

# **Oxytocin:**

## **The Neurotransmitter That Will Replace Friends?**

Bachelor Thesis

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# Oxytocin: The Neurotransmitter That Will Replace Friends?

## ABSTRACT

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The last decennia, it has become clear that oxytocin is an important neurotransmitter for also social behaviour. It is synthesized in the PVN by magnocellular and parvocellular neurons and has different projections throughout the entire brain. It plays a role in parental and sexual behaviour, social memory and recognition, and social bonding and affiliation. Intranasal administering of oxytocin results in an elevation of the mentioned social behaviours and it is suggested that this is due to a rise of central oxytocin level, although it is not clear yet how a nasal spray can influence the central levels. Furthermore, social support attenuates the stress response and so also the HPA-axis. It has been clearly shown that oxytocin levels are lowered in several sociopsychopathologies, like SAD, schizophrenia and autism. Intranasal administration of oxytocin reduces the social deficits in these diseases. On the other hand, social environment can also enhance the central oxytocin levels. From animal studies it can be deduced that both affiliation and isolation enhance the central oxytocin levels. This is also reproduced in humans, although these studies measured peripheral oxytocin levels. On the other hand, the behavioural effects of affiliation and isolation are the opposite of each other; the overall well-being is elevated during social support and reduced during isolation. Taking this into account, the medical profession might focus more on the self activating part of the oxytocinergic system instead of adding oxytocin.

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## Introduction

Every day, we have social interactions. These interactions can provoke emotions, affect our behaviour and influence our well-being. Social bonding, also known as affiliation, has a neurobiological background. One of the components of the neurobiology of affiliation is oxytocin, which is first of all known as a hormone for parturition and lactation. The last decennia it has become clear that this substance is also present in the brain as a neurotransmitter. Here, it affects different kinds of social behaviour, like affiliation, parental and sexual behaviour, and social memory and recognition. Several studies have proved that intranasal administration of oxytocin promotes social behaviour. The commercial industry has used these findings for developing the so-called 'liquid trust', which is an oxytocin nasal spray. They claim that using this spray will cause that other people trust you more and you will be more successful in your live, private and at work.<sup>25</sup>

Besides the social enhancing effects in 'normal' individuals, other studies investigated the relation between oxytocin levels and several sociopsychopathologies, like social-anxiety disorder (SAD), depression and autism. They found a negative correlation between oxytocin levels and the existence of a sociopsychopathology. This taken into account, oxytocin seems to be a promising drug for treating sociopsychopathologies and,

with this, improving (social) well being. However, although it is already sold by companies, the side-effects are not clear yet and it is not sold as a drug for medical purpose. Before intervening the human body with substrates, one could consider the self-activation mechanism of the oxytocinergic system. For this, the focus of my thesis is about the influence of social environment on central oxytocin levels. Does social interaction lead to an increase of oxytocin levels and if one get's social isolated, will this lead to a decrease of central oxytocin levels? The literature findings may offer an eye opener, considering the possibilities of social therapy instead of medical intervention. But before these questions are tried to be answered, there will be an introduction about oxytocin and its function in social behaviour.

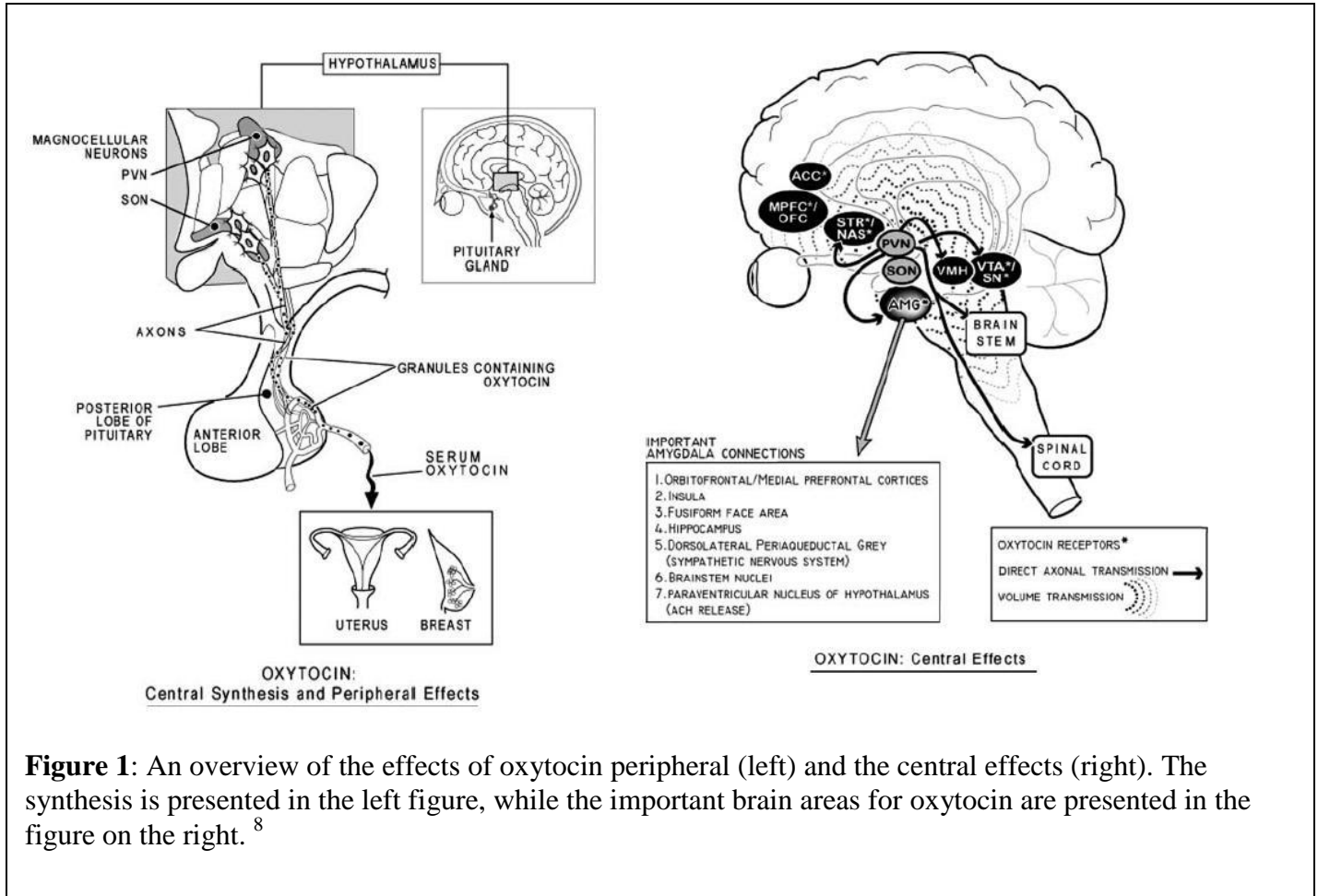
### The molecule oxytocin: production sides and its effects

Oxytocin consists of nine aminopeptides, which are Cys-Tyr-Ileu-Gln-Asn-Cys-Pro-Leu-Gly-NH<sub>2</sub>. There is only one receptor known for oxytocin; this receptor is called the oxytocin receptor. It belongs to the rhodopsin-type (class I) G protein coupled receptors. The receptor is distributed through the entire body, both peripherally and centrally. In humans, the peripheral receptors are located in the myometrium and endometrium of the uterus at the end of the pregnancy. They are also being found in the mammary gland. The peripheral oxytocin is produced in the supraoptic nuclues and the paraventricular nuclues, in the magnocellular neurons. These nuclei reside in the hypothalamus. After a stimulus, these neurons start to fire and release their oxytocin at the posterior pituitary gland. Now, the oxytocin has reached the blood and is transported to the uterus and/or the mammary glands. When oxytocin has reached its receptors in the uterus, the uterus starts to contract. The other peripheral effect is found in mammals, where an increase of oxytocin will cause lactating. <sup>1</sup> This peripheral mechanism consists of a positive feedback. This means that an increase of stimuli, leads to an increase of release of oxytocin. The increase of this hormone does not result in a decrease of stimuli or hormones. The release of oxytocin can only be 'stopped' by removing the stimuli. <sup>17</sup>

Central oxytocin functions as a neurotransmitter and has two sources. The first source is the same as for peripheral oxytocin, namely the magnocellular neurons in the supraoptic nucleus and in the paraventricular nucleus. These neurons secrete oxytocin from their dendrites simultaneously with the release from oxytocin to the blood at the posterior pituitary gland, but this oxytocin stays peripheral. However, this dendritic release can also be regulated independently from the axonal release. The second source of central oxytocin is also found in the paraventricular nucleus. These neurons are not magnocellular neurons, but parvocellular neurons. It takes time before this central release mechanism is in progress, but its effects are long lasting. <sup>1,2</sup>

The central oxytocin receptors are distributed all over the brain, though there are high- and low density regions. The high density regions are found in the hippocampus, amygdala, striatum, hypothalamus, nucleus accumbens, and the midbrain. The distribution differs not only between species, but also within species, due to sex-differences and other individual variation. <sup>4</sup> Thus, the direct function of oxytocin in the brain is affected by the central release and by the density and distribution of the oxytocin receptors.

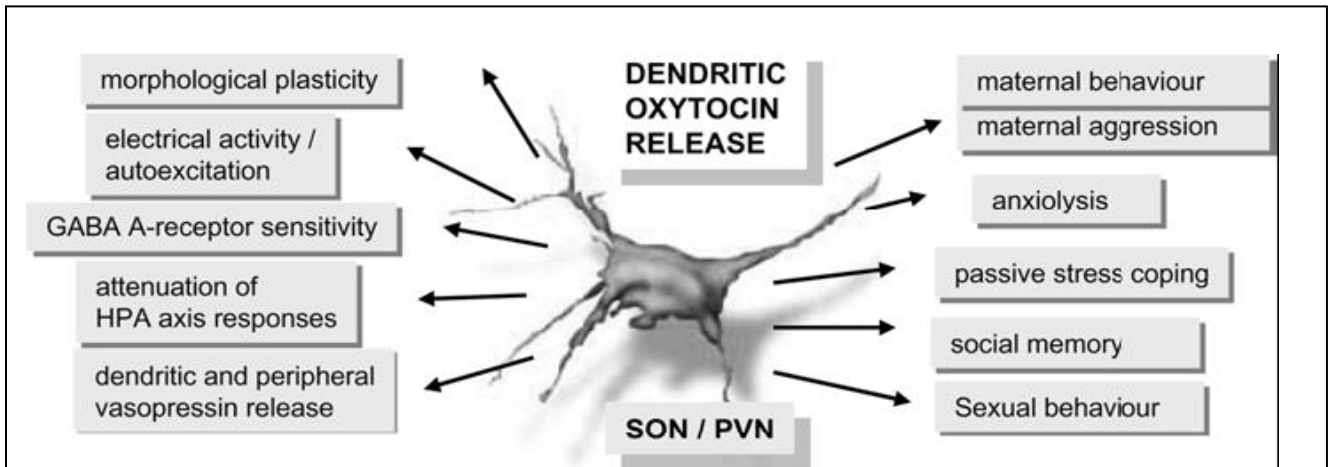
In summary, oxytocin has two functions in the body: peripherally, it acts as a hormone, while it acts centrally as a neurotransmitter. An overview is presented in figure 1. Whether or not the release of these two ‘types’ of oxytocin is independent from each other, is not clear yet.<sup>4</sup>



**Figure 1:** An overview of the effects of oxytocin peripheral (left) and the central effects (right). The synthesis is presented in the left figure, while the important brain areas for oxytocin are presented in the figure on the right.<sup>8</sup>

## Oxytocin, social behaviour and affiliation

Most recent studies on oxytocin are performed by manipulating the central oxytocin levels of the investigated subject. This manipulating often means increasing the central oxytocin levels. In animals (mostly rodents), this is done by intracerebroventricular administration. In humans, intranasal administration is used to increase the central oxytocin levels. How an intranasal spray can moderate the central oxytocin levels, is not clear yet, since the oxytocin molecule is theoretical too big to pass the blood brain barrier. Research has however shown that there is a rise of oxytocin in the cerebrospinal fluid after administering oxytocin with a nasal spray. This rise could induce a behavioural change, especially in the social behaviour field.<sup>5</sup> In figure 2, the effects of elevated central oxytocin levels are presented.



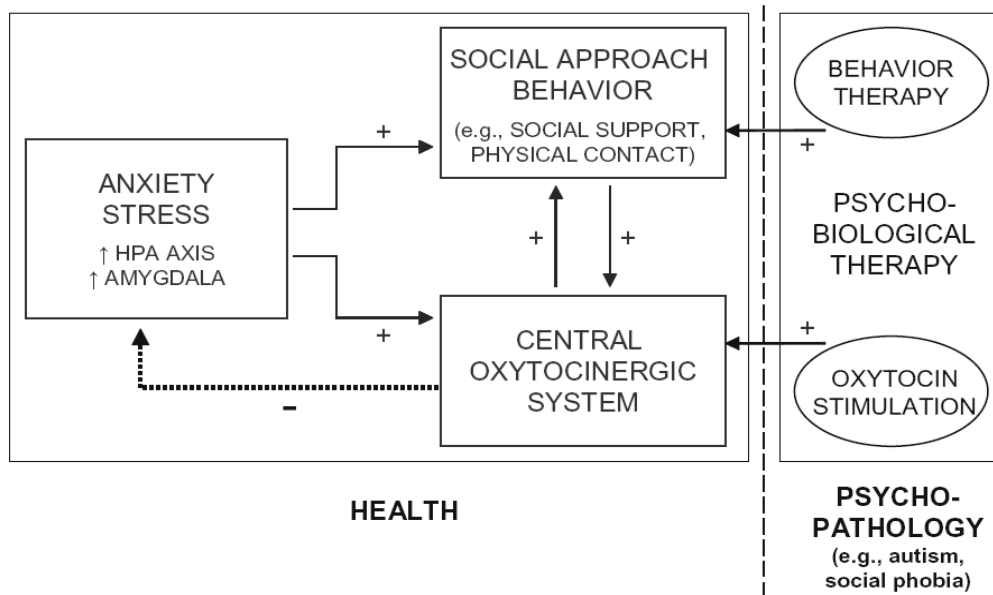
**Figure 2:** This image shows on the left side the physiological changes, induced by the release of dendritic oxytocin and so, elevating the central oxytocin levels. On the right side, the behavioral changes are shown. In this thesis, the focus will be more towards the behavioral part instead of the physiological part.<sup>11</sup>

Social behaviour is an interaction with another individual, most of the times with the purpose of provoking a response or changing the behaviour of another individual(s). Social behaviour is species-specific, and within a species, there are still social differences, due to individual variation (and gender). Social behaviour can involve territorial behaviour, like trying to expel someone from your territory, because he or she is a threat to your resources (food, mate partner etcetera).

On the other hand, social behaviour can also have the purpose to get someone closer to you, e.g. a mating partner. This kind of social behaviour is among other things regulated by oxytocin, and is called affiliation (also known as social bonding between individuals) and is highly important in monogamous sexual relationships. Oxytocin is involved in the process of choosing a partner, parental care and aggression and sexual behaviour.<sup>8</sup> This is confirmed by studies on two different species of voles, namely the montane vole, which is polygamous, and the prairie vole, which is monogamous. Their difference in social organization is due to differences in the oxytocinergic system, like another distribution and density of the oxytocin receptor in the brain.<sup>21</sup>

#### Affiliation and the stress response

The increase of oxytocin mediates different behaviours, both physiological as psychological. One of the functions of affiliation has a physiological background and can also be seen in a change of behaviour. During stress, the HPA-axis is activated, which results in an increase of stress hormones circulating through the body. If the stressor is provided with a friend, a sibling or known mating partner, the HPA-axis response is



**Figure 3:** The interaction between the oxytocinergic system, the stress response and social behavior in relation with psychopathologies.<sup>22</sup>

attenuated. There are also reports of higher levels of psychical wellbeing if a stressful stimulus is presented with social support. And, last but not least, social support combined with an intranasal administration of oxytocin (humans), seems to be a powerful way to beat stressors.<sup>22</sup> Thus, affiliation has a supporting function during stress. With a little further reasoning, social interaction reduces the chance of losing mental health<sup>3</sup>. The influence of affiliation in relation to oxytocin is shown in woman who gave birth, due to the rise of oxytocin by giving birth, lactating and maternal behaviour. Their stress response towards a social stressor is dampened. These women show less HPA-axis response, decreased blood pressure and a higher feeling of social wellbeing.<sup>6</sup> However, it should be taken into account that oxytocin is not the only hormone / neurotransmitter up regulated in the post-pregnancy period and that it is impossible to contribute this to only oxytocin.

The mechanism of how the stress response is attenuated by oxytocin can be seen in figure 3. The following conclusion can be drawn: affiliation attenuates the stress response, due to a rise of central oxytocin levels. This effect is in humans enhanced by administering oxytocin intranasally.

### Sexual behaviour

Oxytocin is also involved in sexual behaviour. Studies in male rodents have shown that oxytocin is important in erectile functioning, copulatory activity and ejaculation. The relationship between doses of oxytocin and penile erections is graphically visualized with

an inverted U; this means that high and low doses of oxytocin do not facilitate an erection, while an 'average' dose does facilitate an erection. It has been suggested that a high dose of oxytocin gives feelings of sexual satiety and in this way inhibits male sexual behaviour. However, even with the right dose, oxytocin alone is not capable of inducing penile erections, as has been shown in castrated animals. Administering testosterone makes the effects of castration 'un-done', which results, with oxytocin, in penile erection.<sup>32</sup> Male human studies have shown that during sexual arousal the oxytocin levels are elevated and even more elevated during orgasm. Deduced from this, another study provided the medical use of oxytocin for treating anorgasmia in men.<sup>31</sup>

In females, oxytocin is involved in the onset of sexual maturity. Oxytocin interacts with the gonadotropin-releasing hormone to coordinate this onset.<sup>33</sup> Besides this, oxytocin induces also sexual behaviour in females. Sexual receptivity is facilitated by oxytocin, as has been measured in rodents by the quantification of lordosis behaviour. But, important, this behaviour is only possible when the animals are not ovariectomized. If they are ovariectomized, oestrogen and / or progesterone should be administered in combination with oxytocin, to induce lordosis. As in male humans, in female humans there also is an elevation in plasma oxytocin levels during sexual arousal and orgasm.<sup>7</sup> Besides the physiological function of oxytocin in both males and females during sexual behaviour, the rise of oxytocin could also have a social 'getting-more-attached-to each-other' function, which is important in monogamous species. One can compare this with the rise of oxytocin during parturition, which also facilitates the maternal – infant bond.

### Parental behaviour

As mentioned before, taking care of your offspring (parental behaviour) induces a change in the level of oxytocin. These changes are not only found in the levels of oxytocin, but also in the number and distribution of the oxytocin receptors. In general, there is an increase of both oxytocin levels and oxytocin receptor expression. The function of this increase is facilitating the onset and maintenance of maternal behaviour.<sup>1</sup> The changes in behaviour of the mother are necessary for the survival of her offspring. However, the increase of maternal behaviour cannot only be contributed to oxytocin. An alteration in the oestrogen levels is also necessary, since this hormone interacts with the oxytocinergic system; i.e. an increase of oestrogen leads to an up regulation of oxytocin. Without oestrogen, a rise of oxytocin will not induce the onset or maintenance of maternal behaviour.<sup>8,7</sup>

In 'dads', the effect of oxytocin is not as much studied as in 'mums'. This is probably due to the small amount of animal species in which there is biparental care or only care by the male. The studies which took place are contradictory and because of this, there is not (yet) a conclusion about the function of oxytocin in paternal behaviour.<sup>7</sup>

Concluding, oxytocin is important in parental behaviour, especially in females. It facilitates different kinds of maternal behaviour, like grooming, maternal aggression and lactating. Though there are several studies that convincingly demonstrate an important role for oxytocin in maternal care, other hormones like oestrogen, should be taking into account as being an important factor as well.

### Social (re)cognition and memory

The ability to distinguish your fellow creature from a stranger is necessary for a successful living in a group. In rodents for sure, odors are important but also oxytocin seems to be critical in social recognition. The first experiment in this field was performed in male rats. They received a central injection of oxytocin, which enhanced the amount of time a conspecific was recognized. On the other hand, an oxytocin antagonist, also centrally administered, did not have any effect on memory performance.<sup>34</sup> How the mechanism exactly acts, is thus not clear yet.

Studies on knock out (KO) mice reveal that KO mice for oxytocin has bigger implications on social recognition and memory compared to KO mice for the oxytocin receptor. There have been suggestions that this difference could be due to a compensation mechanism (involving vasopressin) with the KO-model for the oxytocin receptor, which is not suitable in the KO-model for oxytocin.<sup>9</sup>

In humans, there have been studies performed with intranasal spray. They found that an elevation of oxytocin levels, induced by the nasal spray, led to a better performance on emotional recognition. The volunteers were better able to distinguish different emotions, even with little cues given. Due to this fact, some researchers said that oxytocin has a 'mind reading' capability.<sup>35</sup> In another study with the same design, it stands out that the experimental group increases its gaze towards the eye region. This may be a cause of the better determination of emotions (which probably causes the 'mind reading' calling capability of oxytocin).<sup>36</sup> With these facts, one can say that the oxytocinergic system has interactions with the visual system.

### Oxytocin and social deficits

The impact of social performance is big in our daily interactions with others, and so, for our well-being. Different psychiatric disorders, like autism and schizophrenia, are associated with social deficits. One study has proved that autistic persons have lower levels of oxytocin in comparison to control persons. Administering oxytocin with an intranasal spray in autistic individuals enhanced their ability to recognize emotions on faces and in voices.<sup>9</sup> Another psychiatric disease, also associated with social deficits, is social anxiety disorder (SAD). In this study the effect of administering oxytocin (intranasal) to SAD-volunteers is tested. They showed that the oxytocin group in comparison to the placebo group had an improved mental representation of themselves.<sup>10</sup>



## Summary and continuation to research question

The first part of this thesis summarized the influence of administering oxytocin on social behaviour and makes a small link between oxytocin levels and sociopsychopathologies. There is a clear causal relationship between oxytocin and the behaviours mentioned; oxytocin causes an increase in parental care, trust, social (re)cognition and memory and is important in affiliation and sexual behaviour. The studies made clear that an external change in the oxytocinergic system, causes a change in behavioural expression. Thus, the oxytocinergic system is important for social functioning. This has implications for the treatment of different sociopsychopathologies, because intranasal administration of oxytocin has a health, mental, social and overall well-being improving function. Though oxytocin has not been registered yet as a treatment for this kind of diseases<sup>24</sup>, it is already sold on the internet. Here, oxytocin is called 'liquid trust' ('trust in a bottle...') and is praised for improving social performance and easily trusting other people. One can also spray oxytocin on his or her clothes, and during the whole day, other people will trust you more!<sup>25</sup> Very handy for salesman or other functions in the commercial market world...

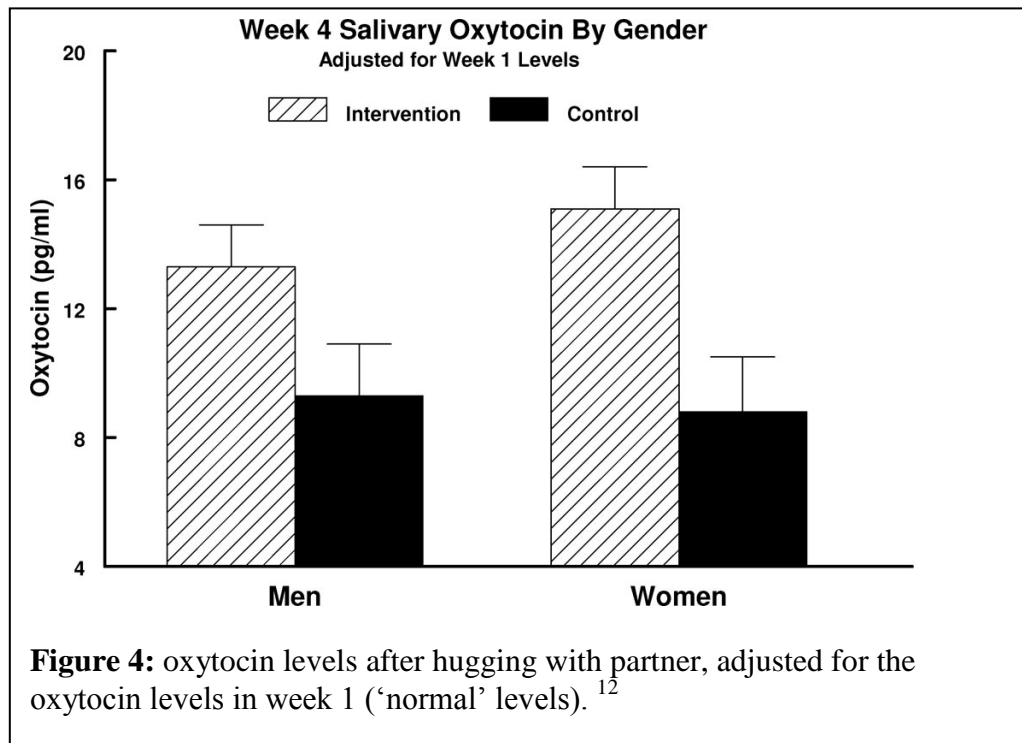
On the other hand, one can also wonder to what extent the social environment is capable of influencing the oxytocinergic system. Instead of influencing a system by medical interventions, which can have several side effects, one can focus on the self activating properties of the system. On the long term, one can think about using the social environment to (de)activate the oxytocinergic system for medical use. So the question is: is the social environment capable of inducing changes in the oxytocinergic system?

My focus will be on two parts of the social system, which are opposite to each other: social support and social isolation with respect to the central oxytocin levels.

### Social support and attachment

Living in groups is for many species an advantage. It provides safety against predators, mating partners and overall increases the fitness of a species. Researchers have investigated this social-living, with respect to different hormones and neurotransmitters among which is oxytocin. It is already known that parental behaviour and sexual behaviour are among other things regulated by oxytocin, but this is extensively peripheral studied.<sup>1,7,8,17</sup> These behaviours are probably also effected by central oxytocin levels. Besides these behaviours, other behaviours involving social support and attachment are being presented with respect to their effect on oxytocin levels.

Research done by Holt-Lunstad et al. (2008), investigated the influence of receiving a hug from your partner. They found that after hugging, the stress response, which was measured by the levels of alpha amylase, became attenuated. There was also a decrease in systolic blood pressure (only in men). And, as shown in figure 4, there was a rise of oxytocin levels after hugging with the partner.<sup>12</sup> This rise facilitates the decrease in stress response and the fall of systolic blood pressure.<sup>14,15</sup>



Another study was performed with guinea pigs by Wallner et al., 2006. They cohabitated pairs of guinea pigs during four days. On the fourth day, a male intruder was presented to the couple. The researchers studied their behavioural response and their change in oxytocin levels. One saw a rise in prosocial behaviour, as well as a rise in oxytocin levels during the cohabitation phase in compare to single-housed guinea pigs. However, this difference has only been shown significantly in male guinea pigs. When the novel stimulus is introduced, in both sexes a rise of oxytocin is measured. The researchers conclude from these results that cohabitation causes a sexually dimorphic change in oxytocin levels and that the release of oxytocin might be an endocrine marker for long-term cohabitation.<sup>16</sup>

The next study had its focus on the health advantages of group housing with respect to cholesterolemia, but had some interesting findings about oxytocin levels. Paredes et al. used for this experiment the so called Watanabe Heritable Hyperlidemic (WHHL) rabbit, which functions as an animal model for human familial hypercholesterolemia. The rabbits were housed in three different types: unstable housing (each week paired with another rabbit), stable housing (same couple during the whole experiment) and individual housing. The oxytocin-related results are shown in figure 5.

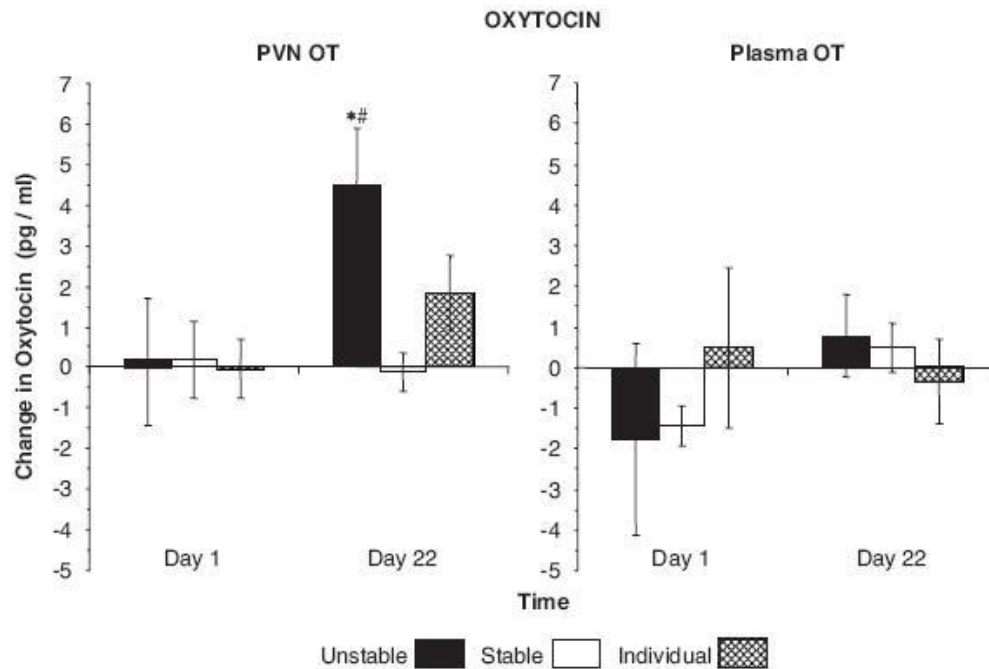


Figure 3 Change in PVN and plasma OT from baseline for each group following the social manipulation on day 1 and day 22. Values are means  $\pm$  SEM. Split-plot ANOVA revealed a statistically significant increase in PVN OT in the Unstable group on day 22. \*,  $p < 0.05$  versus baseline. #,  $p < 0.05$  versus the Stable group.

**Figure 5:** results from the study, performed by Paredes et al.. There is a clear rise of oxytocin levels after 22 days of unstable housing. The other results are not significant.<sup>23</sup>

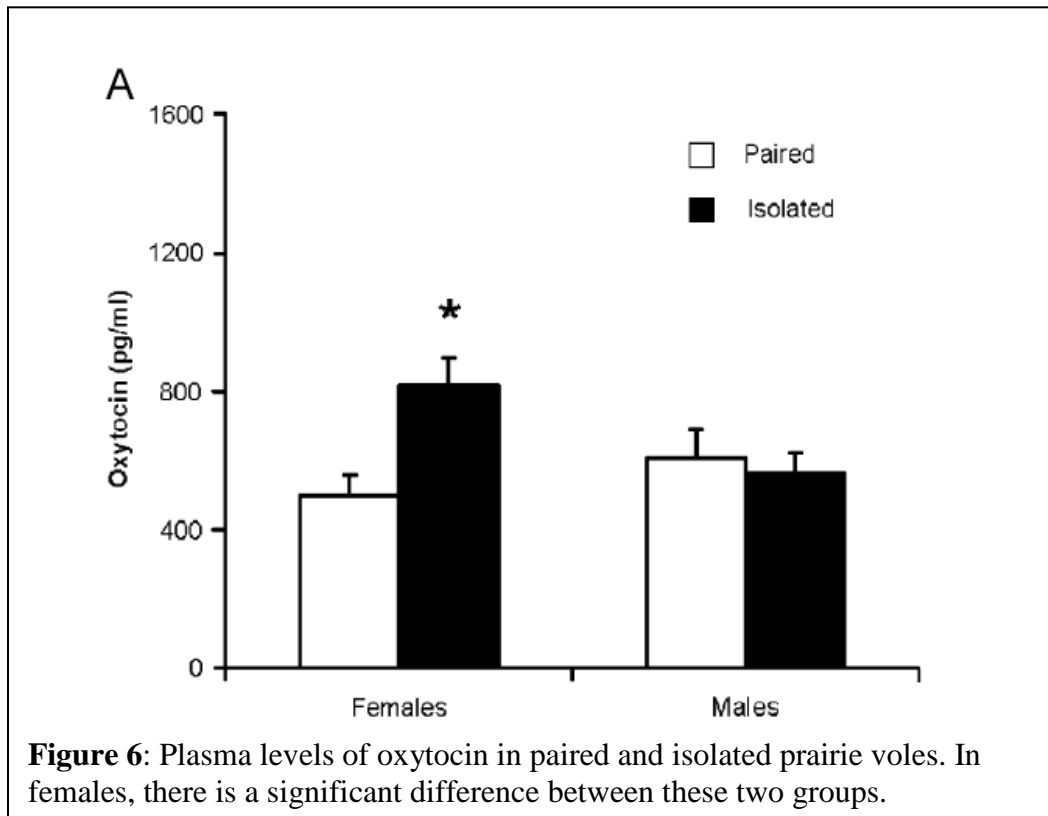
The rise of PVN oxytocin in the unstable group is probably due to the stress-attenuating function of oxytocin in the PVN, though this is not significantly supported by the stress hormone results. The researchers think that this could be due to an indirect de-activation of the HPA-axis (prior to the adrenal step), which cannot be seen within these results. The plasma oxytocin levels are not significant, as mentioned before, but the researchers preferred to call it *'there was a strong, but non-significant, trend for the concentration of plasma OT to be elevated in the Stable group relative to the other social groups'*. This elevation implicates that plasma oxytocin is important in stable social pair bonding. Furthermore, though not so important for the focus of this thesis, it seems that stable-housed rabbits are healthier, with respect to their genetic disorder.<sup>23</sup>

### Social isolation

Considering the effects of social attachment mentioned above, one can make two hypotheses on the effects of social isolation on oxytocin levels. The first hypothesis is that the central oxytocin levels increase, to buffer for the absence of social contact. This increase will attenuate the HPA-axis, which is up-regulated due to the stress of isolation. The other hypothesis is that central oxytocin levels are down regulated. This is based on the opposite line of reasoning: an increase in social contact increases, in general, the central oxytocin levels, so a decrease or absence in social contact might reduce the central oxytocin levels. A combination of both hypotheses is that it depends on the brain region whether or not there is an increase or decrease in central oxytocin levels.

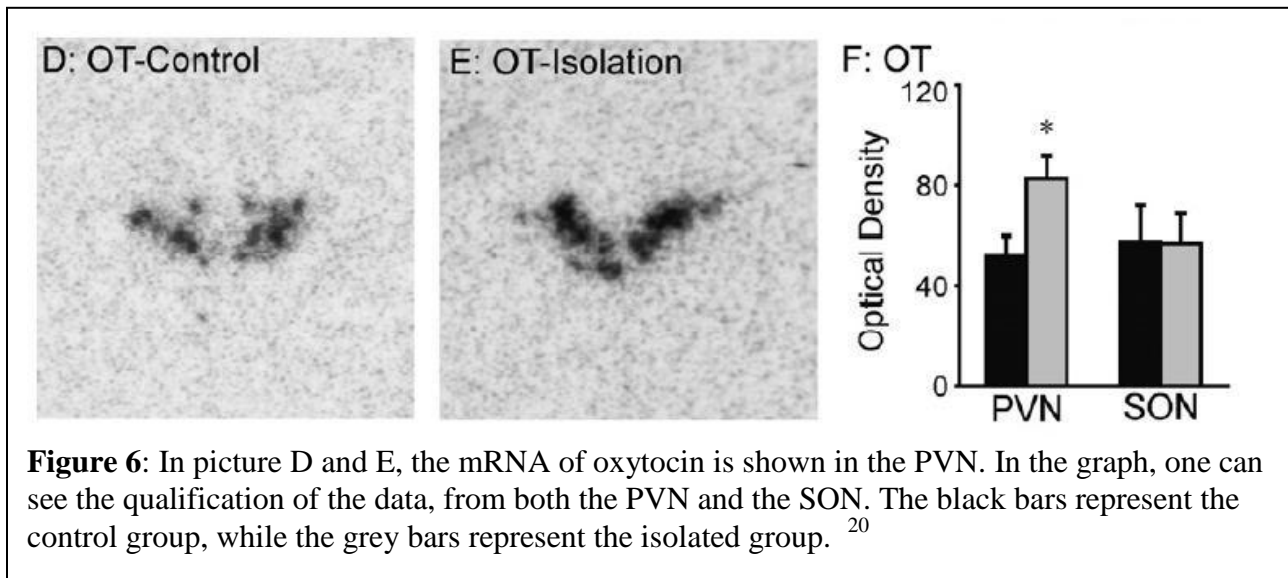
A study performed by Grippo et al., focused on the neuro(-molecular) effects of isolation and used prairie voles. They found a difference between the isolated and the control group; there was also a difference within sexes. In this experiment, isolation induced a significant increase in basal circulating oxytocin in female prairie voles. This cannot be seen in the male prairie vole.

Furthermore, immuno-reactivity has been tested for oxytocin cells in the PVN, as can be seen in figure 6. There is an increase in the cell density in isolated voles, which is significant in female voles. When an intruder (social stressor) is presented towards the voles, the isolated voles, both sexes, have a significantly higher elevation of oxytocin



levels comparing with the control group. As one can see from the other results, it seems that an increase of the HPA-axis and the accompanying hormones is related to the increase of oxytocin levels, due to the isolation procedure and the additional social stress. The behavioural effects of isolation are called depression-like by the researchers.<sup>18</sup> As can be deduced by this study, it seems that the increase of oxytocin has a buffering / compensating function for the lack of social contact. However, the animals still show a 'depression like' behaviour, so the elevation of oxytocin cannot compensate (enough) for the social isolation.

A recent study has also used prairie voles for studying the effect of social isolation on different neuro-endocrine responses, under which oxytocin. For six weeks, male prairie voles were socially isolated. Several behavioural tests were performed after the six weeks, which showed that the experimental groups showed anxiety-like behaviour. This was related to an up regulation of components of the stress system. The effect of social isolation on central oxytocin levels is studied with an mRNA analysis. Below, the difference between the control and the experimental group can be seen on mRNA expression in the PVN.



Furthermore, there is an elevation of the hormones which are a component of the HPA axis in the isolation group.<sup>20</sup> This confirms the findings of a study which is previous mentioned, namely the stress attenuating function of oxytocin.

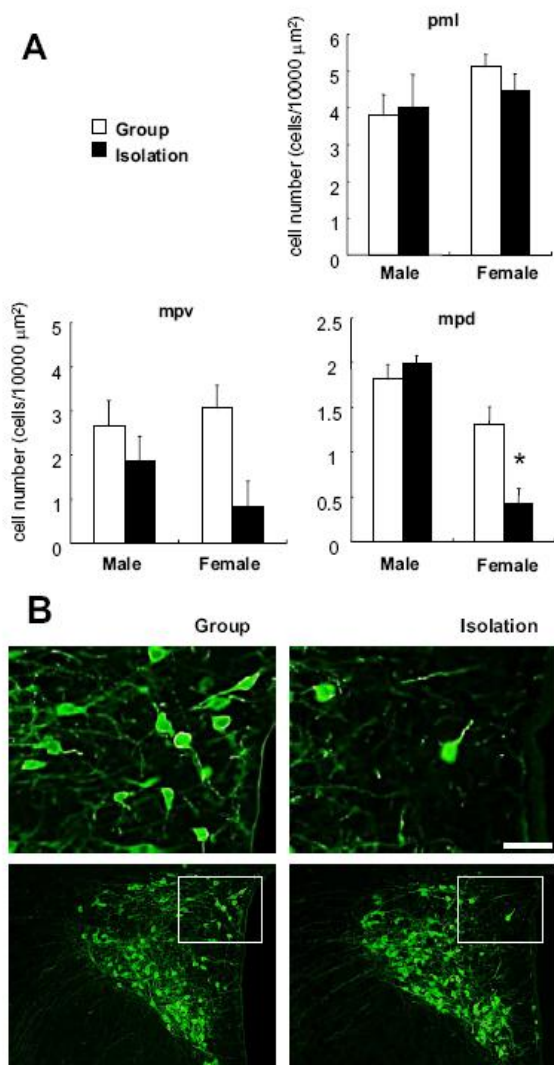
Another recent study reveals a diminishing effect of oxytocin on both physiological and behavioural parameters, which are affected by isolation. The first step in the study is isolating female prairie voles for the experimental group (versus the control group, in which female prairie voles are paired with a female sibling). Next, the experimental group receives oxytocin or saline vehicle. Overall, the physiological and behavioural effects of isolation are reduced by administering oxytocin.<sup>19</sup>

The last important research studying the effect of social isolation on central oxytocin levels, is performed by Tanaka et al.. They studied the effect of isolation in young rats shortly after lactation. For this experiment, rats, who were 23 days of age, were weaned and put into an isolation condition (alone) or a social condition (group housed, with two or three siblings). An immunohistochemical study, an elevated plus-maze test and a social recognition test were performed after at least two weeks staying in the same social condition (on different animals). The results from the immunohistochemical study can be seen in figure 7.

**Figure 7:**

The histogram (A) shows the results of the immunocytochemistry for oxytocin in three different PVN subdivisions (pml: posterior magonocellular part, lateral zone; mpd: medial parvicellular part, dorsal zone; mpv: medial parvicellular part, ventral zone). The results are divided by gender and social condition.

The photographs (B) show the oxytocin staining in the group (left) and isolation (right) in females. The upper photographs are magnifications of the squared part of the photographs down.



The results show that isolation housing has an influence on the PVN oxytocin immunoreactivity. The difference between isolation housing and group housing with respect to oxytocin immunoreactivity is only significant in females, in the subdivision of the mpd part of the PVN. Here, it causes a decrease in the number of oxytocin cells. Overall, the isolation housing seems to have the biggest impact on the female rats' oxytocin levels compared with male rats.

The results from the behavioural assessments shows that rats from both sexes which were social isolated reared, have problems with social recognition. Only the male rats show in the elevated plus-maze test an anxiogenic behaviour.<sup>26</sup> This study shows also the importance of a social rich environment during childhood for the development of the oxytocin system. This is also confirmed by a review from Teicher et al., 2002.<sup>37</sup>

## Overview: influence of social environment on oxytocin levels

The table below gives an overview of papers mentioned above complemented with some other papers, which occurred with respect to the effect of social environment on oxytocin levels.

Attachment / social support	Main author and year of publication	Title	Studie object	OXT central levels after social condition	OXT plasma levels after social condition	Effect on behaviour
	Grewen KM, 2005 <sup>41</sup>	Effects of Partner Support on Resting Oxytocin, Cortisol, Norepinephrine, and Blood Pressure Before and After Warm Partner Contact	Humans	No information available	Increase of OXT plasma levels after partner support	No data available
	Holt-Lunstad J, 2008 <sup>12</sup>	Influence of a "Warm Touch" Support Enhancement Intervention Among Married Couples on Ambulatory Blood Pressure, Oxytocin, Alpha Amylase, and Cortisol	Humans	No information available	Increase of OXT plasma after social intervention (listening touch practice with massage)	No data available
	Wallner B, 2006 <sup>16</sup>	Social stimuli cause changes of plasma oxytocin and behavior in guinea pigs	Guinea pigs	No information available	Increase of OXT plasma in partnerhousing; only significant in males	OXT release triggers male sexual behaviour and is released in both sexes during sexual activity
	Light KC, 2004 <sup>15</sup>	More frequent partner hugs and higher oxytocin levels are linked to lower blood pressure and heart rate in premenopausal women	Humans	No information available	Increase of OXT plasma (females) in a relationship with more physical contact	No data available
	Paredes J, 2006 <sup>23</sup>	Social experience influences hypothalamic oxytocin in the WHHL rabbit	WHHL rabbits	Significant increase of OXT cell expression in PVN in unstable group	No significant results	High levels of affiliative behaviour in the stable group
	Machatschke IH, 2004 <sup>40</sup>	Social Environment Affects Peripheral Oxytocin and Cortisol during Stress Responses in Guinea-Pigs	Guinea pigs	No information available	Higher levels of oxytocin in cohabitated animals	Isolated male guinea pigs rejected females easier; cohabitated animals could better cope with noise stressor

Social isolation						
	Taylor SE, 2010 <sup>42</sup>	Are Plasma Oxytocin in Women and Plasma Vasopressin in Men Biomarkers of Distressed Pair-Bond Relationships?	Humans	No information available	OXT plasma is elevated during distress in relationships, only in women	Correlation between levels of plasma OXT and quality of relationship
	Grippe AJ, 2007 <sup>43</sup>	Depression-Like Behavior and Stressor-Induced Neuroendocrine Activation in Female Prairie Voles Exposed to Chronic Social Isolation	Prairie Voles	Increase of oxytocin immunoreactivity distribution in the PVN during isolation	OXT plasma is elevated in isolated voles	Isolated animals significantly display more agitated behavior and increased behavioral reactivity towards a stressor
	Pan Y, 2009 <sup>20</sup>	Post-weaning social isolation alters anxiety-related behavior and neurochemical gene expression in the brain of male prairie voles	Male prairie voles	Increased mRNA expression of OXT in PVN in social isolated male voles (females were not studied)	No information available	Increase of anxiety-like behavior in isolated male prairie voles
	Grippe AJ, 2007 <sup>18</sup>	Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles	Prairie voles	Oxytocin-immunoreactive cell density higher in the PVN in social isolated voles	OXT plasma elevated in isolated voles, only significant in females	No difference in aggression during resident-intruder test
	Tanaka K, 2010 <sup>26</sup>	Juvenile social experience regulates central neuropeptides relevant to emotional and social behaviors	Long-Evan rats	Isolation reared female rats have decreased oxytocin-immunoreactive cells in the PVN (medial parvocellular part, dorsal zone)	No information available	Isolated males have an axiogenic profile; both isolated males and female have difficulties with social recognition

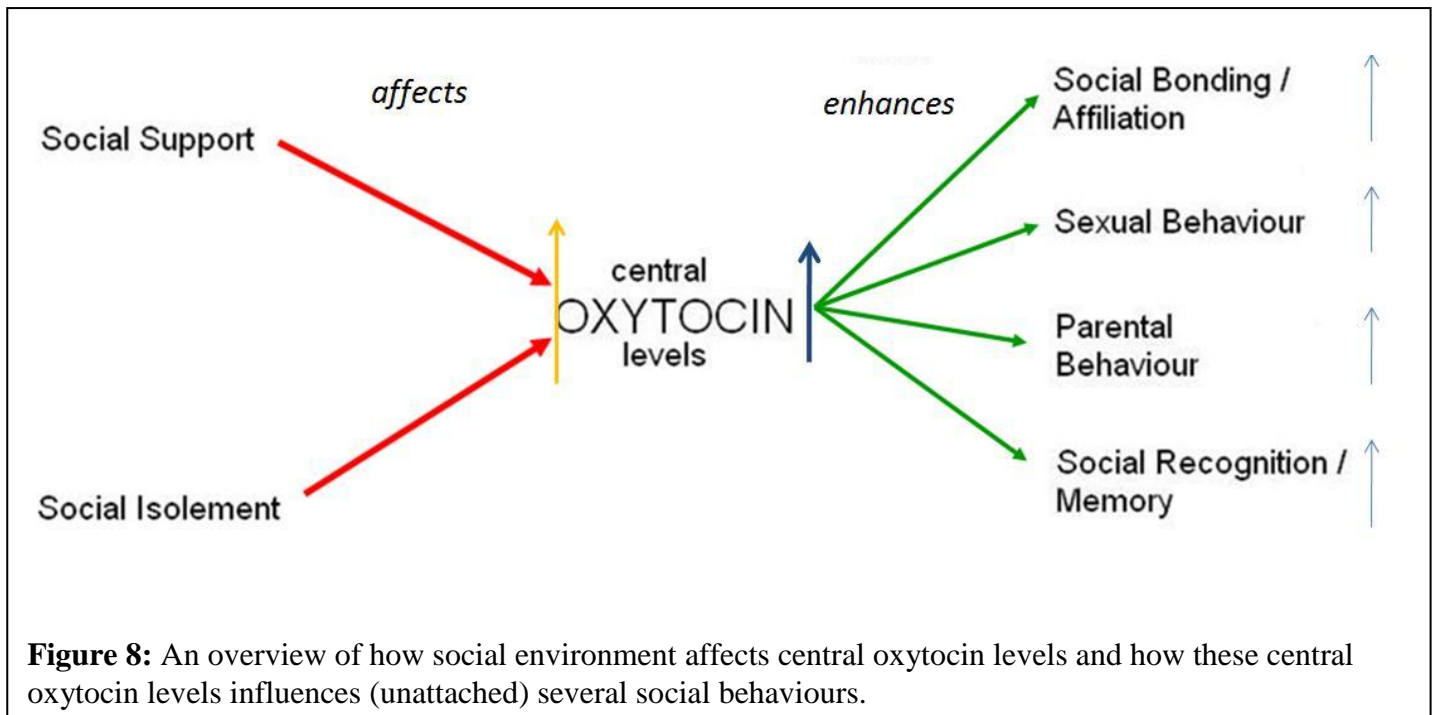
OXT = Oxytocin

PVN = Paraventricular Nucleus



## Discussion

These studies show that social environment certainly has an influence on oxytocin levels and that it heavily depends on the context. The animal studies show a positive feedback between affiliative and supporting social behaviour and central oxytocin levels. In other words, more social interaction results in an elevation of the central oxytocin levels. This has already been suggested by Hennessy et al.<sup>27</sup> Moreover, the absence of a social environment, isolation, leads also to an increase of central oxytocin levels, deduced from several animal studies. An overview is presented in figure 8, together with how central oxytocin levels affect several social behaviours. From these studies can be deduced that oxytocin is an important neurotransmitter for facilitating social behaviour. However, there are some discussion points regarding the impact and reliability of these studies. This will be discussed in the upcoming section.



**Figure 8:** An overview of how social environment affects central oxytocin levels and how these central oxytocin levels influences (unattached) several social behaviours.

### Peripheral versus central levels and intranasal administration

Most peripheral studies mentioned are performed in humans, because of the invasive impact of measuring central oxytocin levels with a lumbar puncture. The animal studies do not have this limitation and are therefore capable of measuring the central oxytocin levels. This is often determined with an immunoreactivity histochemistry. However, to what extent the central and peripheral levels are totally equal to each other, should be asked. A study from Born et al. studied the effects of administering different neuropeptides intranasal in humans and the rise of these neuropeptides in the cerebrospinal fluid and serum. One of the neuropeptides is vasopressin, which has a lot of molecular similarities with oxytocin.<sup>2</sup> Intranasal administration of vasopressin results in a rise of vasopressin

levels, both in the cerebrospinal fluid and the serum.<sup>5</sup> This confirms the hypothesis that intranasal administration leads to an increase of central levels, but it should be taken into account that oxytocin and vasopressin do not have exactly the same molecular properties. It also does not explain how the mechanism works with respect to the blood brain barrier. Though there have been studies about how the blood brain barrier mechanism functions, no study came any further than hypotheses. Furthermore, the Born et al. comment on their study 'Our data cannot be taken to establish that intranasal administration results in a greater CSF uptake of peptides than does intravenous administration'.<sup>5</sup> So, a lot can still be studied regarding the intranasal administration and the equality (or not) between central and peripheral oxytocin levels.

#### The target: an overlooked part

The studies which investigated the central oxytocin levels with respect to social environment had their focus on the releasing and circulating central levels. The target, the oxytocinreceptor (only one is known) has not been studied in relation to social environment during adulthood. However, research has shown that in the early developmental stages, the social environment also determines expression of the oxytocinreceptor.<sup>9,29</sup> Though the plasticity of the brain is thought to be diminishing with the years<sup>9</sup>, it cannot be excluded that social environment during adulthood won't have any effect on the expression of the central oxytocinreceptor.

The distribution of the oxytocinreceptor has not been studied to a great extend. Sabatier et al. state in their mini-review that distribution of the receptor is more important than the site of production of a neuropeptide. This is supported by the fact that brain peptides can travel long distances through the cerebrospinal fluid before reaching their target<sup>30</sup>. Thus, the behavioural implications of a neurotransmitter are more due to the site of action (receptor-ligand binding) than the site of release. The oxytocinreceptor is an overlooked division in this researcharea. More research on the receptor will lead to a better understanding of the whole oxytocin system.

#### Side effects of oxytocin administration?

Though in several studies oxytocin is called a promising drug for treating different kind of psychopathologies, there is no basic literature yet available about the possible side effects of (intranasal) administration of oxytocin. A case study from Germany was about a 33-year old woman who used an intranasal oxytocin spray to promote breastfeeding in combination with drinking a lot of water. This resulted in a cerebral oedema and an overall hypo-osmolarity in her body. One of the effects of oxytocin is also anti-diuretic. This, in combination with drinking large amounts of fluid, was probably the cause of her condition.<sup>38</sup> Though this is a case study, it certainly gives an indication that oxytocin has also less obvious targets in the body and therefore could cause several side effects. An increase of central oxytocin will also lead to an increase of peripheral oxytocin levels, as can be deduced from a study by Born et al..<sup>5</sup> Because the oxytocin receptors are present through the entire body (uterus, mammals, reproductive organs, gastro-intestinal tract)<sup>17</sup>, oxytocin will also have its effects here. To what extent this could be harmful, is not clear yet. Until now, there has neither been a long-term study about the effects of administering oxytocin. All together, the side effects have to be far more extensively studied before oxytocin will be applied for medical purposes.

### Overall remarks

The studies which are performed in animals, say something about the effect on animals, but could be non-suitable to humans, especially when it's about social (well) being or feelings.<sup>39</sup> Another remark is that a lot of genetic, molecular and physiological research can only be done on animals. It is not ethical to accomplish this kind of research on human beings. This is a limitation for studying the oxytocinergic system.

Furthermore, most isolation studies are performed in animals, while most support / attachment studies are performed in humans. This makes it harder to compare these two groups and to say something about the effect of social isolation in humans.

### Recommendations

More research should be performed before one can make clear assumptions about the oxytocinergic system. The oxytocin receptor, its distribution and actions are still poorly studied, while this component of the system is important.<sup>30</sup> Not only the oxytocin receptor has not been enough studied yet; also the blood brain barrier should get more attention to understand the mechanism better. Understanding of this could offer possibilities for a clarified medical application and could also show whether or not peripheral oxytocin levels are equal to central oxytocin levels. Another recommendation should be made in the animal model field. To what extent an animal model is equal to humans, especially social and/or emotional feelings, is by none of the researchers in the studies clarified. More clarity about the similarities between animal and human social organization and behaviour and the accompanying physiology, shows a better view of the applicability of animal models on humans.

My last recommendation is for treating sociopsychopathologies. Before treating this kind of diseases with medicines, social therapy (psychotherapy, group sessions, meditation etcetera) should be considered. As the social support and attachment chapter shows, the oxytocinergic system has a self activating capability, provided with the good conditions.

## **Conclusion**

Returning to the main question, it seems that social isolation as well as social support / attachment lead to an increase of the oxytocin levels, both central and peripheral. However, the rise of oxytocin in both conditions does not account for the behavioural and emotional condition the experimental groups are in, because these are opposite towards each other. The emotional condition of an animal is still hard to verify, but from behavioural tests can be deduced that animals with social support / attachment feel better compared with animals in social isolation. Animals in social isolation are anxious and show a 'depressed like' behaviour. This is comparable with humans in social isolation. From this it is deduced that the self-activating part of the oxytocinergic system should not be overlooked. With respect to sociopsychopathologies, a lot may be achieved with social therapies alone, before using oxytocin. I would like to conclude with the following remark: the medical use of oxytocin can be very useful, but not everything can be replaced. Especially not friends.

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- *Thank you for support. I shall wear it at all times* - Spike Milligan, 1959

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