International OPEN ACCESS JOURNAL

International Journal of Prenatal & Life Sciences
in search of meaning

DOI: 10.24946/IJPLS.20.18.00.00.040604
www.journalprenatalife.com

Title: The Role of Oxytocin in Maternal-Fetal Bonding & Social Interaction

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Abstract
Oxytocin is a small peptide usually associated with its effects in the reproductive system such as induction of labor and lactation. However, recent evidence has indicated that oxytocin plays an important role in social behavior in mammals, including humans. This review article outlines the basics of the role of oxytocin in parental-fetal bond formation and pair-bonding. Social recognition forms the basis of all social interaction and therefore the role of oxytocin in recognition is also discussed. Most studies done as of yet have been conducted of mammals such as prairie voles and rats. However, there has been some evidence which shows that similar mechanisms occur in humans. Pair-bonding and parent-fetal bond formation have very similar mechanisms and oxytocin plays an important role in both. For both processes to occur, there needs to be social recognition and memory of the infant or the partner, both of which are aided by oxytocin and other neurotransmitters, especially arginine vasopressin (AVP) and dopamine. Moreover, once the bond has been established, oxytocin plays a role in persistence of the bond even in the absence of the fetus/parent or the partner. There are similarities between the behavior and mechanisms of social bonding and addiction, therefore oxytocin could play a future role in treatment of social diseases, such as autism and addiction.

Introduction

Oxytocin (OXT) is a small nine-amino acid peptide produced by the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus. It is then primarily released by exocytosis

from the neurohypophysis and nerve terminals as a result of physiological stimuli. OXT binds to oxytocin receptors (OXTR) which causes a release of Ca^{2+}. This calcium release can be blocked using OXTR antagonists such as d(CH2)5,Tyr(Me)2,Orn8]-vasotocin[1]. OXT has long been known for its effects in inducing parturition and lactation. However, recent studies have implicated this peptide in other aspects of mammal and human life, such as the modification of social behavior, including pair-bonding between partners and parental bonding with the offspring[2]. Social bonding is a vital process for the survival of species since it increases the chances of reproduction and protection of the young against predators[3]. Furthermore, social interaction is essential since isolation results in physical and mental disorders, and ultimately even death in a number of animal and human models[1].

Social Recognition

Social recognition is an important aspect and vital first step in the formation of social bonds in mammals (including humans), for example pair bonding and the formation of a relationship between parents and their offspring[2]. In order for social recognition to occur, the mammal must go through steps, which include social approach, investigation, sensory learning, processing, and memory[4]. Olfaction, a way to calculate the degree of olfactory input (amygdala), and the reward circuitry are all essential parts of social recognition. This process utilizes steroid hormones, neuropeptides, and neurotransmitters such as norepinephrine and DOPA[4]. Oxytocin (OXT) also plays a vital part in social recognition[2].

Social Recognition in Different Parts of the Brain

Social recognition in rodents can be induced by OXT administration in the lateral septum, medial preoptic areas and olfactory bulb[5]. The lateral septum (LS) plays an important role in social recognition since rats administered OXT or AVP site-specifically spend more time with familiar rats compared to unfamiliar ones[2]. Vasopressin works with OXT in social recognition, but it acts mainly only in the LS. In fact, when vasopressin in administered in the LS, social recognition improves, while administration of vasopressin receptor antagonist in the LS inhibits social recognition[4]. When OXT is specifically administered to the medial amygdala, it reverses the social memory deficit usually found in OXT-knockout mice. Therefore, the medial amygdala is also involved in social recognition[2].

There is an elevated noradrenergic stimulation in the olfactory bulb initiated by OXT or vasopressin. This decreases the inhibition on the olfactory bulb and there is an increase in the activity of the main output cells of the bulb. This results in plasticity in the olfactory bulb. Difference in the plasticity encodes for the difference between behavior towards strangers later in life[4]. Rodents primarily use olfactory stimuli for social recognition[5] and can retain facial memory for up to two hours following recognition through olfactory cues[5]. When treated with OXT, their social memory is prolonged[4]. The recognition and learning of olfactory stimulus can be reproduced by norepinephrine administration in the locus coeruleus, indicating that norepinephrine is essential for the social recognition process[4].

Social recognition in animals

Social recognition is important since it allows an animal to distinguish between its partner and a stranger[2]. Social recognition increases when rats are administered with both peripheral and central OXT administration[2]. In fact, there is an increase in retention time when the social discrimination test is administered[2]. OXT-knockout mice display a lack of social memory. The lack of social recognition found in OXT knockout mice can be reversed by an OXT intracere-broventricular (ICV) injection given before the first exposure. However, an OXT injection administered after the initial exposure has no effect on social recognition[5]. This shows that OXT plays a role in the formation of social recognition, but not in recognizing the specimen after the first encounter[5].

Pair bond formation is the rewarding mating experience associated with the olfactory sensory cue of the partner[6]. Social recognition and memory are essential for partner preference formation in monogamous mammals, such as prairie voles. In fact, lesions in the olfactory bulb of male prairie voles decrease partner preference formation[4]. Certain studies show that OXT in the mouse brain is not used to discriminate between strangers and familiar animals, but rather discrimination between specific mice to recognize a certain mouse[5]. This corresponds to the formation of a pair bond to a specific mouse[5].

Social recognition in the maternal bond induced by OXT is observed by a variety of mammals including sheep, goats, Southern pig-tailed macaques, rhesus macaques and rodents[2]. In pre-weaning rate, administration of OXTR antagonist prior to the formation of the mother-infant bond inhibits the rat from making the association between the mother's social cues and the odor[4]. Newborn rat pups associate the maternal care they receive, such as licking, with stimuli of the mother, especially the odor[4]. In fact, when newborn pups are "licked" with a paintbrush with the odor of peppermint, the pups show a preference towards the smell of peppermint throughout their life[4]. Mice with defective OXT systems are unable to recognize familiar animals using particular social cues, such as facial features, odor or walk[5]. However, they respond normally to other odors, such as lemon[5].

AVP also plays a role in social recognition since administration of AVP in rats increases their social memory and treatment with AVP receptor antagonist centrally and peripherally inhibits social recognition[2]. CD38-knockout mice show a deficiency in social recognition. CD38 is a transmembrane protein needed for the translocation of Ca^{2+} ions inside the cells by activation cADP ribose. The Ca^{2+} ions induce release of OXT and therefore, lack of CD38 stops social recognition[2]. Total removal of OXT, OXTRs or CD38 in genetically-engineered mice eliminates any type of social memory, even a few seconds after seeing another animal[5]. However, there is no change in non-social memory and learning, indicating that OXT has no effect on memory outside social purposes[5].

Social Recognition in Humans

In humans OXT in used to distinguish between emotions by looking at the faces of familiar people by subtle facial cues. Intranasal OXT administration increases this ability[6]. Administration of OXT increases both the short- and long-term memory in facial recognition of males and

females[2]. When ten people were treated with intranasal OXT and another ten were given a placebo, and they were all shown faces of strangers 45 minutes after administration. They were then asked to choose the faces they saw in the pictures, and the people treated with OXT recognized more people compared to those with the placebo[7]. Therefore, OXT may be used therapeutically in patients with social deficits, although more research is needed[5].

Parental Care

Affectional bonds are a primary human need, especially the one between mother and infant[8]. This bond increases the infant's chances of surviving beyond reproductive age[9]. This relationship is different in rodents and herding animals. While rodents display maternal behaviors universally towards infant rodents, herding animals such as sheep are selective towards their own infants and develop a stronger mother-infant bond[10]. In cases where a mother-infant bond is impossible, such as in rabbits, the infants tend to share their early environment with siblings[11]. In prairie voles, both virgin males and females tend to avoid and, in certain cases, even attack infants, but parturient mothers are attracted to the infants and find them irresistible[10]. Furthermore, blood transfusions from a parturient rat to a virgin female rat show an increase in the parental response of the virgin rat[10].

The oxytocinergic and dopaminergic systems have been associated with the bond formed between parents and their infants. Apart from these systems, other factors such as stress during the pregnancy, early caregiving experience and relationships throughout the life also have an effect on this bond[9]. Increased plasma OXT concentrations in the first six months of the infant's life have shown a positive parental behavior in both parents[12].

Although most studies have been done on other mammals, similar mechanisms support animal and human parenting mechanisms[10]. Apart from its importance in forming the parent-infant bond, OXT is also essential to protect the parents from the stress and demands of the perinatal period[13].

Maternal Behavior

Apart from its well-known effects regarding labor and milk ejection, OXT also increases maternal behavior[14]. The main biological mechanism involved in the onset and maintenance of maternal behavior is the oxytocinergic and dopaminergic systems which induce motivation and reward circuits[15]. OXT has projections to the medial preoptic area (MPOA), the bed nucleus of the stria terminalis, the ventral striatum including the nucleus accumbens and the ventral tegmental area, which are all involved in positive maternal behavior[9]. In fact, the nucleus accumbens of biparental prairie voles contains more OXTRs (OXTR) than non-monogamous species which to not display biparental care[16].

DOPA signals start in the ventral tegmental area and the substantia nigra and project into the ventral striatum, dorsal striatum, prefrontal cortex and anterior cingulate cortex[9]. Onset of reward mechanisms is through the activation of the mesocorticolimbic pathways which involves the ventral striatum and the medial prefrontal cortex and temporal prediction errors activate the nigrostriatal pathway which involves the dorsal striatum and the dorsal prefrontal cortex[9].

The OXT and DOPA systems connect at the mesocotricolimbic pathway system which is involved with motivation and reward in both mother and infant[9]. The mesocotricolimbic pathway induces the onset of maternal care by inhibiting avoidance and violence towards the infant[10].

Recognition of the infant is an essential part of bond formation. This can be selective or nonselective. Nonselective recognition occurs in mothers that give birth to multiple young ones, for example most rodents, including rats. In nonselective recognition, maternal care is focused toward a general stimulus on the infant rather than a specific one, and if another young has the same stimulus the mother will care for it during the postpartum period. Selective recognition usually occurs in species where the mother gives birth to a small number of infants (usually one), such as sheep and most primates. In selective recognition, maternal care is directed toward the specific infant birthed by the mother and other offspring are rejected[17].

Pregnancy & Parturition

During pregnancy, the medial prefrontal cortex (MPOA) enhances the mesocorticolimbic pathways by increasing its effect on the amygdala[10]. The amygdala is involved with learning and memory[18]. Although not a direct part of the mesocorticolimbic pathway, it is linked with reward since memory of previous rewards following certain actions create motivation for similar action by the mesocorticolimbic pathway[18]. The MPOA also monitors the concentration of steroid hormones during pregnancy[18]. During pregnancy there is an increase in plasma progesterone and estrogen which are secreted by the ovaries. This is followed by a sudden drop in progesterone which signals the start of parturition. When the MPOA receives these signals, there is an increase in brain sensitivity to OXT and prolactin induced by an increased production of their receptors[10].

At pregnancy and lactation, there is an increase in gene expression of OXT in brain regions associated with an increase in maternal behavior, such as dopaminergic substantia nigra. There is also neural modification of the hippocampus, which is associated with facilitated learning, spatial memory and emotion processing of facial cues, all of which are essential to form a close mother-infant bond[9].

During parturition, the MPOA activates the ventral tegmental area (VTA) in two ways; firstly, through direct projection, and also indirectly through the PVN of the hypothalamus. This leads to an increased DOPA concentration in the nucleus accumbens, which activates DOPA D1 receptors. This stops the inhibition of the nucleus accumbens on the ventral pallidum, activating the nucleus pallidum. This makes the mother responsive to infant cues via projections of the ventral pallidum to the thalamus, and cortical and mesencephalic motor nuclei, which are all involved in the display of maternal nurturing towards her pup[10].

Infancy

OXT following parturition and throughout infancy is important since it is involved in motor output response towards infant cues[10], own infant recognition[9] and maternal aggression towards intruders[19]. Postnatal stimuli from the infant, such as crying, facial expressions and suckling stimulation aid in reshaping the maternal brain in the period immediately following

parturition, which is a time of high neural plasticity in the mother[9]. OXT is essential since an intracisternal injection of OXT in a rat mother few days following the birth of a pup induces grooming four months later[16].

Several parts of the brain are involved in forming a bond with the infant following parturition[18]. The MPOA is essential for positive maternal behavior. Destruction of the MPOA stops all signs of maternal care in rats and administration of OXT, estrogen, DOPA or prolactin in the MPOA of virgin female rats induce maternal behaviors. There is stronger activation of the nucleus accumbens after seeing pictures of their children in mothers who display more positive behavior and less intrusiveness. Infant cries also activate the anterior insula and prefrontal cortex. The anterior insula is associated with feelings of empathy, which are essential as a motivator for maternal care[10]. The prefrontal cortex is involved in cognition, motivation, decision making and emotion, all of which are needed for positive maternal behavior[18]. Activation of the prefrontal cortex is also linked with maternal sensitivity towards pups, decreased stress responses to separation from her infants and secure attachment following reunion. There is an increased activation of the amygdala of infant when seeing pictures of their mothers compared to pictures of strangers. This increases saliency towards the mother[10].

Recognition of own infant is an important aspect of mother-infant bonds. Sheep mothers start recognizing their offspring after a few hours following parturition[11]. When viewing their own infants, mothers have an increased activation of the mesocorticolimbic pathway and nigrostriatal pathway, which are associated with positive maternal care[9].

In humans, the mesocorticolimbic dopaminergic reward regions and the PVN and SON of the hypothalamus are activated when secure mothers are shown pictures of their children. Furthermore, activation of reward centers, such as the NAcc, is correlated with an increase in peripheral OXT levels in the mother[20]. Conversely, depressed mothers who have lower OXT levels do not have activation of these brain centers and therefore, do not experience reward in maternal behavior, finding it difficult to bond with their child.

Mothers have reduced reactivity to stressors through decreases corticotrophin releasing factor, adrenocorticotropin releasing factor and cortisol[13]. However, mothers have a more aggressive response towards strangers, used to protect the infant, elicited by OXT[21]. In fact, OXT-knock-out mice showed very little aggression towards strangers[21]. An increase in OXT activates the amygdala in humans[19]. This induces fear and aggression, increasing the chances of maternal survival and infant protection[19].

OXT is well known for its role in milk ejection during breastfeeding. However, recent studies have shown that mothers who breastfeed have more activity in the brain areas which are related to maternal behavior, such as the striatal reward regions[14]. Breastfeeding has been shown to improve depressive symptoms[22]. Firstly, mothers who breastfeed improve their feeling of self-efficacy, which is inversely associated with the feeling of helplessness felt by mothers suffering from post-partum depression. Furthermore, breastfeeding increases the bond between the mother and the infant. Breastfed children also sleep more when compared to children who are not breastfed. This allows a more stable sleeping pattern for the mothers,

which can improve her mood[22]. There is also an increase in OXT and DOPA concentrations in the substantia nigra during suckling which explains why breastfeeding is linked with a stronger mother-infant bond compared to mothers who do not breastfeed[9]. Similarly, in mothers who deliver vaginally, there is a greater activation of the hypothalamus when hearing own infant cries, leading to an OXT surge and an increased DOPA release compared to mothers who deliver via Caesarean section[9].

Later Life

OXT is responsible not only for the onset of maternal care, but also for the maintenance of it[9]. The mother-child bond is one which lasts a whole lifetime, especially in humans. Long-term persistence of the mother-infant bond necessitates both maternal and fetal memory, which occurs through synaptic plasticity within the neural circuit regulating maternal behavior. It is hypothesized that the action of dopamine and OXT on the nucleus accumbens is vital for memory formation in the maternal-infant bond (similar to pair bonding). During a study, rats are allowed an hour of bonding postpartum and then the offspring is removed. Then, dopamine agonists, OXT antagonists, and control solutions are injected into the mother's nucleus accumbens. Ten days later, the mothers are exposed once again to offspring. The study shows that both by blocking both D1 and D2 receptors, maternal memory is stopped and there is no maternal-infant bond formation. The OXT antagonists used were relatively non-selective and also block V1a vasopressin receptors, and therefore, the results regarding OXT are not reliable and with regards to this study, these receptors may or may not be involved in maternal memory formation[17]

Most studies are done on rodents since it is difficult to measure central OXT concentrations and there is no evidence that central and peripheral OXT concentrations are correlated[23]. However, certain studies have been done on humans in the past few years to show that even in humans, OXT plays an important role in maternal behavior[14]. Another study shows that mothers who have a secure bond with their child, who display an understanding of emotions and empathy experience a rise in central OXT levels when interacting with their child. This change is not seen in mothers who do not have a secure bond with their child, such as depressed mothers[14].

Furthermore, the rise in OXT levels in secure mothers is correlated with a rise in OXT in their infants, showing the dual effect that a healthy relationship between the mother and the infant has on both parties[24]. Therefore, the quality of maternal care in the early life of the infant affects the OXT system development in the child, and has an effect on the parental behavior of the offspring when they become a parent[9].

Measuring maternal behavior is very difficult, but two methods for doing this are used. These are the Adult Attachment Interview (AAI) and the Strange Situation Procedure (SSP)[9]. In the SSP, a young child (<2 years) and the mother are put in a strange or challenging situation to assess whether the infant chooses the mother over a stranger in such situations[25]. Using this method, it has been found that the development of secure attachment between mother and infant is affected by the mother's attachment history and stress throughout her life[9]. AAI uses an interview, made with both the mother and the child, which is analyzed for specific markers

(words or phrases) and patterns. The relationship between mother and child is then sorted as "secure", "insecure/ dismissing" or "insecure/preoccupied"[9]. During an AAI a difference is made between "cognitive" attentiveness and "affective" attentiveness. Cognitive information is information given during the conversation regardless of emotions felt by the mother and affective information is information regarding the emotions and fears of the mother[9]. "Insecure/dismissing" mothers tend to focus on the cognitive information and "insecure/preoccupied" mothers focus on the affective information. "Secure" mothers coordinate well between the two types of information[9]. OXT levels in the "insecure" mothers tend to be less than in "secure" mothers, indicating that OXT has an important role in providing secure attachment between mother and child[9].

Maternal Neglect

Neglect is most often associated with the mother, since she is normally considered the primary caregiver, even though mothers go through neuroendocrine changes during pregnancy, birth and lactation, which prepares them for caregiving[9]. There are two types of neglect; physical and emotional neglect[9]. While physical neglect is when the mother fails to provide materialistic needs, such as food, hygiene, clothing, or education, emotional neglect is when the caregiving lacks physical affection and emotional warmth[9].

Physical neglect is associated with loss of "cognitive" understanding, while emotional neglect usually results in lack of "affective" understanding[9]. Emotional neglect, unlike physical neglect, produces negative long-term effects on the child's social and emotional behavior[9]. Reduced maternal care is linked with lack of OXT, since depressed mothers have decreased levels of salivary OXT[10]. Also, in rhesus monkeys, there was a decrease in OXT levels of the cerebrospinal fluid (CSF) in monkeys who had non-maternal rearing[9]. Stress throughout pregnancy is associated with decreased OXTR binding in brain areas associated with positive maternal care[9]. This increases anxiety in the mother and reduces licking and grooming, therefore decreasing OXTR binding in the offspring, producing long term effects in the maternal behavior of the offspring[9]. Reduced levels of OXT in late pregnancy are associated with increased symptoms of depression postpartum[26].

Depressed mothers have a lower nucleus accumbens activation which causes reduced caregiving motivation and decreased anterior insula activation. Therefore the mother has reduced empathy towards infant cues such as cries or facial expressions[10]. Empathic over-arousal also has adverse effects on maternal behavior since it can interfere with effective parenting and can lead to intrusive parenting[10]. A reduced level of licking and grooming in rat pups is an indication of maternal neglect. These pups show a higher level of DNA methylation of estrogen receptor - α gene promoter, resulting in an inhibition of the development of the OXT system[9].

Drug abuse in mothers is also associated with negative maternal care[9]. Cocaine abuse decreases OXT levels in the hypothalamus, inhibiting the mesocorticolimbic pathway, which is essential for good maternal behavior[9]. Furthermore, cocaine abuse reduces OXTR levels in the brain, therefore decreasing maternal behavior towards pups[27]. The pups fail to develop the

oxytocinergic system properly, making them more susceptible to future cocaine abuse themselves[27]. A socially rich environment later in life, may compensate for the maternal neglect, but it cannot reverse the effects caused earlier in life[9].

Paternal Behavior

Most studies focus on maternal behavior since the mother is usually considered the primary caregiver. However, OXT also has a role in positive paternal care[10]. When OXT is administered intra-nasally, there is an increase in father-infant touch[10]. This increases the duration of infant gaze towards the father and salivary OXT of the infant[10]. OXT levels in the father correlate with proprioceptive tough and exploratory play between the father and the infant, creating a stronger father-child bond[10]. Fathers who are involved in caregiving have stronger activation of the VTA and the anterior insula following infant stimuli[10]. When anterior insula activation is too high or too low, this interferes with paternal behavior since the father experiences too much or too little empathy towards the infant[10].

Biparental care, such as that found in prairie voles, is associated with a decrease in the father's testosterone levels[28]. Men with a higher testosterone level show decreased sympathy towards the cries of an unknown infant[28]. Men with lower testosterone levels, show an increased involvement in fatherhood at the expense of sexual interaction[28]. They display increased empathy, frustration tolerance, but decreased sexual motivation[28]. This is also important in positive paternal care since it prevents sexual motivation from "competing" with parenting effort[10]. Paradoxically, testosterone is beneficial in paternal behavior since it is converted to estrogen in some species[10]. Estrogen induces the development of the oxytocinergic system[10]

Size of testes also affects paternal care[10]. Men with smaller testes usually show more involvement since testes size has an inverse relationship with VTA activation which is involved in increased paternal behavior[10]. As of yet, there is not enough evidence to correlate oxytocin and testosterone levels in fatherhood, although several studies have shown that an increase in oxytocin levels alters testosterone levels and has an effect on paternal behavior[2930].

Alloparental Behavior

Alloparental care is parental behavior by someone other than the biological parent[31]. OXT treatment increases female involvement in virgin rats to pups[32] as opposed to aversive behaviors which are seen when there is no administration of OXT[9]. In male prairie voles, administration of OXT antagonist decreases alloparental behavior transiently[16]. At 21 days postpartum, male prairie voles treated with OXT antagonist show a decrease in parental care and in time spent with pups, but at 60 days postpartum, none of the above effects are seen[16].

Baby "schema" (cuteness) plays an important role in producing parental care in non-parents[12]. There is stronger ventral striatum activation in nulliparous women when viewing pictures of "cute" babies[12]. There is also an increased in activation of the nucleus accumbens and VTA when non-parents see pictures of "cute" babies[10]. Children who were raised in orphanages and then adopted show an increase in amygdala activation, increasing their trust[10]. Therefore, they tend to approach unfamiliar adults, putting themselves at risk[10].

Pair Bonding

Pair bond formation is when a male and a female animal develop a monogamous relationship beyond reproductive purposes[18]. Monogamous mammals, following the formation of a pair bond, share a territory and defend their nest together with their partner[18]. They also both participate in the rearing of their young[18] and guard each other[2]. Most mammals display non-monogamous relationships, unlike prairie voles and humans, which develop monogamous pair bonds[18]. In fact, pair bond formation is only present in less than 5% of mammalian species[2].

The mechanisms which drive partner preference formation are very similar to those which cause maternal-infant bonding. As with the mother-infant bond, once the bond has occurred, it endures even in the case of absence of partner stimulation. Therefore, pair bonding also involves neural plasticity in selective neural pathways as a result of specific social stimuli from the partner, such as olfactory stimuli (similar to maternal bond in sheep). A noticeable difference is that both male and female prairie voles develop pair bonding following mating, as opposed to parental bond, which is focused mostly on the female[17].

Compared to more promiscuous animals, prairie voles display higher OXTR concentrations in the nucleus accumbens, amygdala, bed nucleus of the stria terminalis and prefrontal cortex[18]. This shows that OXT plays a role in the formation of a pair bond. There are similarities between the mechanisms of being in love and substance addiction[33]. Subjects who are in love experience stress-induced relapse, lack of regard for consequences, are unable to quit, and lose track of time[33]. They also lose their ability to make rational decisions about personal risks involving their choices[33]. All of these behaviors are also seen in people who are suffering from substance abuse[33]. Also, both mechanisms involve OXT stimulation in the brain of the subject[33].

Partner Preference Formation

Partner preference formation differs between the field and the laboratory[5]. In the wild, there is abundant mate choice and monogamy is observed when a male and a female pair are seen together frequently and share their nest. In the laboratory, there is no mate choice and pairs are selected randomly by the experimenter[5]. Sexually naive animals are put together for a period of cohabitation. After the cohabitation period, the animals are tested in a three-hour partner preference test, where the animal is put in a testing chamber consisting of three cages. One contains the partner they spent their cohabitation period with; one contains a stranger animal; the other is empty. The animal can move freely between the three chambers[5]. Monogamous prairie voles show preference for their partner since they spend twice as much time in their cage than in the other two[5]. However, non-monogamous montane voles spend most of the time in the neutral cage[5]. The success of pair bond formation increases when the cohabitation period is longer[5]. In fact, the amount of OXTRs in the *nucleus accumbens* of female prairie voles is directly related to the speed of partner preference formation[18]. When the voles were administered with OXTR antagonist after the cohabitation period, partner preference formation

was reduced, but sexual activity was not affected[5].

Both monogamous and non-monogamous animals have genes encoding for OXT and OXTRs, since both are needed for lactation[5]. Therefore the difference in pair bonding behaviors may be due to OXTR distribution patterns. For example, the *nucleus accumbens* contains higher concentrations of receptors in monogamous mammals compared with non-monogamous species[5]. Moreover, OXT administration induces partner preference formation in both male and female prairie voles, indicating that OXT has a role in both sexes, even though this effect is much less potent in the male[34]. In fact, a higher dose of OXT is needed in male prairie voles for partner preference formation[34].

The difference of the effect of OXT in pair bond formation between male and female voles may be due to the OXTR concentration difference in male and female prairie voles[34]. While in male voles, there is a high concentration of OXTRs in the LS, in the female, there is a high concentration of OXTRs in the prelimbic cortex and the nucleus accumbens[34]. Another difference between partner preference formation of the male and female prairie voles is the importance of mating for this process to occur[18]. In female rats, OXT-induced partner preference formation is present even when mating does not occur[2]. However, in males, prior to mating, OXT treatment does not induce partner preference formation and OXTR antagonist has no effect on pair bond formation[2]. Therefore, mating is essential for the formation of a pair bond in the male[2]. Once the pair bond has been formed, male prairie voles showed aggression towards unfamiliar females[18].

In prairie voles that have not formed a pair bond, OXT or AVP administration, increases social behavior such as side-by-side contact and decreased aggression. In male rats, chronic OXT administration increased social interaction with females[2]. In monogamous marmosets, administration of OXT induces more contact, decreases partner approach latency and increases food sharing. OXTR antagonist inhibits these actions[2].

Social recognition is an important aspect of pair bond formation since it allows the mammal to distinguish between the partner and a stranger. OXT plays an important role in social recognition[2]. OXT-knockout mice have reduced social memory which is restored by treatment with OXT before the first social encounter with a particular partner[33].

While the role of OXT in parturition explains its increase during the formation of the maternal-fetal bond, a study showed that similar vaginocervical stimulation during mating induces OXT release in the NA to facilitate the formation of partner preferences in females[35].

The Interaction of OXT with Other Neurotransmitters & Hormones

One of the chemicals in the brain which interacts with OXT in the formation of all social bonds, including the parental bond and pair bond formation, is DOPA[18]. In fact, administration of haloperidol, which blocks the activity of DOPA, before mating, stops partner preference formation in male prairie voles[18].

Both oxytocinergic and dopaminergic systems work together in the formation of a pair bond[34]. In fact, formation of pair bond stimulated by DOPA receptors in the nucleus accumbens of the female prairie vole is inhibited by OXTR antagonist and partner preference formation stimulated by OXT is inhibited by treatment with DOPA receptor antagonist in the nucleus accumbens of the female prairie vole[34]. Pair bonding is affected by DOPA stimulation in the nucleus accumbens[18]. However, there is also dopaminergic activity in other regions of the mesocorticolimbic pathways, such as the prefrontal cortex[18].

Two DOPA receptors are involved in the regulation of partner preference formation; D1R and D2R[18]. These two receptors produce opposing effects on pair bond formation when activated[18]. Administration of D2R agonists establishes partner preference formation in situations where there should be no partner preference formation[18]. However, when D1R are activated, pair bond formation is blocked[18]. In fact, there is a lower concentration of D1-receptors and a higher concentration of D2-receptors in monogamous prairie voles as compared to non-monogamous meadow voles[18]. Following the formation of a pair bond, activation of D1R in the nucleus accumbens induces aggressive behavior towards strangers, therefore inhibiting the formation of a second pair bond[18].

Cyclic adenosine monophosphate (cAMP) works with both the oxytocinergic and dopaminergic systems to regulate partner preference formation[6]. D2 receptor stimulation decreases cAMP concentration and D1 receptor stimulation increases cAMP levels[6]. In fact, an increase in cAMP signaling induced by a decrease in PKA inhibits pair bond formation, while a decrease in cAMP levels in the nucleus accumbens increases partner preference formation[6].

AVP, which is structurally very similar to OXT produces effects similar to OXT during the formation of a pair bond[34]. However, its effects are more potent in males, whereas females are more responsive to OXT[34].

Corticosterone and OXT work together in the formation of pair bonds[34]. In sexually naive females, exposure to males increases central OXT release and decreases corticosterone release[34]. OXT administration decreases corticosterone concentration and therefore OXT seems to interact with the HPA axis to regulate partner preference formation[34]. When female prairie voles are administered corticosterone, they show an increased preference to strangers compared with controls. This shows that corticosterone in females has the opposite effect of OXT, since administration of OXT increases preference to the romantic partner[36].

Pair Bonding in Humans

Most studies and experiments done so far study pair bonding in animals, mostly prairie voles, however, some research shows that the mechanisms observed in prairie voles are similar to those in humans[2]. In humans, MRI scanning showed that when seeing a romantic partner, there was more activation of the ventral tegmental area and caudate when compared to a familiar person[18].

A male and female participant are treated with OXT and shown a picture of an additional male and female. A day later, the participants are shown pictures of an additional man or woman and

are asked to choose which one they would like to get to know better. The participants show an increased interest in the person they were shown the previous day. However, the participants are only asked to choose the person they want to spend time with, not have a romantic relationship with and therefore, this experiment does not provide reliable proof for the role of OXT in pair bond formation[18].

When the Relationship Closeness Induction Task is conducted, administration of OXT increases intimacy in a conversation in females, but does not have the same effect in males[2]. Hugging, touching, massage, nipple stimulation and orgasm induce release of OXT and promote trust and increased eye contact[33]. A couple were asked to talk about their first date and they were observed for social cues[37]. The subjects showed nonverbal displays such as nods, smiles and leaning towards partner when recalling experiences of romance[37]. This was positively correlated with an increase in plasma OXT levels in the subjects[37].

Certain variations of the OXTR gene, including rs13316193, rs2254298, rs1042778, rs226849413 and rs226849 are associated with a decrease in empathy during a romantic relationship[2]. Rs7632287 is associated with increased pair bonding in females[2]. Interestingly, females who have experienced abuse or neglect early in their childhood have decreased levels of OXT[6]. This affects their ability to form social relationships, such as pair bonds[6].

Initial Stages of a Romantic Relationship

There is a heightened level of OXT in the plasma of new couples. These increased OXT levels are correlated with more interaction between couples and can predict which relationships are likely to have survived six months later[18].

When a person is in love, every encounter with the partner causes OXT release, which enters the mesocorticolimbic pathway, increasing the importance of social cues and memory. Therefore, the person pays more attention towards certain characteristics of their partner such as sights, sounds, odors, behaviors and specific characteristics[33]. During the first phase of partner addiction, high levels of sensory information is gathered about the partner such as looks, touches, words, smells, shape of body and face. This induces positive reward stimulation by releasing DOPA in the nucleus accumbens and activating opioid receptors. The oxytocinergic, dopaminergic and opiate systems work together to form a positive feedback loop, whereas the experiences with the partner create reward outcomes and the reward increases the feelings towards the partner[33].

Long-Term Relationships

In substance addiction, the subject develops tolerance towards the drug, producing negative symptoms when the subject is not under the effect of the substance. In very much the same way, when a person is away from their partner, especially in the initial stages of the relationship, they feel symptoms similar to those of tolerance. OXT seems to play a role in mitigating these symptoms[33].

The positive feedback loop accumulates and ultimately the subject adapts[33]. Therefore, DOPA signaling is altered in favor of D1R, leading to a reduction in reward and an increase in negative of aggressive behavior, producing one of the following three possible outcomes[33].

Once the euphoria at the start of the relationship ends, it is replaced by a sense of constant happiness as opposed to extreme reward felt when the mesocorticolimbic pathway is at its highest activity. This is similar to tolerance in substance abuse[33]. Another possibility is that once the initial euphoria subsides, encounters more frequently contain conflict and the relationship has a high amount of negative emotions[33]. However, the couple increase the amount of encounters despite the negative effects. This is similar to dependence-induced escalation of consumption[33]. The last possibility is that DOPA release continues but receptor signaling favors D1receptors, which are associated with aggressive behavior[33]. Therefore, the subject displays an aggressive behavior when they try to defend their "territory" (jealousy in a relationship). This is similar to compulsive and escalating drug abuse[33]. OXT administration increases good communication behavior in relation to negative communication behavior during a conflict[2]. Positive marital relationships are correlated with increased life expectancy; better immune function; cardiovascular health[2].

The End of a Romantic Relationship

The loss of a partner puts a human at a higher risk of both mental and physical health problems. This has been studied in detail using monogamous prairie voles, which showed signs of depression following bond loss[38]. A study conducted in 2014 uses male prairie voles and allows them to form a pair-bond with a female for 24 hours. Then, some are allowed to remain with their partner while another group are separated for four weeks. It is shown that the male prairie voles which are separated from their partner show a significantly higher level of anxiety in both the elevated plus maze and the light-dark box[39]. Although human studies are limited, similar anxiety and depression symptoms are often seen following the end of a romantic relationship in humans.

Reunion after a break-up is similar to relapse in substance abuse[33]. In both initial stages of sobriety and after a breakup, there are increased levels of dynorphin which induces a negative effect[33]. OXT mitigates the negative effects and decreases the chances of reunion/relapse[33]. Consolation and social encounters after a break up increase release of OXT, which further decreases the symptoms of withdrawal[33].

Conclusion

Although the role of oxytocin in human social behavior and its implications on pharmacotherapy are still not well known, current studies have shown that this neurotransmitter plays an essential role in these processes. Oxytocin nasal spray has been shown to increase trust towards strangers during a game. It also reduces amygdala and caudate nucleus regions of the brain which cause fear, conditioning, and social conditioning[40]. Such studies help reveal the mechanisms involved in normal human interaction and bonding, and can increase the understanding of social disorders. Furthermore, oxytocin could play a vital role in future

therapeutics battling social disorders such as autism[41], and has also been implicated in treating addiction[42].

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