Falling in love: is oxytocin the magic spark?

Effects of oxytocin and dopamine on the human and animal brain

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Abstract

People who are in love seem to be absent-minded and sometimes even behave like children. What in the brain causes these romantic feelings and do animals have similar feelings? Comparable to humans, monogamous relationships are also seen in several animal species. To examine what causes pair-bonding, researchers observed partner-preference tests and found out that in prairie voles oxytocin and arginine vasopressin (AVP) emerged as important mediators of partner-preference formation. More recent studies revealed an even more general role for oxytocin in modulating affiliative behavior in both sexes. They also discovered an important interaction of dopamine and the reward system with the oxytocin system concerning partner-preference, as mating induces elevated oxytocin levels and dopamine release in the NAcc of prairie voles. A possible explanation for the fact that there are also non-monogamous vole species with the combination of CSF oxytocin and dopamine, is that in non-monogamous species the dopamine system and the oxytocin/AVP systems probably are uncoupled due to the low densities of oxytocin receptor/ vasopressin 1a receptor in this pathway. Nevertheless, more research has to be done to fully understand the cooperation between these neural systems. Untill now the only concluding thing to say is that humans and animals all have a similar biological mechanism when it comes to pair-bond formation.

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Introduction

It was a stormy autumn day when Emily just came out of the library. The sky was grey and a cold wet wind blew her straight blonde hair in all directions. She didn't seem to notice. She had to hurry, because in less than ten minutes she had to be at the train station if she wanted the train not to leave without her. The street was crowded with people hurrying home. With a pile of books under her arms she rushed into the crowd trying to avoid all the bad-tempered people. Elbows and shoulders bumped against her but she pressed the books firmly against her body and moved on. Suddenly, she couldn't interpret where it came from, a push from the left hit her in her flank. To prevent not to fall she spread her arms and her books spread out all over the street like water in a fountain. People didn't seem to notice. Startled she watched her books. Some of them blew open and the pages flared up in the wind, almost tearing out of the cover. Quickly she tried to grab as fast as she could all the books together. When she reached out her hand to grab the last book, suddenly another hand appeared that also reached out to the same book. It all went so quickly but at the same time in slow motion, but nevertheless it was impossible to prevent. The man's hand grabbed the book together with her hand, that grabbed it just half a second earlier. Startled she looked up and looked straight into the deep blue eyes of a handsome young man…

It was as if her heart stopped beating, as if the earth stopped turning, as if she got hit by lightning...

It felt like she was drowning forever in the most pure form of perfection. Suddenly he blinked with his eyes and pulled back his hand. "I'm sorry" he said and quickly he stood up. "Are you all right?" She nodded yes and stared at the ground. What a clumsy girl she could be sometimes! She looked up again, but as sudden as he had appeared, he was also gone. Like everything was still the same, like he had never been there, but for her the world had changed completely …

1. The vole story

This romantic story is about two human-beings, seeing each other for the first time, falling in love at the same moment. They don't even know each other, but they do know they are devoted to each other. People who are in love seem to be absent-minded and sometimes even behave like children. What is it with people and their sense of falling in love and their emotional feelings? Maybe even more interesting is the question: what in the brain causes these romantic feelings and do animals have similar feelings?

Comparable to humans, monogamous relationships are also seen in several animal species. An extensively studied species in this respect is the prairie vole (*Microtus ochrogaster*) a little rodent that lives in central North America. They are monogamous, which means in this context that in nature they display selective (but not exclusive) affiliation and copulation with their partner, as well as biparental care of the offspring and nest sharing [2]. The prairie voles form enduring pair bonds and are biparental. On the contrary, montane voles (*Microtus montanus*) and meadow voles (*Microtus pennsylvanicus*) do not form enduring pair bonds. They are non-monogamous and typically do not display biparental care [6, 9, 13].

These remarkable differences between closely related species can be used to study the neurobiology of pair bonding. To examine what causes this pair-bonding, researchers observed partner-preference tests and found out that in prairie voles oxytocin and arginine vasopressin (AVP) emerged as important mediators of partner-preference formation.

More recent studies even revealed a more general role for oxytocin in modulating affiliative behavior in both sexes. 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 [11]. Centrally released oxytocin also coordinates the onset of maternal nurturing behavior at parturition and plays a role in mother–infant bonding [11,7].

Clearly there are many mechanisms to think of how partner-preference and romantic feelings are being regulated. Interesting studies have been done with humans as well as with animals, one even more spectacular than the other, but this essay will focus on the role of oxytocin.

A lot is known about peripherally released oxytocin, but what are the effects of centrally released oxytocin and where in the brain does it work out? In the next chapter brain oxytocin is elucidated to get to know more about the effects of this neuropeptide.

2. Brain oxytocin

It is generally known among biologists that oxytocin is a small neuropeptide produced in the hypothalamus, and that it is released by the neurohypophyseal system into the peripheral circulation. There it plays an important role, especially during orgasm in both sexes and giving birth in women [15]. When a mother gives birth, a cascade of neurochemical events take place caused by vaginocervical stimulation, including the release of oxytocin [11], which facilitates parturition and milk ejection during nursing [11, 12]. However, centrally oxytocin is an almost completely different system that plays an important role in both women and men. To understand the effect of oxytocin in the brain, let's first take a closer look at this neuropeptide.

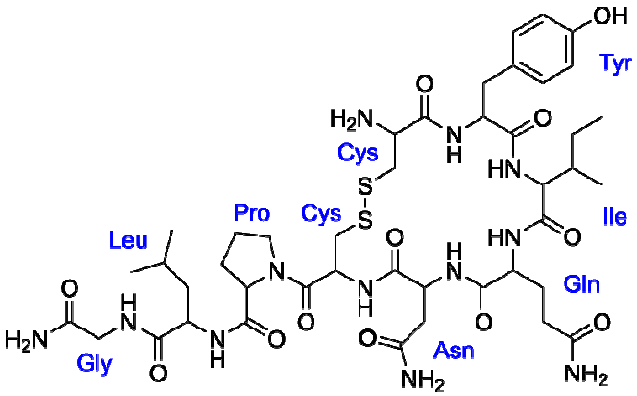


Fig. 1. Oxytocin [i]

Oxytocin is a cyclic peptide with nine amino acids; a nonapeptide (fig. 1). The family to which oxytocin belongs, involves both vertebrate and invertebrate peptides, which suggests that the ancestral gene encoding of the precursor peptide already existed before the two groups separated, around 700 million years ago [5].

Oxytocin is able to diffuse through the extracellular space due to a long half-life [11]. For example, the half life values of oxytocin are about 28 minutes in the CSF (compared to 2 minutes in the blood plasma) [12]. Because of their relatively long half lives, neuropeptides (like oxytocin) have a high binding affinity for their receptors to achieve peptide specificity to prevent every random peptide from binding every random receptor [11]. The difference between the half life values of oxytocin in the CSF and the blood plasma seems remarkable. However, this large difference in time is not surprising if you consider the fact that peripheral and central oxytocin mechanisms operate almost independent of each other: peripheral oxytocin does only contribute for a negligible amount (0.002%) to the oxytocin levels in the cerebrospinal fluid (CSF) [12]. Furthermore, out of many other literature findings can be concluded that CSF levels of oxytocin are different from peripheral levels and that these levels are controlled by different independent mechanisms [12]. The levels of oxytocin in the CSF, naturally as well as experimentally, show very different reactions to natural or experimental situations and seem to be more then enough to create a signal to sensitive brain areas [12].

Although the oxytocin levels vary considerably daily and between species, oxytocin has been detected in the cerebrospinal fluid (CSF) of many species [12]. Most of the production and release of this centrally oxytocin occurs by partly overlapping and interconnected neurons located in two hypothalamic areas: the paraventricular nucleus of the hypothalamus (PVN) and the supraoptic nuclei (SON) (fig.2) [11, 12]. In the PVN two types of oxytocin releasing neurons exist: large magnocellular neurons and smaller parvocellular neurons, which both differ in size and projection side [11, 12]. In the SON only magnocellular neurons are found [11, 12].

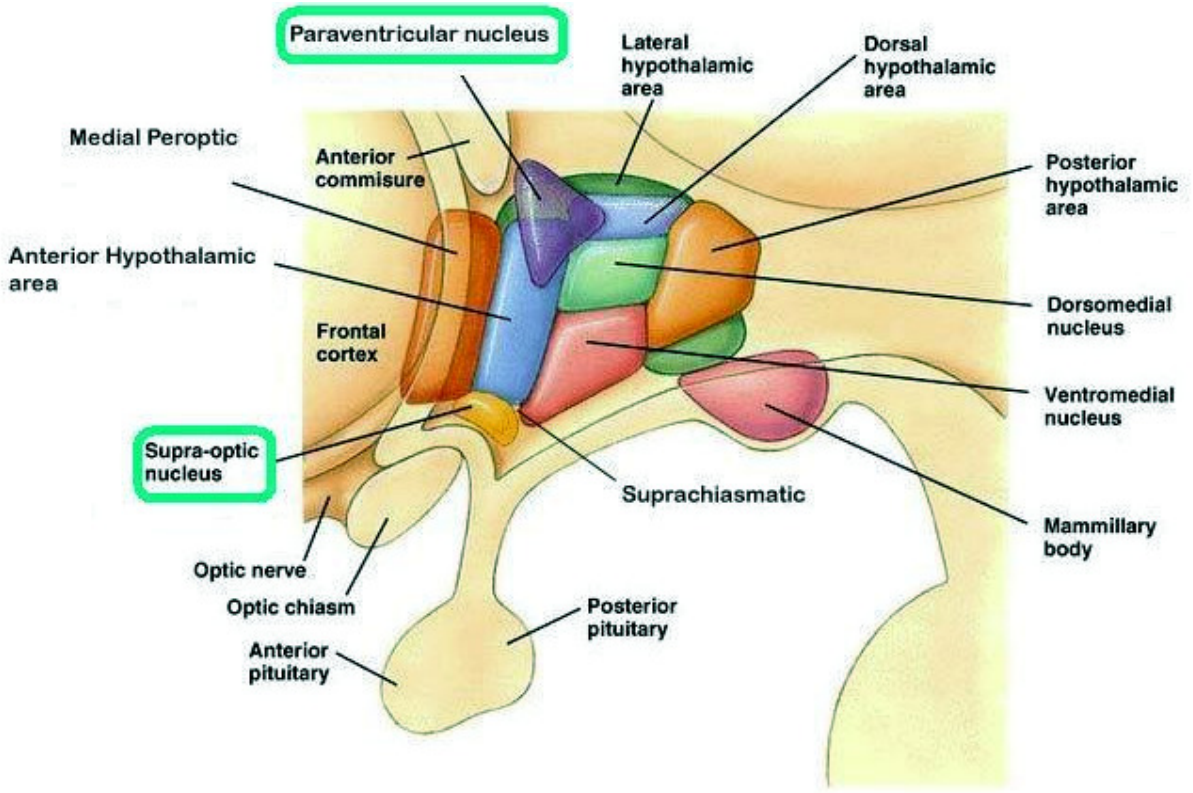
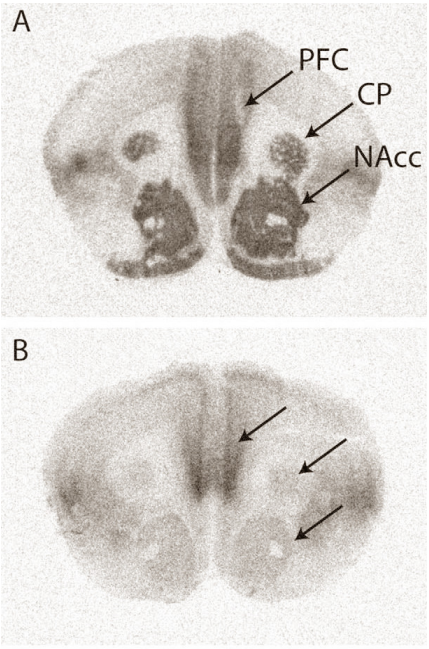


Fig. 2. Nuclei of the Hypothalamus in the human brain [ii]

These magnocellular neurons are large neurons which release oxytocin from their axons into the posterior pituitary, and from their dendrites into the extracellular fluid (ECF) [11, 12]. Once the oxytocin enters the ECF, a chain reaction of massive oxytocin release occurs, whereas oxytocin has a strong excitatory effect on the activity of other oxytocin neurons [12]. This massive release leads to a thousand fold increase of ECF oxytocin levels, which subsequently results in an elevated oxytocin level in the CSF, since there is no barrier between the ECF and the CSF [12].
The parvocellular neurons release oxytocin from their axons to many distant brain areas and to the spinal cord [11, 12], and many of their axonal projections border or surround the ventricular system [12]. Additionally, oxytocin releasing neurons can also be found in the bed nucleus of the stria terminalis and the lateral hypothalamic area, and oxytocin fibers are found spread throughout the entire brain like in the NAcc, amygdala, lateral septum and hippocampus [11].

About the receptor: the oxytocin receptor is a seven transmembrane G-protein coupled receptor and is spread through many parts of the brain, ranging between and within species [11, 12]. Some of these parts of the brain are activated during both romantic and maternal love, others only during the one or the other [15]. Since much of the brain studies have been done with prairie voles, it is intelligible to look closer to their oxytocin receptor distribution and density.

There is a remarkable difference between the distribution of oxytocin receptor density within different vole species. Monogamous prairie voles have significantly higher densities of oxytocin receptors in their nucleus accumbens (NAcc) and caudate putamen than non-monogamous meadow and montane voles (fig.3), but they both have oxytocin receptors in the prefrontal cortex [2, 11]. Furthermore, there is also a remarkable difference in oxytocin receptor density within prairie voles. In rats, natural variation in brain oxytocin receptor expression levels tends to be amendable by the amount of giving maternal care [11]. Mothers that raise their pups with high licking and grooming behavior show an



increased oxytocin receptor density in the medial preoptic area, the bed nucleus of the stria terminalis, the lateral septum, the amygdala and the PVN compared to mothers with low licking and grooming behavior, as observed by Ross and Young [11]. Subsequently, pups that where often licked and groomed by their mothers generally became high licking and grooming mothers themselves [11].

Fig. 3. Differences in oxytocin receptor expression in prairie and montane voles. Notice the higher level of oxytocin receptor binding in the caudate (CP) and nucleus accumbens (NAcc) of the prairie vole (A) than the montane vole (B). Both species have oxytocin receptor binding in the prefrontal cortex (PFC) [11].

3. The function of oxytocin

Maternal bonding

A reason to focus on brain oxytocin is because of it's role in mother-infant bonding. This form of bonding seems to be the perfect link between oxytocin and pair-bonding since mother-infant bonding seems to be a primary function for oxytocin. To understand the role of oxytocin in maternal behavior, a lot of research has been done with rats, mice and sheep by injecting oxytocin or inhibitors, and with oxytocin and oxytocin receptor knockout animals. The outcomes of these studies indicate an important role for oxytocin in the onset of maternal behavior [11, 4, 8].

For example, in 1979 Pedersen and Prange already studied the induction of maternal behavior by injecting oxytocin into the cerebral ventricles of virgin rats, and remarkably they observed nurturing behavior towards pups within two hours (table 2) [10].

Estrous state	Oxytocin	Vasopressin	Saline
D_2	2/4	0/1	0/1
P	3/5	0/4	0/2
E	6/8	0/2	0/1
Total	11/17	0/7	0/4
D_1	0/3	0/1	0/1
Prolonged mid-D	1/9	0/2	—
Total	1/12	0/3	0/1

P, proestrus; E, estrus; D_1, day after estrus; D_2, day before proestrus; prolonged mid-D, diestrus between D_1 and D_2.

Table 2. Ratio of numbers of animals showing full maternal response to total number injected in each estrous state [10].

This initial experiment was criticized by other researchers who showed conflicting results, possibly due to differences in testing protocol and/or rat strains, and therefore it seems likely that beside oxytocin there are some other factors that increase the probability of spontaneous maternal care in virgin rats, like estrogen priming [11]. Yet, support for oxytocin as a regulator for the onset of maternal behavior has been derived from studies where an oxytocin antagonist or oxytocin antisera was infused into the brain of rats that had just given birth, resulting in blocking the onset of the maternal behavior [11, 8].

A same type of experiment has been done with prairie voles, where an oxytocin antagonist was injected in the NAcc of adult virgin females, resulting in a total block of alloparental maternal behavior (fig. 4) [11]. In addition, mice with a deletion in either the oxytocin or oxytocin receptor gene were used in genetic experiments, of which the results also support the onset effects of oxytocin in maternal behavior [11]. It seems that oxytocin is not needed for the maintenance of maternal behavior, since after nurturing the pups, oxytocin antagonists fail to inhibit maternal behavior [11, 8].

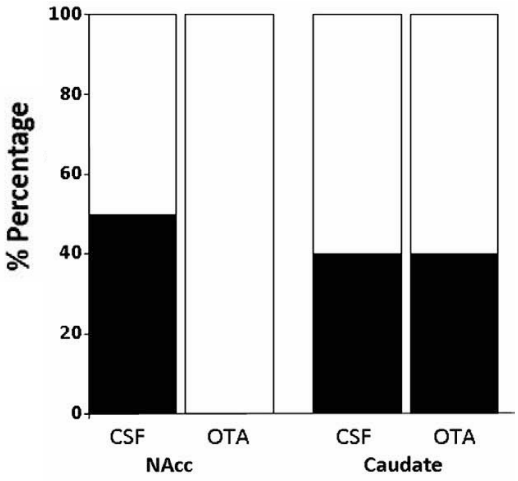


Fig. 4 Graph showing the effect of administering oxytocin antagonist (OTA) or cerebral spinal fluid (CSF) into the NAcc or CP on alloparental behavior of female prairie voles [11]. Nulliparous females injected with CSF in the NAcc or CP, or OTA in the CP, showed the normal variation in propensity for alloparental behavior, with about half showing nurturing care [11]. 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 [11].

However, rodents typically display promiscuous maternal behavior as they do not form a particular mother-infant bond, but ungulates such as sheep do [11]. As they live in large herds and their offspring is able to walk within a few hours after birth and they all give birth during a defined season, the possibility of accidently nursing the wrong lamb is significantly present. To prevent putting effort in the wrong offspring, sheep evolved mechanisms to form particular mother-infant bonds [11]. During birth a cascade of neurochemical events take place in the mother caused by vaginocervical stimulation, including the release of oxytocin [11]. With an in vivo microdialysis in multiparous sheep, Da Costa et al showed that oxytocin concentrations increased significantly in the PVN region at the time of giving birth (Fig.4) [4]. In addition, oxytocin receptor expression also increases in the hypothalamus and the medial preoptic area when estrogen levels increase during pregnancy [8].

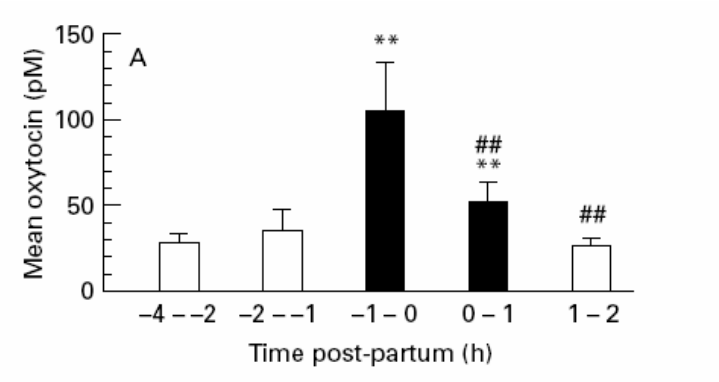


Fig.4. Shows mean ± SEM concentrations of oxytocin in microdialysis samples taken from the PVN of 8 sheep at -4 to -2 h and -2 to -1 h prepartum, from -1 h pre-partum to birth (the animals were all in the final stages of labor for the whole of this hour), from 0-1 h post-partum and 1-2 h post-partum. **P<0.01 compared to pre-partum (-4 to -2 h and -2 to -1 h) concentrations; ## P<0.01 compared to mean concentrations during the previous time point [4].

It is even possible to promote maternal behavior for a foreign lamb in non-pregnant estrogen-primed sheep in less than a minute with intracerebroventriculary (ICV) administered oxytocin [11, 12]. Besides, maternal behavior in sheep is partly accountable by the fact that the olfactory areas (where the density of oxytocin receptors is generally high) are surrounded by CSF [12]. They are therefore easily accessible for oxytocin and based (partly) on the development of an olfactory memory of the odor of the lamb, and these mechanisms ultimately result in a specific mother-infant bond [11, 12]. However, these bonding effects of oxytocin only count for firstborns [5].

In summary, in sheep as well as in rodents, vaginocervical stimulation at birth results in increased oxytocin levels and administered/increased oxytocin levels combined with increased estrogen levels result in maternal behavior, in particular in sheep where it even creates a particular mother-infant bond. Since mating also results in vaginocervical stimulation and subsequently in oxytocin release in the brain [11], this raises the question: what about mating and pair-bond formations? Fortunately, pair-bond formations and partner preference have been extensively studied within closely related vole species.

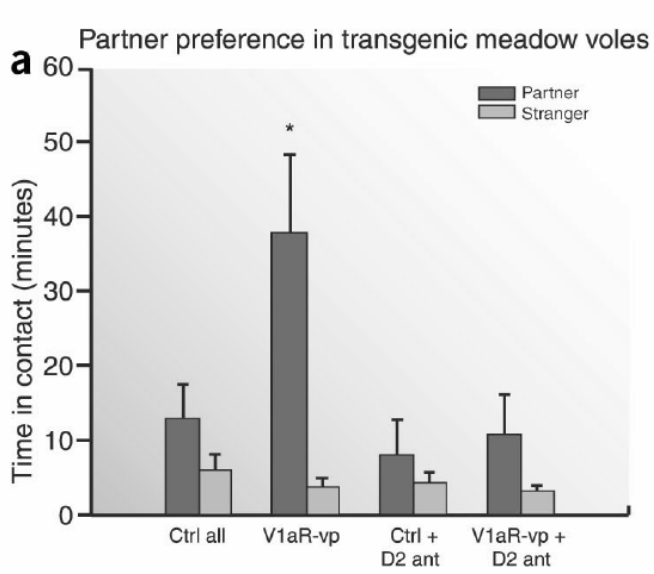
Pair bonding

In nature, prairie voles form mating pairs for extended periods of time and both parents take care of their offspring [11]. This phenomenon is known as a pair bond, and the formation of it can be tested in the laboratory by using a partner preference test [11]. For this test, a male and a female are placed together and are allowed to co-habitate, during which time mating may or may not occur [11]. After cohabitation, the actual test begins. One individual of the pair is tethered in the side chamber of a three-chamber apparatus, and a novel 'strange' animal with an equal stimulus value is tethered at the opposite side chamber [11]. Now the other individual of the mating pair, the test animal, is placed in the middle chamber and is allowed to explore all three chambers freely [11]. A preference is accredited to the test animal when the test animal spends at least twice as much time at a close proximity/huddling with the co-habitated individual as with the stranger over a three hour testing period [11].

A lot of partner preference tests have been done since this test was designed and it is clear that females typically display a partner preference when mating occurs because of the vaginocervical stimulation [11]. However, when cohabitation is long enough, mating does not even have to occur to form a partner preference or a pair bond [11]. Convincing evidence for oxytocin playing a critical role in the development of partner preference in female prairie voles is found in ICV infusion experiments [11]. Infusion of oxytocin (ICV) during a six hour cohabitation with a male results in a partner preference in female prairie voles without mating [2, 11]. The involvement of oxytocin receptors has been demonstrated by Ross and Young, who showed that an ICV infusion of an oxytocin antagonist is able to block mating-induced pair bond formation even after 24 hours of cohabitation [11].

In male prairie voles the role of oxytocin is less clear when looking at pair bonding. Some studies show that in males ICV infusion of oxytocin for 24 hours is not enough to form a pair bond and that an oxytocin antagonist is not able to inhibit partner preference formation in males [2, 11]. Nevertheless, vasopressin appears to play a more important role in males in partner preference. For example, central vasopressin infusion facilitates pair bond formation in male prairie voles without mating [14].

The NAcc has a much higher oxytocin receptor density in monogamous prairie voles than in nonmonogamous montane voles (fig. 3). Therefore the NAcc may be an indicator for the differences in mating behavior between these species. An even more interesting question is whether the NAcc is directly involved in partner preference. Ross and Young tested this, using an adeno-associated viral vector carrying the prairie vole oxytocin receptor gene, to increase the oxytocin receptor levels in the NAcc of adult female prairie voles [11]. The results showed that these females needed less time to form a partner preference than control animals, suggesting that higher levels of oxytocin receptors in the NAcc accelerate pair bond formation [11]. However, increasing accumbal oxytocin receptor densities in females of an asocial vole species like meadow voles was not sufficient to induce partner preference formation [11]. This is interesting, because this suggests that variation in oxytocin receptor densities in the adult NAcc directly modulates the ability to form social attachments, but that oxytocin receptor expression in the NAcc is not sufficient to produce the differences in bonding behavior normally seen between prairie and meadow voles [11].



Earlier, Young did a comparable experiment together with Wang (2004) and tested whether male meadow voles would form a pair bond when using a viral vector-mediated gene transfer to overexpress the gene for vasopressin 1a receptor (V1aR) [2]. They found that partner preference was enhanced in males compared to controls, but they also found that pretreating virus-treated voles with a dopamine2 (D2) receptor antagonist prevented the development of a partner preference (fig. 5) [2].

Figuur 5. Male meadow voles overexpressing the V1aR receptor in the ventral pallidum (V1aR-vp) showed enhanced mating-induced partner preferences compared to control animals (Ctrl all). Infusion of a D2 receptor antagonist (D2-ant) before mating abolished the partner preference in these males (V1aR-vp + D2-ant) [2].

This suggests dopamine has something to do with partner preference too. Several results from anatomical and pharmacological studies also indicate that the prefrontal cortex, the ventral pallidum and the NAcc are all critical brain regions in pair-bonding, and interestingly these brain regions are also part of the mesolimbic dopamine reward system [2]. This suggests that pair-bond formation uses the same neural circuitry as reward [2].

4. Dopamine

Animals

The NAcc contains a high density of oxytocin receptors and is one of the target areas of oxytocin. It also happens to be part of the reward system, suggesting that there is a direct interaction between oxytocin and brain structures involved in reward processes. Because of this, let's take a closer look at the reward system and dopamine.

The reward system, or mesocorticolimbic dopaminergic system, is called the reward system since dopamine release within this circuit is critically involved in reward (natural, like food intake and mating, as well as maladaptive, like drugs) [2]. Dopamine neurons in the ventral tegmental area project to and release dopamine within the NAcc, the prefrontal cortex and other brain areas (fig. 6) [2]. The ventral pallidum is a major target of the NAcc, which processes and relays stimuli from the NAcc to mediate locomotor responses to rewarding stimuli [2].

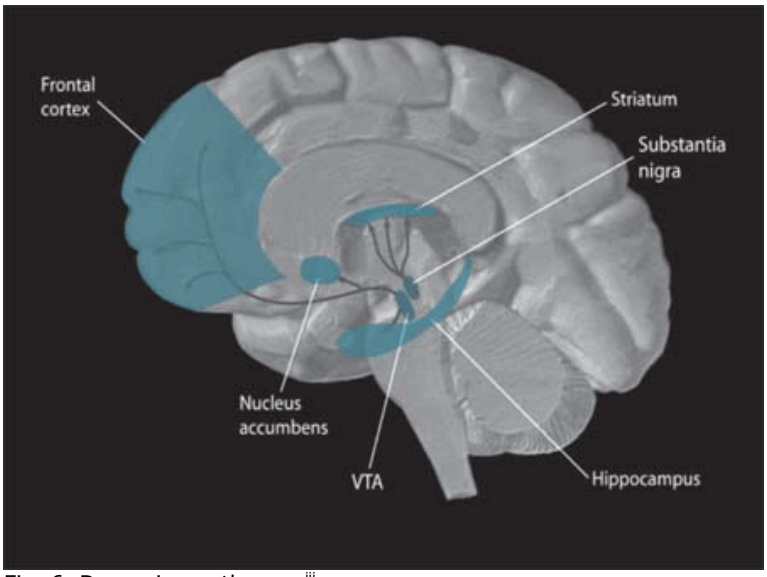
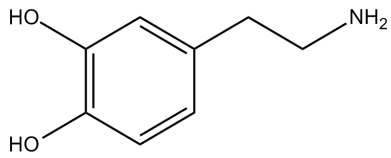


Fig. 6. Dopamine pathways [iii]



Dopamine [ii]

Dopamine receptors come with different forms and functions. For example, the D2 receptor is one of the five known types of dopamine receptors (D1 to D5, and their variants) [16]. These receptors differ in their actions, for example: D1 receptors are coupled to a G protein which activates adenylyl cyclase, which increases intracellular cAMP concentrations, whereas D2 receptors are coupled to a G protein that inhibits cAMP formation by adenylate cyclise [iv].

Experiments

Beside a high oxytocin receptor density in the NAcc, prairie voles also have dopamine receptors and dopamine projections in their NAcc coming from the ventral tegmental area [11]. It may not be surprising that beside elevated oxytocin levels, mating also induces dopamine release in the NAcc of the prairie vole [2]. Blocking D2-like dopamine receptors in the rostral shell of the NAcc results in the prevention of partner preference formation, and D2 agonists are able to induce partner preferences without mating [11]. In addition, activation of D1-like dopamine receptors prevents partner preference formation induced by either mating or by D2 activation [11].

Considering these results, it seems very plausible that in the NAcc of female prairie voles the dopamine and the oxytocin system interact to promote a partner preference, rather than acting sequentially [2]. Especially since a seminal study showed that oxytocin receptor and D2-type receptor activation have to occur simultaneously to develop partner preference in female prairie voles [11]. Blocking D2-type receptors in the NAcc shell prevented oxytocin-mediated partner preferences and vice versa: blocking the oxytocin receptors in the NAcc shell prevented D2-type receptor mediated partner preferences in female prairie voles [2, 11]. Furthermore, dopamine administration induces central oxytocin release, whereas oxytocin administration increases central dopamine levels in the rat, but this interaction may be indirect [2]. Electrochemical studies in male rats showed an increased dopamine release higher than during copulation in the dorsal and ventral striatum when a receptive female rat was present [1].

Contradicting is the fact that mating induced dopamine release in the NAcc also occurs in the NAcc of other rodents like rats, which do not form pair-bonds [2]. How is this possible? The answer may have something to do with uncoupled dopamine and oxytocin/AVP systems because of the low densities of the oxytocin receptors and vasopressin 1a receptors in this pathway in rats [2]. Nevertheless, more research has to be done to fully understand the cooperation between these neural systems.

In summary, we can say that mating in pair bonding species ultimately results in the concurrent activation of D2 receptors in the NAcc of both sexes, with oxytocin receptor activation in the prefrontal cortex and NAcc of females and vasopressin 1a receptor activation in the ventral pallidum of males [2]. In non-monogamous species the dopamine system and the oxytocin/AVP systems probably are uncoupled due to the low densities of oxytocin receptor/ vasopressin 1a receptor in this pathway [2].

Humans

That reward and neuropeptide circuits are involved in pair bonding is also seen in human imaging studies. Using functional magnetic resonance imaging (fMRI), specific brain area activity is seen in the VTA and striatal dopamine regions when human subjects viewed photographs of persons they claimed to be romantically in love with (similar to cocaine infusions!) [2]. Many of these activated brain regions also contain oxytocin or oxytocin receptors [2]. A similar test with mothers viewing pictures of their own children showed similar results, which implicates that there is an overlap between the neural mechanisms of maternal love and romantic love [2].

In several neuroimaging studies both romantic and maternal love were associated with regions specific to each, as well as overlapping regions in the brain's reward system (for example the caudate putamen) [3]. For several researchers this is possible evidence for the existence of a general, modality-independent network that would be specialized to mediate attachment [3]. Maternal and romantic love may share a similar evolutionary origin and a common evolutionary purpose: the maintenance and perpetuation of the human species [3]. Being rewarding experiences, both maternal and romantic love ensure the formation of firm bonds between individuals [3].

Pharmacological studies have suggested that oxytocin can enhance human social cognition by intranasal administration [11]. When intranasally administered, an increase and continuation of interpersonal trust occurs during economic games, even after betrayal [11]. Also the amount of gaze-to-the-eye-region of human faces increases, which is a possible explanation for the improved identity recognition memory for neutral and angry faces (independent of participant's gender) [11].

Several other studies have been done in humans concerning the relation between oxytocin levels and human pair bonding. It is proven that in humans, oxytocin levels are increased in the plasma during sexual arousal, vaginocervical stimulation and orgasm, similar to the release seen in prairie voles during mating and in rats and sheep during vaginocervical stimulation [11]. However, these studies do not say anything about the

oxytocin levels in the CSF. But, if these speculations are correct, it would be consistent with the hypothesis of the overlap between the neural mechanisms of maternal love and romantic love.

Contributing to this hypothesis is the way human sexuality has developed. Humans copulate face to face, which enhances the gaze-to-the-eye-region and increases interpersonal trust [11]. It is also remarkable that humans are the only species where the female breasts have become a secondary sexual characteristic, as nipple stimulation (in both males and females) increases oxytocin release in the plasma [2, 11]. At last, human female sexual receptivity is not coupled to the reproductive cycle, as in most other species it is [11]. So more frequent copulations can occur, which will lead to oxytocin release in females by vaginocervical stimulation [11]. Sexual intimacy in humans seems to summarize the physiological stimuli of delivery and nursing, increasing the release of oxytocin, which may serve to strengthen the sexual bonding between the male and the female, which in turn amplifies that oxytocin is involved in human social attachment [2,11].

Conclusion/discussion

Comparable to humans, monogamous relationships are also seen in several animal species like prairie voles. To examine what causes this pair-bonding, researchers observed partner-preference tests and found out that in prairie voles oxytocin (in females) and arginine vasopressin (in males) emerged as important mediators of partner-preference formation. They also discovered an important interaction of dopamine and the reward system with the oxytocin system concerning partner-preference.

It is plausible that there is an overlap between the neural mechanisms of maternal love and romantic love: sexual intimacy in humans increases the release of oxytocin in a similar way as nursing and delivering. This may serve to strengthen the sexual bonding between male and female, which in turn amplifies that oxytocin is involved in human social attachment. But before intimacy and vaginocervical stimulation take place, a kind of preference has to exist already in order to let the vaginocervical stimulation occur voluntarily. When cohabitation is long enough, mating does not have to occur to form a partner preference or a pair bond [11]. Oxytocin seems to be underlying this partner preference, since an ICV infusion of an oxytocin antagonist is able to block a (mating-induced) pair bond formation (even after 24 hours of cohabitation) [11]. This indicates the role of oxytocin on a short-term base in females. In males, vasopressin appears to play the role of oxytocin in partner preference, as central vasopressin infusion facilitates pair bond formation in male prairie voles without mating [14]. Since oxytocin is not needed for the maintenance of maternal behavior, it is very likely that it acts on a short-term base.

However, whether oxytocin causes the 'magic spark' on a short-term base ("at first sight") is not completely clear. Considering the short-term effects in rats, prairie voles and sheep, oxytocin plays a very important role in short-term bond formations. Whether this is about bonding or about these romanticized feelings of the magic spark I think is not clear.

Mating induces elevated oxytocin levels and dopamine release in the NAcc of prairie voles [2]. D2 agonists are even able to induce partner preferences without mating [11]. Blocking D2-type receptors in the NAcc shell prevents oxytocin-mediated partner preferences and vice versa: blocking the oxytocin receptors in the NAcc shell prevents D2-type receptor mediated partner preferences in female prairie voles [2, 11]. This strongly supports the hypothesis of an interaction between the dopamine and the oxytocin systems in the NAcc of female prairie voles to promote a partner preference, rather than acting sequentially [2].

This mating induced dopamine release in the NAcc also occurs in the NAcc of other rodents like rats and meadow-voles, which do not form pair-bonds [2]. A seminal study showed that oxytocin receptor and D2-type receptor activation have to occur simultaneously to develop partner preference in female prairie voles [11]. So a possible explanation for the question why there are also non-monogamous species with CSF oxytocin and dopamine is that in non-monogamous species the dopamine system and the oxytocin/AVP systems probably are uncoupled due to the low densities of oxytocin receptor/ vasopressin 1a receptor in this pathway [2].

In humans the dopamine system and the oxytocin system also seem to interact. When human subjects viewed photographs of persons they claimed to be romantically in love with, specific brain area activity was seen in the VTA and striatal dopamine regions [2]. Many of these activated brain regions also contain oxytocin or oxytocin receptors [2]. A similar test with mothers viewing pictures of their own children showed similar results, which implicates that there is an overlap between the neural mechanisms of maternal love and romantic love [2]. Nevertheless, more research has to be done to fully understand the cooperation between these neural systems.

Clearly there are many mechanisms to think of how partner-preference and romantic feelings are being regulated. Interesting studies have been done with humans as well as with animals, one even more spectacular than the other. Based on the information used in this paper I think the magic spark is not accountable by just the dopamine system or the oxytocin system. As with many forms of behavior, I think falling in love is a complex behavior regulated by a combination of many (neural) systems and hormones (and perhaps even environmental input) that interact, ultimately leading to the famous magic spark. For example, what is the role of pheromones in partner preference? And what about females who can smell complement MHC-complexes? After all, the specific mother-infant bond in sheep is (partly) based on the development of an olfactory memory, accountable by the fact that the olfactory areas are surrounded by CSF where the density of oxytocin receptors is generally high [12]. I am not denying that oxytocin plays an (and maybe even the most) important role in partner preference, romantic feelings and the 'magic spark', but I think that at least oxytocin/vasopressin, dopamine and adrenaline are needed to create this 'magical spark'. More research has to be done to be able to fully prove this.

Whether animals have these same romantic feelings of falling in love as humans do, I cannot say. Animals do not have a similar higher consciousness like humans. They don't 'think' about partner choice the way humans do and they don't 'romantisize' their emotions. Nevertheless, I believe (some higher) animals may feel a kind of 'magic spark', as in a way of being excited and attracted to a subject of the opposite sex, probably by the crave of reproduction. Untill now the only concluding thing to say is that humans and animals all have a similar biological mechanism when it comes to pair-bond formation.

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