other prosocial functions in humans. First, OT has been found to cause increased trust in humans. Trust plays a very important role in friendship, love, families and in organizations (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). In a study by Kosfeld et al. (Kosfeld et al., 2005), subjects played a trust game after intranasal administration of OT. In this trust game, two subjects played the role of investor or trustee in an anonymous setup. The investor had the option to transfer money to the trustee. Transferred money was tripled by the experimenter. After that, the trustee was informed about the transfer by the investor and had the option to give money back to investor. In the case the trustee gave a part of the money back, both ended up with a higher payoff. In this game, the investor had to make a decision between transferring money to the trustee, thereby trusting that this player gives some money back, or not trusting the other player. Results of this study showed that OT causes a significant increase in trust. 45% of the participants in the OT group showed the

maximum trust level, as compared to 21% of the participants in the placebo group. These findings were not caused by an increase in the level of risk taking of the investor, due to OT administration, because there was no difference in trust between the OT and placebo group in a game in which social interactions were replaced by a random mechanism.
Moreover, another study with the same trust game showed that higher OT levels are associated with a social intention of trust. Peripheral OT levels were higher in persons who had received money from the investor that was voluntary given with an intention of trust, as compared to persons who had received money without the latter. In addition, higher OT levels have also been associated with trustworthy behavior of the trustee (Zak, Kurzban, & Matzner, 2005). In contrast to the results obtained by Kosfeld et al. (2005), these findings suggest that OT is associated with signals of trust, rather than with production of trust itself.

The experiments provide evidence for OT playing a role in human prosocial behavior. Further evidence for a link between OT and stimulation of prosocial behavior is provided by a couple of other experiments. These experiments reveal that OT is able to enhance cognitive and emotional empathy. In one of the experiments, subjects had to infer the mental state of a person through the eyes in a "Reading the Mind in the Eyes Test" (a cognitive empathy test) (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Mind reading is involved in almost all social interactions between humans. This study showed that intranasally administered OT causes a significant increase in the ability to read the mind. Improved inference of other's internal state could help to reduce ambiguity in social interactions and, thereby, it might improve social approach, affiliation and trust (Domes et al., 2007). Another experiment carried out by Guastella and colleagues (Guastella, Mitchell, & Dadds, 2008) supports these findings. Men who were given an intranasally dose of OT fixated more and gazed longer to the eye region of face stimuli on a screen than placebo controls, in this study. The combined results of both studies show that OT might be able to improve communication between persons, because of the hormone's ability to improve inference of another's emotions. Improved inference of another's emotions by OT might occur via a mechanism that influences eye-gazing, which, in turn, enhances face-perception (Domes et al., 2007; Guastella et al., 2008). In addition, Guastella et al. suggested in their report that improvement of eye-gazing could be the result of inhibition of amygdala activity by OT. A reduction in amygdala activity might help participants to calm down, thereby allowing them to make direct eye contact. This hypothesis is in line with the previously discussed theory concerning OT's influence on amygdala activity and diminished fear in lactating mammals.

3. Oxytocin, the love hormone?

In the previous chapter I reviewed animal studies that show the involvement of OT in bonding, affiliation and maternal behavior. Furthermore, the last paragraph showed that OT appears to have a clear effect on prosocial behavior in humans. Therefore, the results discussed so far suggest that OT could be seen as a "love hormone". However, as mentioned before, OT has also been found to influence aggression in various species. Moreover, a couple of recent studies have shed new light on the function of OT and the findings call into question the view of OT as a "love hormone".

Results of a study by De Dreu et al. (De Dreu et al., 2010) show that OT has a role in the regulation of intergroup conflicts, by promotion of parochial altruism. People who display parochial altruism sacrifice themselves to benefit the group they belong to (the in-group), while they aggress against the out-group. Out-group aggression could be driven by the wish to increase the status and power of the in-group, compared to the out-group. It could also be driven by the wish to defend and protect the in-group against threat. In the first experiment of this study, males played the "intergroup prisoners' dilemma-maximizing differences game". Participants had to decide how much money they kept for themselves (every Euro kept was worth €1.-) and how much they contributed to the within-group pool (every Euro added €0.50 to all members of the in-group) and the between-group pool (every Euro added €0.50 to all members of the in-group and subtracted €0.50 from each out-group member). Contributions to the within-group pool were associated with in-group love, while contributions to the between-group pool were associated with out-group hate. Males who had taken OT were more likely to be in-group lovers. In fact, 58% of the participants in the OT condition were in-group lovers, as compared to 20% in the placebo condition. There was no significant difference between the placebo and OT condition for out-group hate. In another experiment of the same study, participants made decisions between cooperation or non-cooperation with the out-group. Decisions made by the in- and out-group yielded four different payoffs (see figure 6) in the following order: temptation (T), reward (R), punishment (P) and sucker (S). Across the game, payoffs were manipulated in such a way that the magnitude of greed and fear varied. In the case of greed, participants would get higher outcomes for non-cooperation when the out-group was to cooperate. In the case of fear, participants would get higher outcomes for their in-group for non-cooperation when the out-group was to non-cooperate.

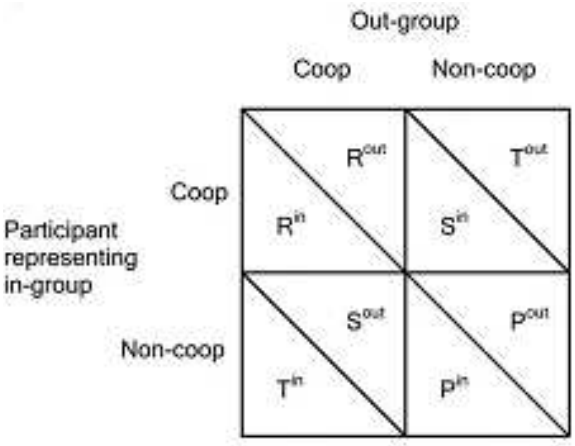

Figure 6: between-group prisoner's dilemma game

Payoffs to the in-group (in) are found below the diagonal line in each cell and payoffs to the out-group (out) are found above the diagonal line in each cell. Non-cooperation by the in-group, while the out-group cooperates yields the most money for the in-group (De Dreu et al., 2010).

They found that OT promotes non-cooperation toward the out-group, especially when fear for the out-group is high. This finding shows that OT is able to cause increased defense-motivated aggression, aggression toward the out-group to protect the in-group. This might be in line with the previously mentioned findings in animals concerning maternal aggression. OT has been found to influence aggression in several species and this type of aggression serves to protect the offspring from intruders (Campbell, 2008).

Findings of another study by De Dreu et al. (De Dreu, Greer, Van Kleef, Shalvi, & Handgraaf, 2011) suggest that OT also promotes ethnocentrism. Ethnocentrism is the tendency to believe one's group is centrally important and superior to other groups. In one experiment, participants had to combine words with a positive or negative valence with the name of an in-group or out-group member. Out-group targets were Germans and immigrants from the Middle Eastern. Results showed that OT promotes in-group favoritism. In-group favoritism was computed by subtracting latencies for out-group/positive word blocks from latencies for in-group/positive blocks. In addition, male participants who had received intranasal OT associated secondary emotions, like humiliation, more with members of their in-group than with members of the out-group (Muslim). This finding also shows that OT promotes in-group favoritism. Moreover, OT treated males were more likely to sacrifice out-group targets, persons with an Arab or German name than in-group targets with a Dutch name, in a moral choice dilemma task. This tendency was driven by a decreased readiness to

sacrifice in-group members. In sum, these three experiments together show that OT promotes in-group favoritism.

Both studies by De Dreu and colleagues illustrate that OT cannot really be seen as a "love hormone", because it promotes in-group favoritism and parochial altruism. Both can lead to conflict and violence between groups (De Dreu et al., 2011). Although OT seems to stimulate prosocial behavior in humans, this behavior might be restricted to members of the in-group.

Discussion and conclusion

This thesis discussed the role of the hormone oxytocin in social behavior. Various studies have shown that oxytocin plays a role in establishing maternal bonds and bonds between pairs in monogamous species. Maternal care in various species is also highly coordinated by oxytocin. Although human social behavior is less coordinated by hormones like oxytocin, this hormone seems to play a role in prosocial behavior, trust and empathy in humans. However, results of recent studies suggest that oxytocin cannot really be seen as the hormone of love and cuddling, because oxytocin appears to promote ethnocentrism and parochial altruism in humans. Both could lead to intergroup conflict and violence. Promotion of love by oxytocin seems to be restricted to members of one's own group. Moreover, oxytocin has been found to play a role in maternal aggression in various mammals.

Precise mechanisms through which oxytocin acts to facilitate social behavior in animals and human are not known. A couple of researchers have speculated that pair bonding and mother-infant bonding result from coupling of the oxytocin system with the dopamine reward circuitry in the brain of certain animals, but further research is needed to elucidate the exact brain mechanisms and to clear up the sometimes conflicting results.

Although it has been shown that oxytocin promotes human in-group love and in-group favoritism, the question remains how oxytocin is able to specifically promote love toward in-group members. My hypothesis is that oxytocin helps to discriminate between in- and out-group members, in a similar way as might occur during selective bonding in animals. It has been thought that oxytocin in the olfactory bulb of sheep acts to facilitate the link between odor memory of the lambs and the motivational system (Levy et al., 1995). It does not seem likely that odor memory formation per se is the mechanism in humans through which in-group members are recognized. However, my hypothesis would be that oxytocin assists in

learning and recognition of other, specific, group characteristics and, in turn, facilitates coupling between social recognition systems and the dopamine reward circuitry. In this way, oxytocin helps motivating humans to specifically love and trust members of one's own in-group (Figure 7). This suggestion is in line with prior studies that have shown that oxytocin causes improvement of face perception in humans (Guastella, Mitchell, & Dadds, 2008) and improvement of social learning and sensory cue processing in mice (L. J. Young & Wang, 2004). It might be speculated that oxytocin causes a general improvement of processing of sensory input in humans as well, which, in turn, could lead to better learning and recognition of in-group characteristics.

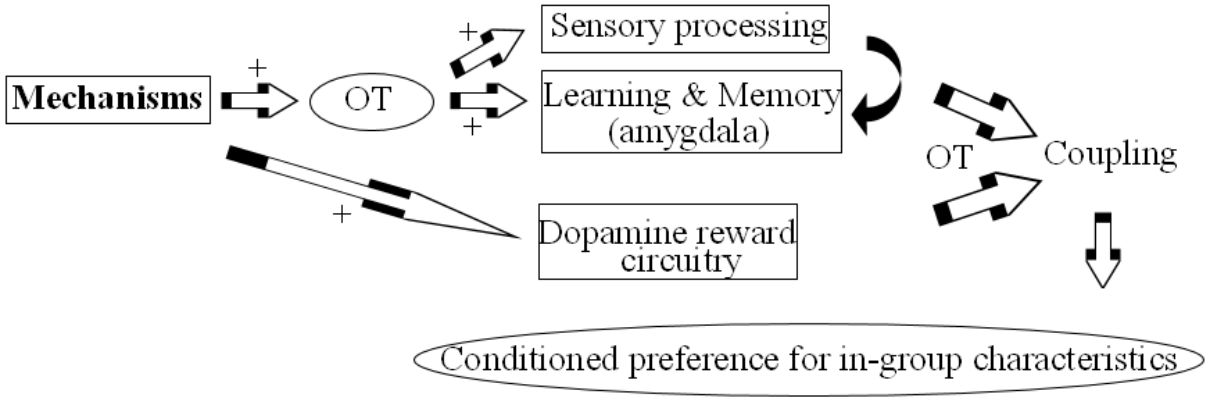

Figure 7: A proposed model for in-group preference

In this model, oxytocin stimulates preference for in-group characteristics via coupling between social recognition systems and the reward system.

OT: oxytocin, + : stimulation

I must stress that the model described here is oversimplified. It is likely that other neurotransmitters and hormones play a role as well in establishing in-group favoritism. Moreover, higher-order brain structures are not mentioned, but are also likely to influence preferential behavior toward in-group members in humans. However, this model could provide a framework for understanding how oxytocin might influence in-group favoritism and for testing hypotheses on this topic.

Future research could invest in testing this model, by combining in-group preference experiments with oxytocin treatment in an fMRI study. In-group preference experiments have already been combined with fMRI in prior studies (Cikara et al., 2010; Hein et al., 2010).

However, none of these experiments have looked at the effect of oxytocin administration on the brain. Cikara et al. (Cikara et al., 2010) subjected participants to a moral dilemma task in the scanner and found activation of the medial and left dorsolateral prefrontal cortex, the anterior cingulate cortex and the left lateral orbitofrontal cortex when subjects sacrificed out-group targets to save in-group targets. Hein et al. (Hein et al., 2010) analyzed helping behavior toward in- and out-group members suffering pain. Helping an in-group member was predicted by insula activation, while not-helping the out-group member was predicted by nucleus accumbens activation. This last observation could mean that seeing a negatively evaluated out-group member in pain also activates reward processing areas.

To test the proposed model, one could, for example, subject participants to an adapted version of the helping task described above. It is, however, important that emphasis is on helping an in- or out-group member, rather than on sacrificing one of them. This is important in order to be able to investigate brain processes in response to in-group favoritism only. If the proposed model is correct, one would expect to find increased brain activity in regions associated with reward and social recognition when helping or saving an in-group member, in a in-group versus out-group member-trial. In contrast, one would expect to find significantly less activity in these areas during trials in which participants have to choose between two out-group or two in-group members. Moreover, activation of social recognition areas during in-group versus out-group member-trials should be increased in oxytocin treated subjects, as compared to control subjects.

The final point to stress is that, given the effect of oxytocin on social cognition in humans, a better understanding of oxytocin system might have important implications for the treatment of individuals with disorders that involve social deficits, like social phobia and autism (Kosfeld et al., 2005). However, a better understanding of the mechanisms underlying social behavior might also give rise to some ethical issues concerning the use of oxytocin. Commercially available oxytocin could, for example, be used as a “trust spray” to manipulate stock market investments. Oxytocin might also be used in politics to promote in-group love for a specific political party and out-group hate against other parties. The question is, however, whether or not people should be allowed to use oxytocin for such commercial purposes.

Given that oxytocin is involved in promotion of in-group love and out-group hate, it would also be interesting to investigate whether oxytocin has an influence on political party preference. For example, it might be speculated that supporters of extreme right-wing political parties are more likely to have high levels of oxytocin.

In sum, it has become clear that oxytocin inluences animal and human social behavior. Oxytocin has been found to promote prosocial behavior in humans, but this behavior might be restricted to members of one's in-group. Because of the latter and because oxytocin promotes defense-motivated aggression, the hormone cannot be seen as the traditional "love hormone". In any case, further research is still needed to understand exactly how oxytocin is able to influence social behavior. This is especially important given the potential implications of oxytocin in the treatment of certain psychiatric disorders.

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