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Oxytocin and the Neural Mechanisms Regulating Social Cognition and Affiliative Behavior

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Abstract

Oxytocin is produced in the hypothalamus and released into the circulation through the neurohypophyseal system. Peripherally released oxytocin facilitates parturition and milk ejection during nursing. Centrally released oxytocin coordinates the onset of maternal nurturing behavior at parturition and plays a role in mother-infant bonding. More recent studies have revealed a more general role for oxytocin in modulating affiliative behavior in both sexes. Oxytocin regulates alloparental care and pair bonding in female monogamous prairie voles. Social recognition in male and female mice is also modulated by oxytocin. In humans, oxytocin increases gaze to the eye region of human faces and enhances interpersonal trust and the ability to infer the emotions of others from facial cues. While the neurohypopheseal oxytocin system has been well characterized, less is known regarding the nature of oxytocin release within the brain. Here we review the role of oxytocin in the regulation prosocial interactions, and discuss the neuroanatomy of the central oxytocin system.

1.1 Introduction

Oxytocin (OT), derived from Greek meaning “rapid birth,” is a nine amino acid, cyclic neuropeptide produced in the brain that has well characterized functions both on peripheral reproductive tissues and in the central nervous system [for a review see: [1]]. This molecule has an impressive history in the biological sciences. In 1906, Sir Henry Dale found that extracts of the posterior lobe of the pituitary contained substances that promoted contractile activity of the uterus [2]. OT was the first peptide to have its structure chemically identified and synthesized in the laboratory, leading to a Nobel Prize for Vincent du Vigneaud in 1955. Later neuroanatomical studies revealed that in the brain, OT is synthesized primarily in magnocellular neurons of the hypothalamus which project directly to the posterior pituitary where it is released into the bloodstream. This neurosecretory component of the OT system is known as the neurohypophyseal OT system, and it plays a critical role in the onset of parturition and milk ejection during lactation. For the past seventy years, the neurohypophyseal OT system has been a quintessential neuronal model for understanding the regulation of neurosecretion and more recently of dynamic neuronal-glial interactions [3,4]. Beginning in the late 1970's, pharmacological studies began to reveal a role for OT not only in birth and lactation, but in coordinating a suite of behavioral changes in the mother necessary for the survival of the

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offspring, i.e. maternal behavior. Since that time, it has become apparent that OT has many functions within the brain, modulating a constellation of behaviors associated with sociality. While many of the early studies have focused on the role of OT in regulating female behavior with a focus on reproduction, it is now clear that OT modulates social cognition and affiliative behavior in both sexes. In contrast to the well understood neurosecretory OT system, the neuroanatomical details of central OT release have been woefully understudied. In this review, we will focus on OT's role in regulating a subset of its central nervous system affects; social cognition and affiliative behaviors. We will first review the literature pertaining to its role in initiating maternal nurturing behavior and the mother-infant bond. We will then briefly describe studies demonstrating a role for OT in the formation of social memories. Then we will review in detail the growing literature suggesting that OT is involved in social bond formation in monogamous rodents. We also briefly discuss the evidence that OT modulates social cognition in humans. Finally, we will discuss recent neuroanatomical studies on the OT neuronal systems that likely regulate affiliative behaviors in rodents. We will then speculate on how the central OT system is organized to promote the coordination of peripheral physiology and behavioral changes associated with reproduction.

1.2 Coordinating Birth and Parental Care

During pregnancy and parturition, a series of hormonal changes occur i) to prepare the womb for nurturing the developing fetus, ii) to facilitate delivery and iii) to produce nutrients for the offspring after birth. These include a rise and fall in progesterone, a steady increase in estrogen, and release of pituitary hormones, including OT and prolactin (for a review see [5]). These hormones prepare the uterus for supporting the placenta, are involved in initiating birth, and are critical for the lactation process. However, it is clear that each of these signaling molecules are also critical for the change in behaviors of the mother that are necessary for the survival of her offspring. Thus, nature uses conserved biochemical pathways to coordinate peripheral physiology with behavioral motivation. Here we will focus on the role of OT in regulating the maternal brain, with an emphasis on the induction of maternal nurturing behavior and the mother-infant bond.

1.3 Maternal Care in Rodents

In most rodents, virgin females are either indifferent to, or have an aversion to, conspecific pups. However, around the time of birth, there is a dramatic shift in behavior of the dam towards maternal nurturing behavior. In rodents, maternal behavior includes nest building, retrieving pups to the nest, licking and grooming, hovering over, and nursing pups. Adult nulliparous female rats are neophobic and will avoid or attack pups presented to them. This fear of pups diminishes at the time of parturition and pup odors become attractive. However, a virgin female will eventually begin caring for pups if exposed to them over multiple days [6]. The first suggestion that OT plays a role in regulating the onset of maternal behavior came from a study showing OT injected into the cerebral ventricles (ICV) of a virgin rat could produce nurturing behavior towards pups within two hours [7]. Since this initial study, there have been conflicting reports possibly due to strain differences and testing protocol [8,9]. It has been determined that along with OT, estrogen priming, as well as anosmia, will increase the probability of spontaneous maternal care in virgin rats [10,11]. Support for the role of endogenous OT in regulating maternal behavior has been derived from studies showing that an OT antagonist or OT antisera infused into the brain blocks the onset of maternal behavior in rats that have just given birth [12] [13]. OT appears to play a more important role in regulating the onset of maternal behavior than the maintenance of maternal behavior since OT antagonists fail to inhibit maternal behavior once nurturing behavior has been established [13].

Genetic experiments using mice with a deletion in either the OT or oxytocin receptor (OTR) gene have supported these initial pharmacological studies in rats. In addition, they have challenged the long held belief that OT is critical for the onset of parturition. Surprisingly, OT knock-out (OTKO) and OTR knock-out (OTRKO) mice give birth on time and without incident [14,15] [16]. Thus, while OT may play an important role in initiating parturition, there appears to be redundant mechanisms whereby prostaglandin activation is able to compensate for the loss of OT to promote labor [17]. Although these genetically altered mice were able to give birth, they were unable to lactate, confirming an essential role for OT in lactation. As a result, their pups perish within 24 hours of birth.

Initial results in two independently generated OTKO lines of mice produced paradoxical results with regard to the role of OT in regulating maternal behavior [14,16]. In both lines, maternal motivation appeared grossly normal. Indeed, even virgin mice of these strains displayed pup retrieval and licking and grooming behavior [18]. Later, however, more detailed studies of these mice revealed that nulliparous OTKO mice displayed decreased levels of retrieval and licking and grooming of pups compared to wild-types [19]. In a separate study, OTKO mice housed in a social semi-natural environment were significantly more likely to display infanticidal behavior than wild-type mice in the same environment [20].

Compared to peptide knock-out mice, receptor deficient females display a more robust deficit in maternal behavior. Both wild-type and OTRKO post partum females build nests and crouch over their pups. However, pups of knock-out females are often observed scattered throughout the cage. When tested for pup retrieval, OTRKO dams display longer latencies to retrieve the pups and spend less time crouching over their pups [15]. The discrepancy between the results of maternal behavior testing in OTKO and OTRKO mice suggest that in OTKO mice another ligand, perhaps vasopressin, partially compensates for the lack of OT, allowing for the expression of maternal behavior.

Other knock-out mouse studies provide additional evidence for a role of OT involvement in the regulation of maternal behavior. Mice lacking CD38, a transmembrane receptor involved in the immune response and mobilizing of Ca^{++} from intracellular stores, display maternal nurturing deficits almost identical to the retrieving and crouching deficits seen in OTRKO dams. Furthermore, studies revealed that these mice display deficits in OT release. Interestingly, a subcutaneous infusion of OT rescued the deficits in maternal nurturing [21]. A second line of mice provides circumstantial evidence that is consistent with a role for OTR in regulating maternal behavior, although alternative explanations are equally plausible. The OTR is a seven transmembrane G-protein coupled receptor that signals through the G(q/11) family [22]. Mice have been generated that lack the alpha-subunits of the two main members of the G(q/11) family, Galpha(q) and Galpha(11), selectively in the forebrain. These forebrain Galpha (q/11)-deficient females have a profound deficit in maternal behaviors. They do not display nest building, pup retrieving, crouching, or nursing [23]. Taken together, these genetic manipulation studies provide convincing evidence that OT plays a role in some aspects of maternal nurturing behaviors in mice.

There is some evidence that natural variation in maternal nurturing received by pups alters brain OTR expression levels, which in turn may alter the quality of maternal behavior that they provide to their own offspring when they reach adulthood. Post partum rat dams can be classified as high licking and grooming (LG) or low LG. In cross fostering experiments, pups reared by high LG dams display high LG when they become mothers, while pups reared by low LG mothers display low LG when they become mothers, regardless of the maternal behavior of their biological mother [24]. High LG moms have increased OTR density in the medial preoptic area, bed nucleus of the stria terminalis, lateral septum, amygdala and the paraventricular nucleus of the hypothalamus (PVN) compared to low LG moms [25].

Furthermore, infusion of an OTR antagonist reduces LG levels in high LG dams [26]. The maternal nurturing received as pups has a long term impact on OTR expression in the brain as female pups reared by high LG dams have increased OTR binding in the central amygdala when they reach adulthood [27]. Post-weaning social and environmental enrichment also affects both maternal behavior and adult OTR densities in the brain. Pups from low LG dams weaned into socially and environmentally enriched cages display higher LG and elevated OTR density than LG dams weaned into impoverished isolated housing conditions [28]. Thus it appears as though the transgenerational transmission of maternal behavior may be mediated by changes in the expression of OTR.

1.4 Maternal Bonding in Sheep

Rodents typically display promiscuous maternal behavior, and maternal dams will nurture any pup placed in her nest. There is no particular bond between the mother and the pups, since the likelihood of a foreign pup being in the dams nest is rather low. However, ungulates such as sheep live in large herds and give birth to precocial young during a defined breeding season. Mothers therefore need to discriminate between their own lamb and foreign lambs, and have subsequently evolved mechanisms to produce selective maternal-infant bonds. Vaginocervial stimulation during labor initiates a cascade of neurochemical events that ultimately leads to the development of the selective bond between the mother and the lamb [29]. The selective bond appears to be mediated in part by the development of an olfactory memory of the lamb which occurs in the main olfactory bulb [30]. Once the odor is learned, the mother actively rejects any other lamb from nursing. Vaginocervical stimulation is a potent releaser of OT in the ewe [31], and is capable of promoting adoption of a foreign lamb in estrogen-primed ewes [32]. Furthermore, OT administered intracerebroventricularly can induce full maternal behavior in less than a minute in estrogen-primed nonpregnant ewes [33]. In addition to initiating maternal nurturing behavior, OT also facilitates the formation of olfactory memories by modulating noradrenaline and influencing the release of neurotransmitters in the olfactory bulb. After giving birth, there is a strengthening of the mitral to granule and periglomerular cell synapses to bias the network to respond to lamb odor, with a higher number of output mitral cells responding to the ewes own lamb odor [34-36]. As a consequence of this olfactory learning, the ewe accepts her own lamb, but rejects foreign lambs, indicative of a selective mother-infant bond.

1.5 Alloparental Behaior in Voles

Monogamous prairie voles (*Microtus ochrogaster*) have been instrumental in understanding the role of OT in the regulation of affiliative behaviors. Prairie voles display biparental care and often nest in communal dens comprised of a breeding pair and multiple litters of their offspring [37]. Perhaps as an adaptation to this communal living, prairie vole juveniles and some adult females display nurturing behavior toward pups who are not their own. This “baby sitting” behavior is referred to as alloparental care, and provides an opportunity to investigate the regulation of maternal-like behavior in the absence of the physiological changes associated with pregnancy and parturition. The majority of juvenile prairie voles (< 20 days of age) display high levels of alloparental behavior when exposed to novel pups [38]. However, as females reach puberty, only about 50% of the females will spontaneously retrieve, lick/groom, and hover over pups presented to them, with the remainder of the females either ignoring or attacking pups [38-40]. The transition from juvenile to adult patterns of alloparental behavior in females does not appear to be related to changes in sex hormones [40]. In prairie voles, the rearing environment is able to influence the amount of affiliative behaviors exhibited as an adult. For example, females are more likely to be alloparental as adults if they remain in the natal nest after weaning, with continued exposure to parents being a more critical factor than

previous pup exposure [41]. The presence of the father in the natal nest also increases the amount of time juveniles spend in alloparental behavior towards their younger siblings [42].

While gonadal steroids do not appear to influence the expression of alloparental behavior, there is evidence that OT may play an important role, at least in female prairie voles. There is a remarkable amount of individual variation in OTR density in the nucleus accumbens (NAcc) in prairie voles, and OTR density in the NAcc is significantly correlated with the display of alloparental behavior in both juvenile and adult virgin females [43,44]. Indeed, adult females that display alloparental behavior have higher densities of OTR in the NAcc than those that either ignore or attack pups [44] (Figure 1A, B). Administration of an OT antagonist into the NAcc, but not into the adjacent caudate, is able to block all expression of maternal-like behavior towards pups in adult females (Figure 1.C). This relationship between OTR density in the NAcc and the natural variation in alloparental behavior in adult female prairie voles led us to hypothesize that differences in OTR density in the NAcc could directly contributes to individual differences in behavior. To test this hypothesis, we used a viral vector expressing the prairie vole OTR gene to enhance the OTR density in the NAcc of adult females. We expected to see that increased OTR expression would lead to a higher proportion of females displaying alloparental care towards pups. However, there was no difference between OTR viral injected and control groups in the proportion of females displaying alloparental behavior [45]. These results suggest that perhaps the level of OTR during development, when the pups are interacting with their mother and siblings, is critical for shaping nurturing behavior in adulthood. For example, a single treatment with OT 24 hours after birth alters the expression of alloparental behavior in female prairie voles when they reach adulthood [46]. The mechanism by which OT produces these long-term effects are unknown, but suggest that like gonadal steroids, OT can have both activational and organizational effects on social behavior.

1.6 Pup-Mother Interactions

There is some evidence that OT may also modulate the infant's response to the mother. For example, when mouse pups are separated from their mother, they emit ultrasonic vocalizations in protest of the separation. OTKO and OTRKO pups emit significantly fewer vocalization following separation from their mother than do wild-type littermates [15,47]. This difference could reflect differences in emotionality (e.g. anxiety-like behavior), but could also reflect a decreased motivation to be in contact with the mother. To support this latter interpretation, tests were performed in OTKO pups to assess motivation to reunite with their mother. In the first test, 10 day old pups were placed in one chamber of a two chambered testing arena in which the mother was restricted to the other chamber. After an initial training trial, OTKO pups exhibited a significantly longer latency than wild-type pups to cross into the mother's chamber in the second and third trials (Young, unpublished data) (Figure 2). The second test used a three-chambered arena to determine if 15 day old pups exhibited a preference for their mother over a novel lactating female. Wild-type pups showed a strong preference for their mother, spending significantly more time in the mother's chamber than with the novel female. By contrast, OTKO pups show no preference (Young, unpublished data). OT also appears to influence the attraction of the pups to their mother since OT antagonist is able to block a preference for maternal odors in 15 day old rat pups [48]. In this experiment, pups were conditioned to a lemon odor associated with maternal reunion. This was done by removing the pups from the maternal nest for three hours and then returning them to their now lemon-scented mother or to a control lemon-scented cotton ball. Pups were given OT-antagonist or saline ICV before placement with the lemon odor. When tested the next day, pups that had received OT-antagonist did not show a preference for the maternal-associated odor, while those receiving saline did.

1.7 Social Bonding in Adults

Monogamous prairie voles have become an important model for understanding the neurochemical basis of social bond formation between mating pairs, known as the pair bond. In nature, a large percentage of mating pairs nest together for extended periods of time and display biparental care [49]. In the laboratory, the formation of a pair bond has been investigated by using a partner preference test [50]. In this test, a male and female are paired and allowed to co-habitate, during which time mating may or may not occur. At the time of testing, the co-habitation partner is tethered to one side chamber of a three-chamber apparatus. A novel animal of equal stimulus value, termed the 'stranger', is tethered to the opposite side chamber. The test animal is placed in the center chamber and allowed to explore all three chambers freely. The amount of time this test animal spends in close proximity to, or huddling with either the partner or the stranger is recorded over a three hour testing period. The experimental animal is said to have a partner preference if it spends at least twice as much time in contact with the partner compared to the stranger [51].

Females who have cohabitated with a male typically display a partner preference if mating occurs. However, longer cohabitations without mating can also result in the development of a pair bond. Because of the role that OT plays in mother-infant attachment, and since mating results in vaginocervical stimulation, which is known to release OT in the brain, OT was a prime candidate for regulating the formation of the pair bond. Indeed, there is now convincing evidence that OT plays a critical role in the development of partner preferences in female prairie voles. Intracerebroventricular infusion of OT during a six hour cohabitation period with a male is able to induce a partner preference in unmated female prairie voles [52]. Likewise, an OT antagonist blocks mating-induced pair bond formation after a 24 hr cohabitation [51]. The role of OT in partner bonding in male prairie voles is less clear. The original study in males showed that ICV infusion of OT for 24 hours was not enough to induce a pair bond, nor did OT-antagonist inhibit partner preference formation [53]. However, another group found that a central infusion of a high dose of OT followed by a one hour cohabitation was enough for males to prefer a partner over a stranger. Conversely, giving either an OT-antagonist or a vasopressin antagonist blocked OT-induced partner preferences [54]. These data suggest that exogenous OT may stimulate partner preference formation in males through interactions with the OTR and vasopressin receptors, but it is not clear whether endogenous OT is released in males during mating, or whether it contributes to partner preference formation in males. Rather, the related peptide, vasopressin appears to play a more important role in partner preference formation in male prairie voles, particularly since OT antagonists have not consistently been shown to prevent partner preference formation in males [53,55,56].

Comparative studies in voles with different social organizations have been useful for identifying the neuroanatomical substrate on which OT acts to promote partner preference formation. For example, monogamous and non-monogamous species of voles have remarkably different distributions of OTR within the brain. Prairie voles have significantly higher densities of OTR in the NAcc than non-monogamous meadow and montane voles [57] (Figure 3A,B). To test whether these areas are involved in partner preference formation, OT antagonist or vehicle was injected site specifically into the NAcc, prefrontal cortex, or caudate putamen of female prairie voles prior to cohabitation with a male. Following pairing, the females were tested for a partner preference. Females receiving vehicle into any brain region or OT antagonist into the caudate putamen formed a partner preference, while those receiving the antagonist into the NAcc or prefrontal cortex failed to display a partner preference [58] (Figure 3C). Recently, *in vivo* microdialysis has been used to show that extracellular concentrations of OT increase in the NAcc during mating in female prairie voles and the release is more readily detected during mating bouts than during non-contact social exposure [59].

In addition to the remarkable species differences in the expression of OTR in the NAcc, there is also significant individual variation in receptor density among individual prairie voles, which we suspect may contribute to natural variation in affiliative behavior. As mentioned above, OTR density in the NAcc correlates with the likelihood of displaying alloparental behavior. There is evidence that individual variation in accumbal OTR density may also contribute to variation in the development of adult social attachments. By using an adeno-associated viral vector carrying the prairie vole OTR gene, we were able to increase the levels of OTR in the NAcc of adult female prairie voles, as mentioned above (Figure 4A,B). These OTR-enhanced females took less time to form a partner preference than controls, indicating that higher levels of OTR in the NAcc accelerates pair bond formation (Figure 4C). However, increasing accumbal OTR in female meadow voles was not sufficient to induce partner preference formation in this asocial species [45]. These results suggest that variation in OTR density in the adult NAcc directly modulates the ability to form social attachment, in contrast to the results on alloparental behavior discussed above. Further, it suggests that OTR expression in the NAcc is not sufficient to produce the species differences in bonding behavior seen between meadow and prairie voles. Rather, species differences in OTR expression in additional areas, throughout development, or in other neurotransmitter systems altogether may contribute to the species differences in social bonding in female voles.

The NAcc is a key component of the mesolimbic dopamine reward/reinforcement pathway and has been implicated in mediating the effects of drugs of abuse as well as addiction [60] [61]. In addition to a high density of OTR, the NAcc of prairie voles also contains dopamine projections from the ventral tegmental area, and dopamine receptors. Blocking D2-like dopamine receptors in the rostral shell of the NAcc prevents partner preference formation, and D2 agonists induce partner preferences in the absence of mating [62]. Activation of D1-like DA receptors inhibits partner preference formation induced by either mating or by D2 activation [63,64]. Aragona and colleagues have begun to elucidate the second messengers involved in DA receptor mediated partner preference formation. They found that reducing cAMP signaling in the shell of the NAcc also facilitates partner preference formation. Conversely increasing cAMP signaling, by decreasing PKA activity, blocks mating-induced partner preference [65]. These results are consistent with the fact that D2 receptor activation decreases cAMP while D1 receptor activation stimulates cAMP production. The dopamine and OT system interact in the NAcc of female prairie voles to promote partner preference formation. A seminal study showed that OTR and D2 receptor activation must occur concurrently for partner preference to develop in female prairie voles [66]. Blockade of D2 receptors in the NAcc shell prevented OT-mediated partner preferences, while blockade of OTR in the NAcc shell prevented D2 receptor mediated partner preferences in female prairie voles. Future studies are needed to determine whether and how the second messenger systems of OT and DA interact to produce a partner preference.

The fact that OT is involved in mediating maternal nurturing, mother-infant bonding, alloparental behavior and pair bonding raises an intriguing hypothesis about the evolution of pair bonding in monogamous species. Maternal behavior is present in all mammalian species, while pair bonding has evolved multiple times independently in unrelated monogamous species, and is quite rare. We propose that the ability a female to form an attachment with her male partner arose from a modification of the cellular machinery and circuitry involved in regulating maternal behavior. Indeed, OTR in the NAcc is involved in both alloparental nurturing behavior and partner preference formation. Vaginocervical stimulation during parturition stimulates central OT release, while similar stimulation during mating bouts also promotes OT release. We predict that similar exaptations of maternal behavior circuitry may have occurred in the evolution of monogamy in other species as well. It will be important to determine if OT is involved in pair bonding in other monogamous species as well.

1.8 Social Recognition in Rodents

We hypothesize that pair bond formation is the result of an association between the rewarding mating experience and the olfactory signature of the partner [55]. The ability to distinguish familiar conspecifics from strangers and to remember individuals previously encountered is critical for successful group living and survival in many social species. This process is called social recognition, and OT has been shown to be important for this memory ability (for a detailed review see Choleris in this issue [67]). The modulation of social recognition in rodents was first investigated in rats [68], and central injection of low doses of OT enhanced the amount of time a male remembers a conspecific [69,70]. There have been many sites of action implicated for OT in rat social recognition, including the ventral hippocampus, septum, medial preoptic area, and olfactory bulb [71-74]. It should be noted that although OT in these areas have been shown to enhance memory, antagonist to the OTR have not been able to block memory performance. Thus the mechanism by which OT acts in these regions to enhance social recognition is unclear. It is known, however, that OTs effects in the olfactory bulb on social recognition are mediated by norepinephrine [75,76].

Studies of OTKO and OTRKO mice have been instrumental in further investigating the mechanisms by which OT enhances social recognition [15,77-81]. OTKO mice have been studied most extensively with regard to the neuroanatomical localization of OT actions in mediating social recognition. Social recognition is assessed by quantifying the duration of olfactory investigation upon repeated exposure of the experimental mouse to a stimulus mouse. Wild-type mice habituate to familiar mice as reflected by a decreased investigation time over subsequent exposures. However, OTKO males fail to habituate after repeated exposures to the same mouse [78]. This is not due to deficits in general learning and memory or olfaction since they do habituate to non-social odors [78]. A single intracerebroventricular infusion of OT before, but not after, the initial exposure completely rescues the deficit in social recognition [82]. This suggests that the deficit in OTKO mice lies in the processing of the olfactory signals or encoding the memory. Analysis of neural activation patterns using Fos immunohistochemistry revealed that following a social encounter, Fos activation is normal in the olfactory bulb, but is markedly impaired in the medial amydala and downstream projection sites of the amygdala [82]. Site-specific infusion of OT into the medial amygdala, but not into the olfactory bulb rescued the social recognition deficits [82]. Likewise, infusion of OTR antisense oligonucleotides into the medial amygdala of wild-type females impairs social recognition abilities [83]. The medial amygdala receives olfactory information directly from the olfactory bulb and is therefore in an exquisite position to process social odors. OTKO female mice also are unable to discriminate parasite load on potential mates, which would increase their risk of infection [79]. OTRKO mice had a milder deficit in social recognition in that they were unable to distinguish inbred mouse strains (C57BL/6) but could differentiate females of an outbred strain (CD-1) [15]. The reason for the milder deficit on social recognition is unknown, but could involve some compensation by other systems, such as vasopressin, since OTRKO mice experience no OTR activation at all throughout development, while OTKO mice may experience OTR activation induced by vasopressin.

A further line of evidence suggesting that OT is required for social recognition comes from studies in the CD38-KO mouse mentioned above. This mutant has a deficit in OT secretion and is also impaired in its ability to recognize familiar conspecifics. Expressing CD-38 in the hypothalamus using a lenti-viral vector or by infusing OT was able to rescue this deficit [21].

These studies suggest that OT is involved in enhancing the processing of social information. Precisely how OT enhances social information processing is unknown, but it may serve to mark the social signal with saliency or alter the valence of the signal. It is unknown whether OT is involved in the processing of social information of other modalities (e.g. visual, auditory), or

whether it is specific for olfactory information. However, we hypothesize that OT may be acting in multiple brain regions to enhance the saliency of social stimuli and to encode social memories, and that this may play a pivotal role in mother-infant interactions, pair bond formation, as well as in the formation of other social relationships.

1.9 Mediation of the Positive Effects of Social Support: stress response and immune function

In social species, social support provides beneficial effects on immune function and stress reactivity. There is some evidence that OT may play a role in mediating these effects but more research is needed in this area, particularly with respect to immune function (for a review see Neumann in this Issue [84]). Functioning of the immune system has become of interest in the context of autism spectrum disorders since these disorders have been associated with a vulnerability to toxins and excessive food allergies [85-88]. Social support accelerates healing time and can be beneficial to those dealing with potentially fatal diseases [89]. When stressed, wounds are bigger in isolated than paired hamsters [90]. However wound size was similar in groups that were pair housed and stressed, pair housed with no-stress, and isolated with no-stress. Cortisol levels post-stress are higher in isolated than paired individuals and wound size is larger in stressed than adrenalectomized individuals with stress or no-stress. In other words, stress-induced cortisol release inhibits wound healing and social housing buffers against stress-induced activation of the HPA. To test whether OT was facilitating the positive effects of pair housing, OT was given intraperitoneally to isolated animals. Treatment with OT decreased wound size and lowered the release of stress-induced cortisol; while OT-antagonist centrally administered into the ventricles impaired wound healing in paired hamsters [90]. The physical contact during pair housing may stimulate the release of OT to promote these healing effects. Innocuous somatosensory stimulation such as touch, warm temperature, vibration, and electroacupuncture increase oxytocin levels in plasma and cerebrospinal fluid [91,92].

Although these experiments suggest that OT affects wound healing by modulating the hypothalamic, pituitary adrenal axis, there is a possibility that it can directly interact with the immune system. OT and OTR are present in the thymus, the organ where lymphocytes mature into T cells that are involved in the adaptive immune system [93]. The human OTR gene has a binding site for the inflammatory cytokine nucleofactor interleukin-6 (NF IL-6) and for acute-phase response elements, which are induced by infection or inflammation [[94] for review see [93]]. Binding to these sites on the OTR gene may explain why immune elements have the ability to induce labor [for review [17,93]]. In fact, cytokines like interferon-γ, can affect OTR mRNA levels in a manner not matched by the sex hormones progesterone and estradiol [95]. In the brain, interleukin-1b directly stimulates intranuclear release of OT from the supraoptic nucleus (SON) [96]. Furthermore, infusion of interleukin-6 increases OTR expression in the brain of female rats [97]. Further studies are needed to understand the relationship between OT, social buffering, and the immune system.

1.10 Social Cognition in Humans

In recent years, pharmacological studies have suggested that OT is also able to enhance human social cognition (for a detailed review see Heinrichs in this issue [98]). When administered intranasally to human subjects, OT stimulates behaviors consistent with an enhancement of interpersonal trust during economic games [99]. In fact, when given intranasal OT, human subjects continue to trust others even after having been betrayed by another [100]. This increase in trust, and lack of feedback following betrayal may be due to a decrease in activation of circuits involved in fear processing, such as the amygdala [101] [100]. Intranasal OT also improves identity recognition memory for neutral and angry faces, independently of participant's gender [102], perhaps by increasing gaze to the eye region of human faces

[103]. A more recent study revealed that OT increased the accuracy of judging a face that the subject previously viewed as familiar [104]. This finding is remarkably consistent with the well documented role of OT on social recognition in rodents, and suggests that OT enhances social information processes from multiple modalities, including visual. Intranasal OT also improves the ability to infer the emotional state of others based on subtle facial stimuli, a phenomenon referred to as “mind reading” [105]; which could have profound effects on the maintenance of social groups.

The effects of OT on animal social behavior and the impact on social cognition in the human studies has important implications for psychiatric disorders associated with social deficits such as autism spectrum disorders and schizophrenia. A single study has reported that plasma OT is decreased in autistic subjects compared to typical control subjects [106], but this finding has not been replicated. Subjects with autism spectrum disorder or schizophrenia often do not attend to the appropriate facial cues of others [107,108]. These observations have led to the hypothesis that OT may be a viable pharmacotherapy to enhance social cognitive abilities in subjects with autism spectrum disorder [109]. In fact, a single study has shown that OT can increase autistic individuals' ability to recall emotion in a voice intonation task. A more important finding of this study was that prior exposure to OT increased the learning ability to subsequent emotional tasks [110]. Further studies are needed to determine whether targeting the OT system may be a viable treatment strategy for enhancing social cognition in psychiatric disorders.

1.11 Human Social Relationships

Animal studies have implicated a role for OT in mediating maternal behavior, mother-infant bonding, and pair bonding and beg the question of whether OT might modulate human social relationships. Data addressing this issue is scarce and inconclusive. However, there are reports that plasma OT concentrations are correlated with emotional responses of mothers to their infant. In particular, active maternal behavior, which comprises mother's gaze at infant's face, positive affect, affectionate touch, and motherese vocalizations and cognitive maternal representations, which include feelings of attachment and frequent checking behavior, are correlated with high OT levels during the first trimester and first postpartum month [111].

Another interesting possibility worthy of speculation is whether OT may play a role in human pair bonding. It has been shown that OT is increased in the plasma during sexual arousal and ejaculation or orgasm in humans [112] similar to the release seen in prairie voles during mating [59] and rats and sheep following vaginocervical stimulation [31,113,114]. Human sexuality may have evolved to promote pair bonding by the incorporation of behaviors that maximize the frequency and extent of OT release during intimacy. For example, in most species female sexual receptivity is tightly coupled to the reproductive cycle. However, in human females sexual desire has become uncoupled from fertility, resulting in more frequent copulations. Humans copulate face to face, maximizing exposure to visual stimuli of the partners face. In addition, humans are the only species where the female breast has become a secondary sexual characteristic. Indeed, nipple stimulation can be sexually arousing to both men and women [115], and both vaginocervical and nipple stimulation increases OT release in plasma [116]. Thus, in humans, sexual intimacy recapitulates the physiological stimuli of delivery and nursing, maximizing the release of OT, which may serve to strengthen the bond between the female and the male. If this speculation is correct, it would be consistent with our hypothesis that the mechanisms underlying pair bonding emerged through alterations in the mechanisms underlying the mother-infant bond.

There is evidence that early life social relationships can alter the adult OT system. In rhesus macaques, adolescents raised in a nursery by human caregivers have lower OT concentrations

in their cerebrospinal fluid compared to those raised by their mother [117]. A recent study suggests a similar phenomenon in humans. Women who experienced early childhood abuse or neglect had significantly lower levels of OT in their CSF compared to women who did not experience early abuse or neglect [118]. This provides evidence that, as mentioned above in rats, early parent-infant interactions can have enduring consequences on the OT system, which may impact adult social cognition and the ability to form social relationships. For a more detailed review of the role of OT on human behavior see Heinrichs et al., in this issue [98].

1.12 Neural Circuitry of the Oxytocin System

With the emerging interest in the central effects of OT on affiliative behavior, attention should be directed in understanding the distribution and modes of release of OT within brain regions regulating affiliative behavior. While numerous studies have documented the release of OT within the PVN and SON reviewed in [119,120], little attention has been given to the source and mode of release of OT within structures that modulate social behavior, such as the NAcc. Here we briefly describe the brain OT system, including forebrain OT projections, and speculate on the origin of behaviorally relevant OT. We will focus on the prairie vole system where appropriate.

The PVN and SON of the hypothalamus are the main sites of OT production in the brain. In the rat, there are two types of OT neurons present in the PVN, large magnocellular neurons and smaller parvocellular neurons, which differ not only with respect to size, but also with regard to their projections [121]. The SON contains only magnocellular OT cells [121,122]. In prairie voles, OT neurons can also be seen in the medial preotic nucleus, median preoptic nucleus, and preoptic paraventricular nucleus; all which are continuous with the PVN population. Additionally, individual OT labeled neurons can be found in the bed nucleus of the stria terminalis and the lateral hypothalamic area [123]. Although the soma of OT neurons are mainly restricted to the hypothalamus, OT fibers are spread throughout the entire brain. Sparse, large caliber fibers can be found in the NAcc, amygdala, lateral septum and hippocampus (Figure 5, also see Supplementary Figure 1). In the rat, one of the densest central OT projections is to the brainstem and spinal cord [122].

These dense OT fibers in caudal brain areas caught the attention of early researchers. Tracer experiments were done to determine if individual PVN cells project to the brainstem and spinal cord, to the pituitary, or both. It was found that magnocellular cells of the PVN project to the posterior pituitary; while the smaller parvocellular cells project to the hind brain or spinal cord, with 0.2% projecting to both the pituitary and brainstem [124-127]. Since these studies, it has been assumed by many in the field that all the central OT fibers originate from parvocellular cells of the PVN, creating a dissociation between the centrally projecting OT system and the neurohypophyseal system. This separation of projection targets is supported by microdialysis studies showing that peripheral and central release are dissociated under certain circumstances [128-130].

Unlike classical neurotransmitters, which are released primarily at the synaptic cleft, neuropeptide neurons can release peptide from its entire surface area [131] and can diffuse through the extracellular space due to long half-lives. Peptide specificity is achieved through a high binding affinity for the receptors, about 1000× higher than classical neurotransmitters [119,132]. Dendritic release of OT has been well characterized and is independent of neuronal firing [for review see [120]]. Ca^{++} released from intracellular stores favors dendritic release, while Ca^{++} influx from ion channels favors axonal release. Recent studies have begun to elucidate the mechanism by which dendritic release occurs. First, glutamate can trigger dendritic release of OT through the activation of NMDA receptors without producing action potentials [120]. Alpha melanocyte stimulating hormone (αMSH) evokes dendritic release of

OT and inhibits axonal release in the SON. OT neurons in the PVN and SON express the MC4 receptor that binds αMSH and triggers intracellular calcium release to evoke dendritic OT release. At the same time, αMSH inhibits electrical activity and reduces OT release from axons by releasing endocannabinoids to presynaptically inhibit afferent glutamate release [[133, 134], for review see [120,135]]. It has been speculated that dendritically released OT from the SON or PVN diffuses to distant brain regions where it activates OTRs mediating social behavior [119,120]. However, little attention has been given to the release of OT from the sparse network of OT fibers coursing through forebrain limbic regions.

As OTR in the NAcc plays a critical role in regulating alloparental behavior and partner preference formation in prairie voles, we have performed a detailed characterization of OT-immunoreactive fibers in the NAcc. The density of OTR binding in the NAcc is highly species specific, with prairie voles having high densities of receptors throughout the striatum, rats having intermediate receptor binding, and mice and meadow voles having little or no OTR binding in the Nacc (Figure 6A-C). This variability in OTR localization may provide a mechanism by which evolution acts to change social systems from one species to another, as seen between the monogamous and polygamous voles.

Since the expression of OTR varies across species, particularly in the NAcc, we were interested in knowing whether the presence of OT fibers in this area also varied concordantly. Surprisingly similar densities of OT-immunoreactive fibers are found in the NAcc of rats, mice, meadow voles, and prairie voles [59] (Figure 6D-F). A recent study in the naked mole rat has shown OT fibers are present in the NAcc of this eusocial species as well [136]. Thus it appears that in contrast to the localization of OTR, the distribution of OT fibers is remarkably conserved across species. Although not shown in a photomicrograph, OT fibers in the NAcc have been mentioned previously in rats using immunohistochemisry [122] and radioimmunoassay [137]. However, there have been no studies that have investigated the origin on these NAcc OT-immunoreactive fibers in any species.

The ultrastructure of these accumbal OT fibers has revealed that they are thick unmyelinated processes filled with dense core vesicles. A minority of these fibers form synapses (23%) and terminate mainly on spines (83%) and to a lesser extent on dendritic shafts (17%) [59]. This is in accordance with OT synapses in other areas of the brain which showed a preference for dendritic over axonal contacts [138]. Interestingly, the synaptic boutons of the OT-immunoreactive fibers were devoid of dense core vesicles. These synapses make asymmetric contacts and therefore appear to be glutamatergic. However, the majority of OT-immunoreactive elements in the NAcc are packed with OT-immunoreactive vesicles and do not posses synapses [59]. This suggests that OT may be released from the fiber surface in an *en passant* manner. From our studies, it is not possible to determine conclusively whether these processes are axonal or dendritic in nature. However, the presence of synapses associated with some terminals suggests that at least some fibers are axonal projections.

To identify the source of the OT fibers to the forebrain, we injected the retrograde tracer fluorogold (FG) into the NAcc of female prairie voles. We found that OT+ neurons that were also FG+ were only present in the PVN and the SON [59]. The SON was unexpected since it contains only magnocellular cells that are thought to project exclusively to the posterior pituitary [122]. However, there is evidence to the contrary. Lesions of the PVN and SON effect different populations of OT fibers, using radioimmunoassay [139]. Important for our investigation, both types of lesions produced a loss in caudate OT content. A study injecting 3H-leucine into the SON found multiple extrahypothalamic projections, including olfactory bulb, amygdala, cingulum, and locus coeruleus [140].

To determine if the OT-immunoreactive fibers are coming from pituitary-projecting cells, we injected FG peripherally; where it can be taken up by regions outside the blood brain barrier, such as the pituitary. In the prairie voles, the majority (~96%) of OT cells in the anterior and medial PVN contained FG. In the posterior PVN there was a dorsal group of smaller OT cells that remained unlabelled, implying that these are the parvocellular cells that project to the hindbrain [59]. In addition, the PVN cells retrogradely labeled from the NAcc were never seen in this parvocellular population, again suggesting that the OT fibers in the NAcc are coming from magnocellular soma in the PVN.

1.13 A Model for Behaviorally Relevant OT Release in the Forebrain

Based on our observations in the prairie vole system, and notions prevalent in the literature, we can propose three cellular models with respect to the origin of the OT immunoreactive processes in NAcc. First, the prevailing assumption is that separate neuronal populations comprise the neurohyphyseal OT system and the centrally projecting system (Fig 7A). More specifically, many investigators favor the notion that magnocellular neurons only project to the posterior pituitary while the parvocellular neurons project throughout the brain. Alternatively, some investigators have proposed that sufficient OT is released somatodendritically within the hypothalamus to activate receptors in distant brain regions from diffusion (Fig 7B) [120]. Finally, centrally projecting OT fibers may arise from the magnocellular neurons that project to the posterior pituitary, and may be axon collaterals of neurohyphyseal OT neurons that are diverted from the path toward the pituitary (Fig 7C). In all three scenarios somatodendritically released OT may be contributing to brain OT concentrations.

Based on the tract tracing studies discussed above, we hypothesize that many of the OT projections coursing through the forebrain are projections from magnocellular neurons, or collateral of magnocellular axons projecting to the posterior pituitary. In the mouse, a minority of PVN magnocellular axons produce collaterals around the level of the fornix that turn anteriorly and become perpendicular to the section, exactly as would be expected if going to the NAcc [141]. In addition, axon collaterals from the magnocellular SON has also been reported [142]. In fact, it was noted thirty years ago that the multipolarity of neurosecretory cells, containing more than one axon, would allow for simultaneous release from the pituitary and in extrahypothalamic sites [138]. However, this view has not gained wide acceptance in the field. If the prairie accumbal OT fibers are indeed collaterals of magnocellular hypothalamic neurons, this would provide a direct mechanism for coordination of central release deep in the forebrain with peripheral release under the appropriate physiological conditions, such as vaginocervical stimulation during mating or parturition, or sensory stimulation during suckling. Coordinated release has been suggested for other neuropeptides to aid in body temperature regulation [143]. Indeed, it is possible that extracellular OT in the NAcc reflects a combination of somatodendritic release within both the PVN and SON that diffuses to the NAcc, and *en passant* or terminal release from OT fibers located in the NAcc and originating from PVN and SON. These multiple modes of central release of OT may allow high temporal and spatial resolution and a theoretically unlimited variability in OT signaling modes [119]. While central and peripheral release patterns may be coordinated to trigger synergistic effects, local release independent of peripheral secretion may also be possible [119,120,128].

1.14 Conclusions

Historically, the neurohypophyseal OT system has served as a model of neurosecretion. Decades of research have demonstrated the role of this neuropeptide in the regulation of reproductive physiology, including parturition and lactation. OT is an excellent example of how the same hormone can coordinate peripheral physiology with behavior as can be seen in

its role in initiation of maternal nurturing behavior and mother-infant bonding following parturition. More detailed studies have now revealed that OT also plays a role in focusing the brain's attention to social stimuli in both males and females. Evolutionarily, the behavioral effects of OT are shaped by the plasticity in the neural expression of OTR. At least in prairie voles, this maternal behavioral circuitry has been co-opted to promote social bond formation between mates. Elegant human pharmacological studies are revealing an intriguing constellation of effects of this neuropeptide on social information processing and interpersonal relationships. Despite these discoveries, major gaps remain in the presynaptic side of OT function. Further study is needed to examine the relationship between peripheral and central release within the structures where OT modulates behavior, so that we may gain a more complete understanding of the circuitry regulating the social brain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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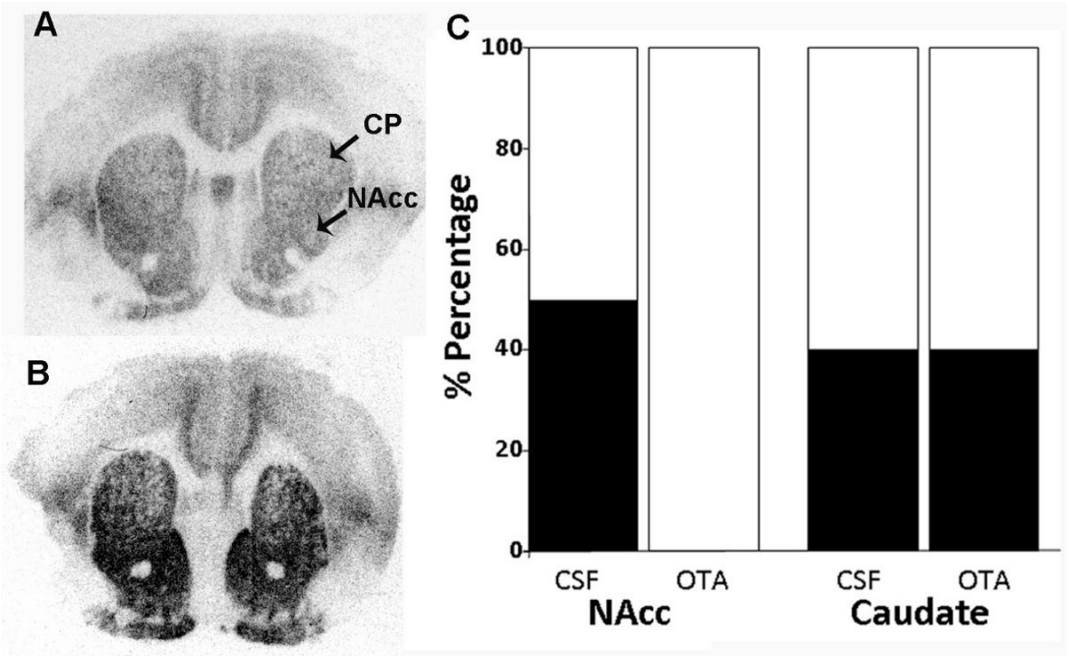

Figure 1.

OTR and alloparental behavior in female prairie voles. Autoradiography showing oxytocin receptor density in the nucleus accumbens (NAcc) and caudate putamen (CP) in non-maternal (A) and spontaneously maternal (B) female prairie voles. Females that have a high density of OTR in the NAcc are more likely to exhibit alloparental care than those with a low level of accumbal OTR. C) Graph showing the effect of administering oxytocin antagonist (OTA) or cerebral spinal fluid (CSF) into the NAcc or CP on alloparental behavior of female prairie voles. Nulliparous females injected with CSF in the NAcc or CP, or OTA in the CP, showed the normal variation in propensity for alloparental behavior, with about half showing nurturing care. However, injecting OTA into the NAcc inhibited alloparental behavior in all the females, suggesting that endogenous oxytocin is necessary for the expression of alloparental behavior in female prairie voles. Adapted from [44] with permission.

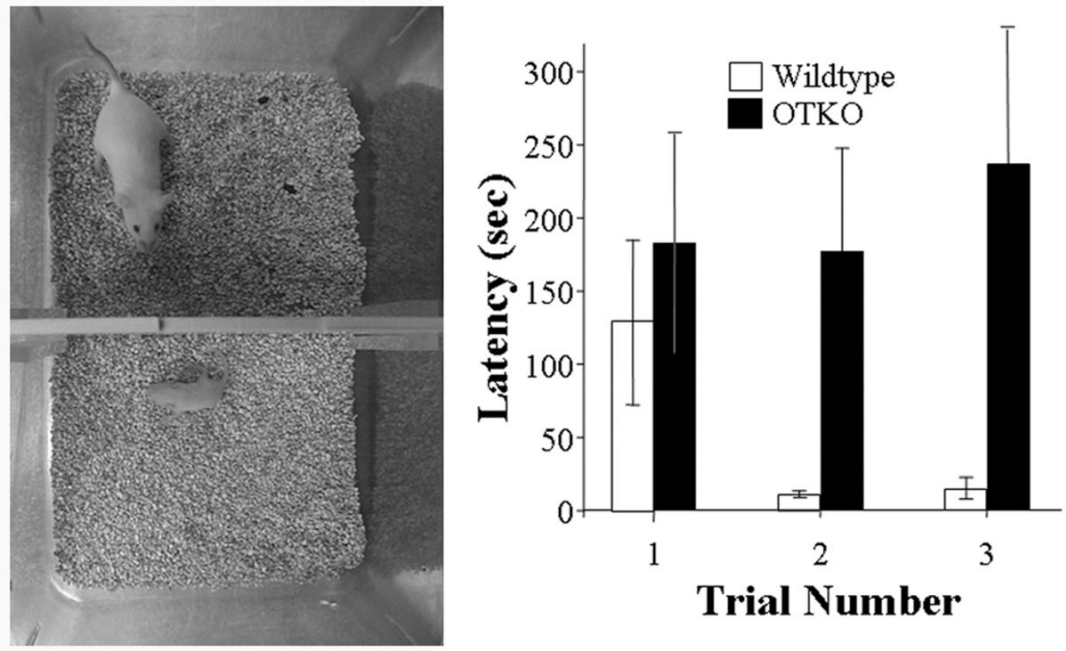

Figure 2.

Infant-mother interactions of oxytocin knock-out (OTKO) pups. Ten day old pups were place in one chamber of a testing arena in which the mother was restricted to a second chamber. The divider contained small holes that were large enough for the pup to pass through, but that prevented the mother from entering. The latency for the pup to enter the mother's chamber was recorded on three successive trials. There was no difference between wildtype and OTKO pups in the initial training trial. However, in the subsequent trials OTKO pups exhibited a significantly longer latency than wild-type pups to cross into the mother's chamber ($p < 0.05$). Thus OT may be involved in motivating pups to seek contact with their caregiver.

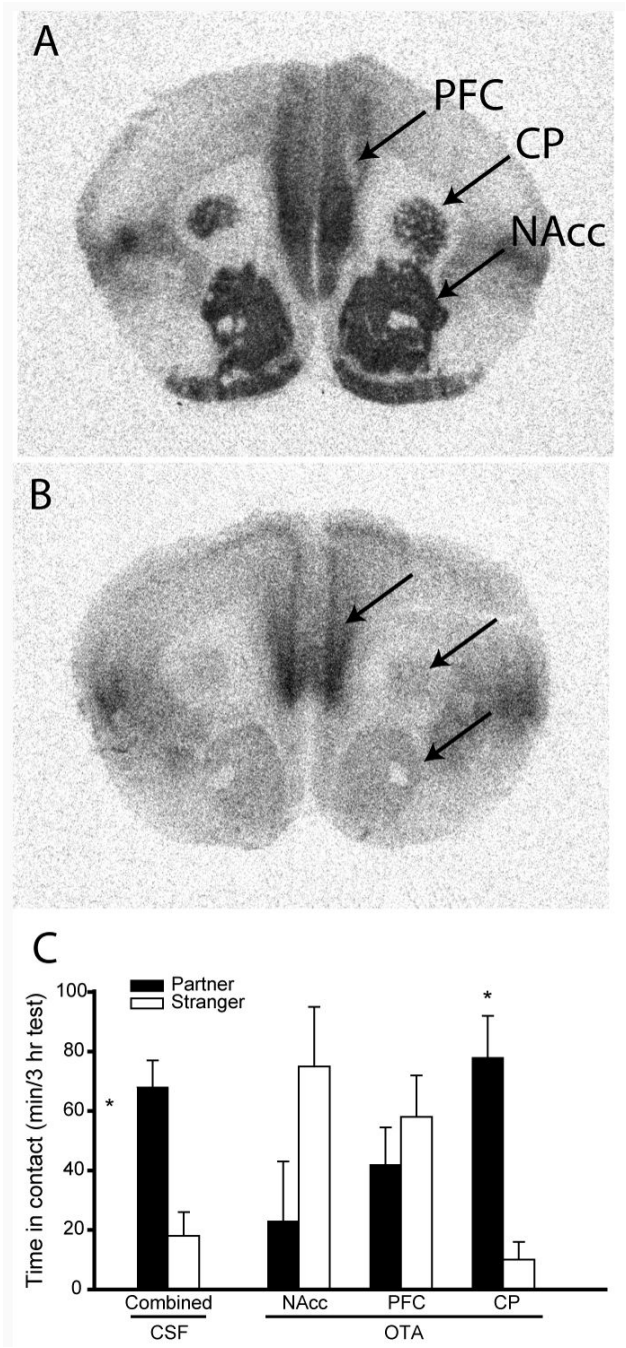

Figure 3.

Species differences in oxytocin receptor (OTR) expression in prairie and montane voles. Notice the higher level of OTR binding in the caudate (CP) and nucleus accumbens (NAcc) of the prairie vole (A) than the montane vole (B). Both species have OTR binding in the prefrontal cortex (PFC) C) Graph illustrating the effects of administering oxytocin antagonist (OTA) or cerebral spinal fluid (CSF) into the PFC, CP, or NAcc on pair bonding behavior in female prairie voles. Administering OTA into the CP or CSF during a 24-hour cohabitation with mating, does not effect the formation of a partner preference. However, injecting OTA into the PFC or NAcc blocked females from bonding with their mating partner, showing that oxytocin

in these areas is important for affiliative behavior in a monogamous vole. Adapted from [55, 58] with permission.

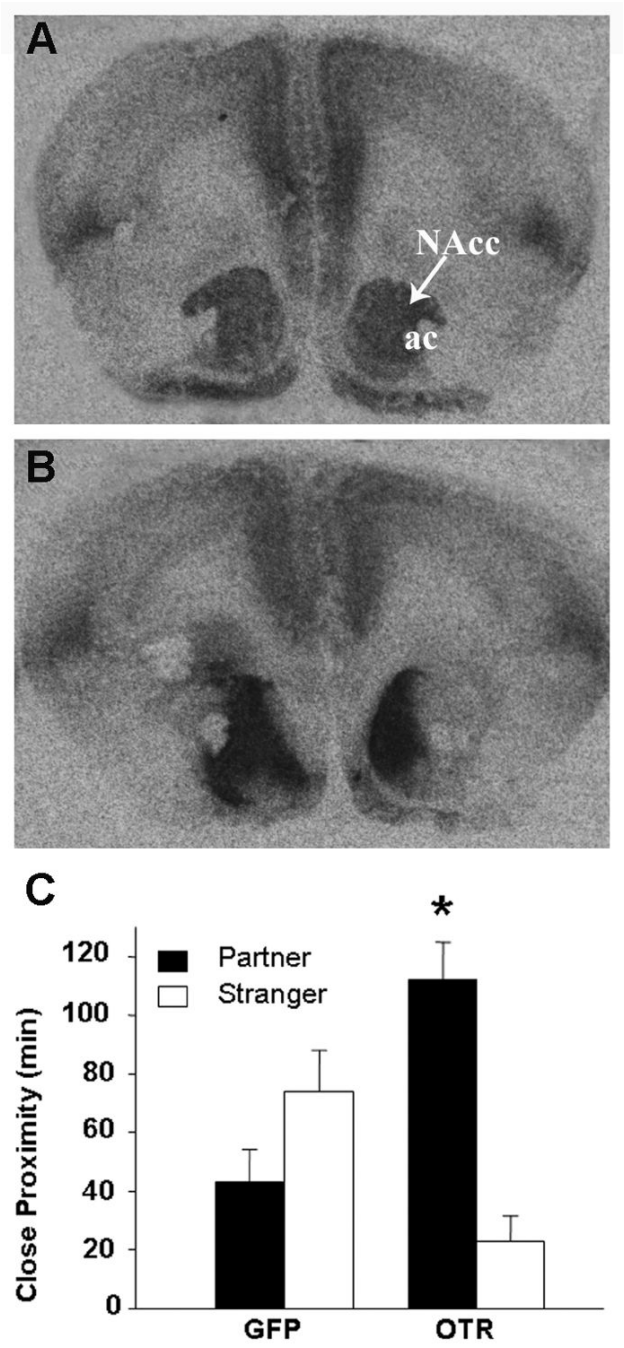

Figure 4.

Viral vector mediated over-expression of oxytocin receptor (OTR) in the nucleus accumbens (NAcc) of female prairie voles enhances partner preference formation. Shown is the OTR binding density in female prairie voles receiving bilateral injection into the NAcc of an adeno-associated viral vector expressing green fluorescent protein (GFP) (A) or the prairie vole OTR gene. C) After a cumulative 18 h cohabitation with a male partner, females over-expressing OTR in the NAcc spent significantly more time with the partner, than the stranger, during a partner preference test ($p<0.001$). The GFP injected females did not spend significantly more time with either male. Adapted from [144] with permission.

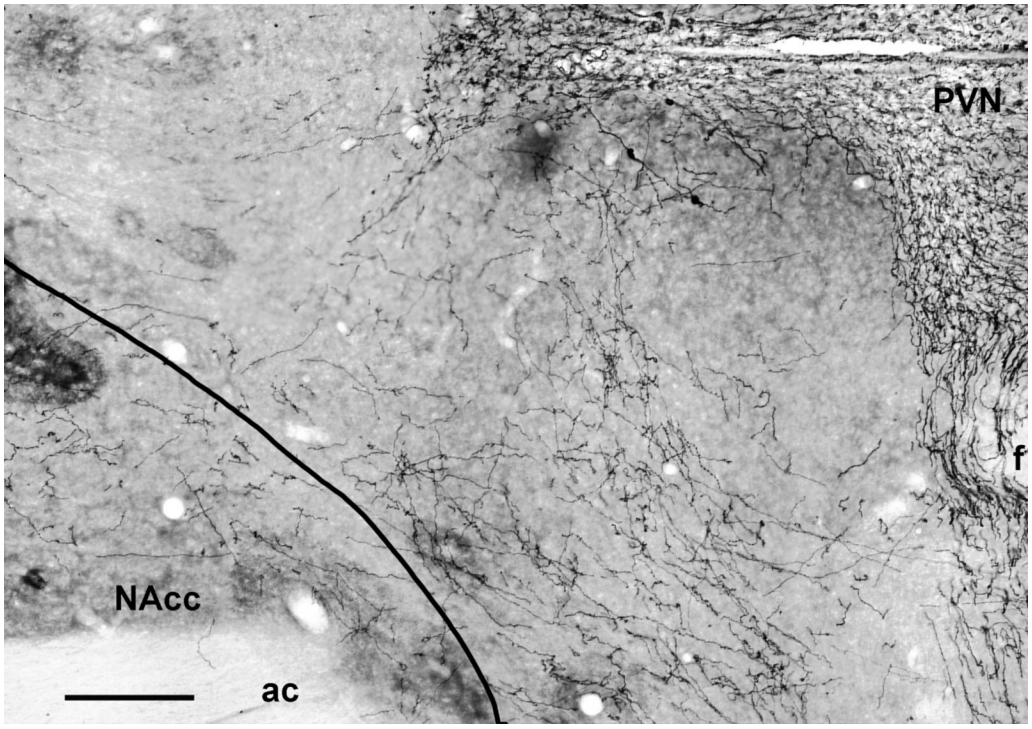

Figure 5.
Light micrograph of oxytocin-immunoreactive fibers in the prairie vole from a horizontal section. Notice that a few fibers deviate from the neurohypophysial pathway of the paraventricular nucleus of the hypothalamus (PVN) and project toward the nucleus accumbens (NAcc). Scale bar = 100 μm. ac = anterior commisure, f = fornix. Reprinted from [59] with permission.

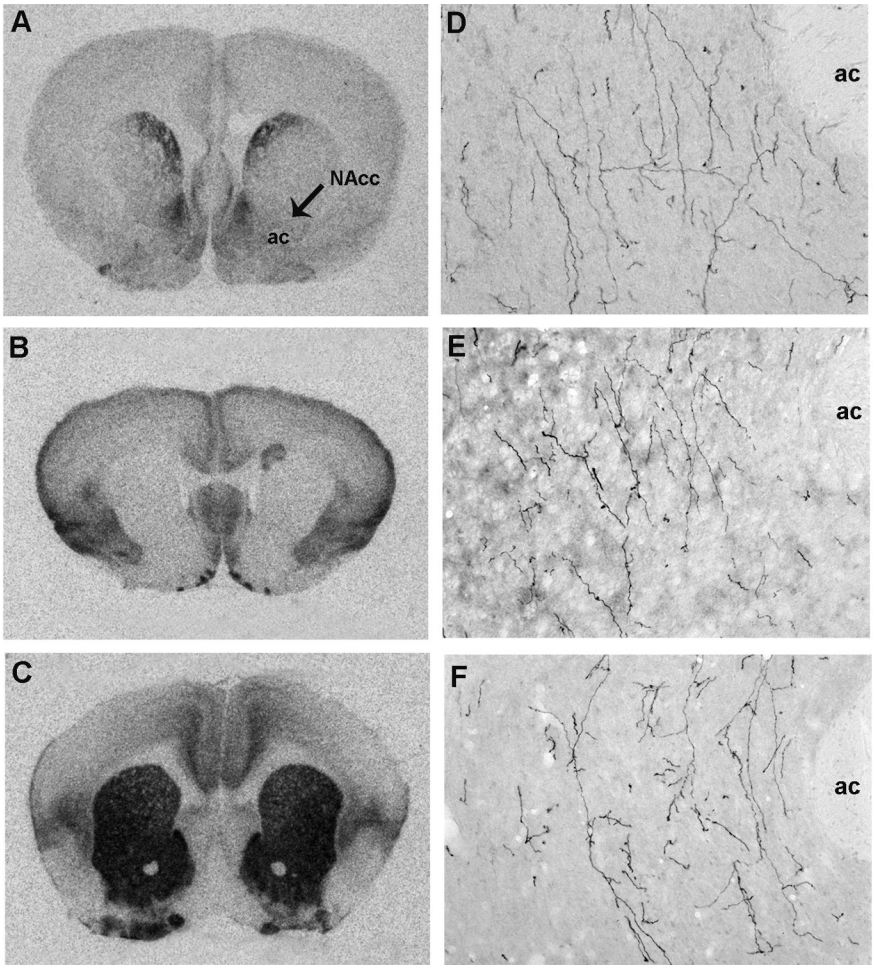

Figure 6.

Oxytocin receptor binding (A-C) and oxytocin-immunoreactive fiber distribution (D-F) in rats (top), mice (middle) and prairie voles (bottom). Note the remarkable species differences in oxytocin receptor binding in the nucleus accumbens (NAcc), but similarity in oxytocin-immunoreactive fibers. ac = anterior commisure. Adapted from [1,59] with permission.

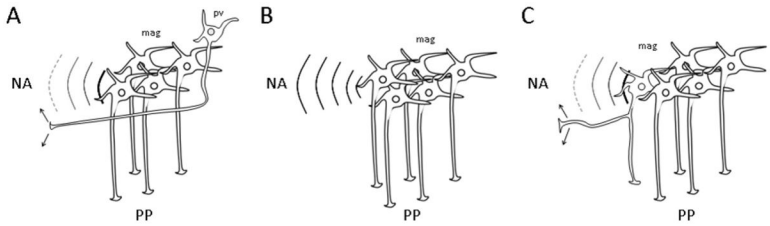

Figure 7.

Models of the possible origin of the oxytocin (OT)-immunoreactive processes in NAcc. A) Separate neuronal populations comprise the neurohyphyseal OT system and the centrally projecting system. Magnocellular (mag) neurons project to the posterior pituitary while parvocellular (pv) neurons project to specific brain regions. This is the prevailing view of many investigators. B) Somatodendritically released OT from magnocellular hypothalamic neurons diffuses to distant brain regions in a paracrine fashion. C) Centrally projecting OT fibers may be axon collaterals of neurohyphyseal OT neurons that are projecting towards the pituitary. From our research in prairie voles, this model is most likely. Note that in models A and C, OT may influence OT receptor populations by either direct release from local processes, or after diffusion following somatodendritic release within the hypothalamus.