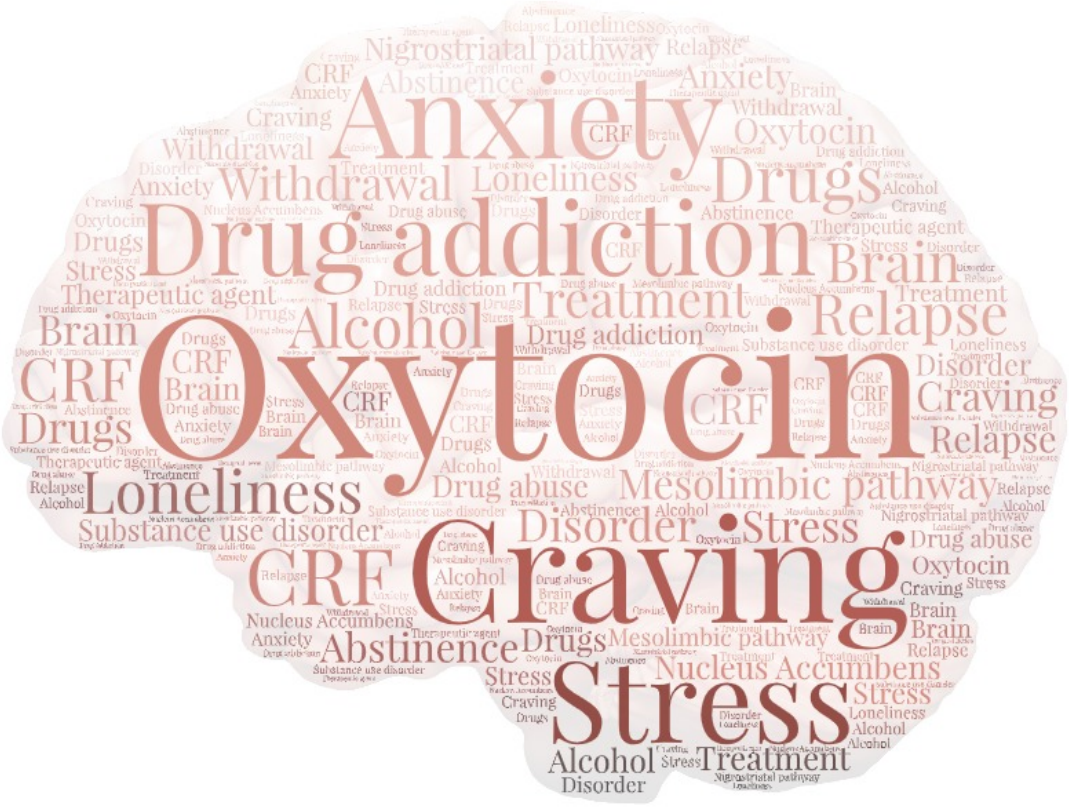
Oxytocin and drug addiction

The potential use of oxytocin as a therapeutic agent in treatments of drug addiction



Anne Eilander

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Supervisor: Prof. Dr. Anton Scheurink

Department: Behaviour & Neuroscience

University of Groningen

Foreword

In front of you lies the thesis “The potential use of oxytocin as a therapeutic agent in treatments of drug addiction”. This thesis is part of my bachelor study Biology at the University of Groningen. Combining a hormone, oxytocin, with drug addiction stemmed from my interest in endocrinology and the desire to help individuals in need. Drug addiction is a major health issue that affects many individuals. Unfortunately, an effective treatment is not found yet. My research statement was formulated together with my supervisor, Anton Scheurink. Writing this thesis was very interesting and a true learning experience.

Abstract

Drug addiction is a major global health issue that affects many individuals. It is a chronic disorder characterized by relapses and long-term changes in the brain. Drug addiction is a source of a variety of problems, such as economic-, physical- and mental problems. An important characteristic of drug addiction is that a drug addict continues to use the drug despite adverse consequences. The mesolimbic pathway (i.e., dopaminergic pathway) is an important pathway of the brain involved in reward and drug addiction. When an individual loses control over the intake of a drug and develops a drug addiction, there is a switch from liking to wanting the drugs, and a shift from the ventral striatum to the dorsal striatum in the brain. At this point, the usual rewarding feeling after drug use disappears, and the drug is used only to feel normal again. High levels of anxiety, stress and loneliness are symptoms experienced during drug abstinence. These factors give rise to high-intensity cravings, that is, an extreme desire to use the drug. These symptoms of withdrawal (anxiety, stress) and loneliness cause cravings and increase the probability of relapse. There is no cure available for drug addiction yet. There are various treatments such as behavioural- and pharmacotherapies, however, these are not very efficient as the number of patients that relapse is still very high. It is important to find an effective pharmacotherapy or behavioural therapy (or a combination of both) that reduces craving and subsequently reduces the numbers of patients that relapse after a period of drug abstinence. Oxytocin (OXT) is an important hormone in the periphery involved in contraction during childbirth and milk ejection and a neurotransmitter in the brain. Besides the role of OXT in the periphery, different studies revealed that central OXT administration is anxiolytic, exhibits anti-stress effects, and attenuates loneliness. Besides this, a study showed that there might be a direct effect of OXT on dopamine (DA) release in areas of the mesolimbic pathway important for drug addiction. As there are many connections between the symptoms of withdrawal and the effects of OXT in the brain, it seems that OXT might be used in the treatment of drug addiction. OXT buffers exactly those factors (anxiety, stress, loneliness) that cause an increase in drug craving and a higher probability of relapse in drug addicts that try to maintain abstinence.

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Chapter 1 – Introduction

Drug addiction, also known as substance use disorder, is a major global health issue. A drug report of the United Nations in 2019 stated that there were 35 million individuals worldwide suffering from drug addictions [1]. According to data of the World Health Organization, more than 180 thousand deaths in 2019 are directly related to drug use disorders, alcohol abuse leads to 3 million deaths every year [2,3]. Drug addiction is a chronic disorder that gives rise to many problems for the individual suffering from the addiction and for the individuals in the direct environment of the addict. Economic-, physical-, and mental problems are common. Unfortunately, there is no cure for drug addiction found yet. However, there are treatments available that help individuals manage the addiction and keep them from abusing the drug. Examples of available treatments are psychological therapies such as cognitive behavioural therapy and family behaviour therapy, and pharmacotherapies [4]. Treatments for drug addiction are, unfortunately, not very successful. Quite a lot of individuals relapse after a period of abstinence. According to the National Institute on Drug Abuse, about 40 to 60% of patient's relapse [5].

Recently, there are a lot of news articles and blog posts due to COVID-19 about social isolation and how we, human beings, need social interaction. When we experience something joyful with someone else, for instance when exercising, cooking, cuddling or laughing together, oxytocin (OXT) is released in the brain and the periphery. As we have to restrict our social contacts, the majority of individuals likely have a lower level of OXT compared to normal levels. A recent blog post by Hart Psychologen pleaded for more social contact (cuddling, intimate experiences, going for a walk with a friend) as it will lead to an increase in OXT level. In this blog post, it was also mentioned that higher levels of OXT will make people more resilient to stress and addiction [6]. This suggestion is a bit out-of-the-blue as it is well-known that OXT plays a very important role in the periphery as it is in control of the contractions of the uterus during labour and childbirth and the ejection of milk when breast-feeding. Besides the role of OXT in birth and breastfeeding, OXT has popularly been known for a long time as the "cuddle hormone". However, this blog suggests that there might be an additional role for OXT in the treatment of drug addiction, as higher levels of OXT will increase resilience to drug addiction. This link between OXT and drug addiction is relatively new and the reasoning behind the potential use of the "cuddle hormone" OXT as a protective agent for drug addiction is not well-known. Based on the blog post by Hart Psychologen, it is important to find out if and why OXT might be used as a pharmacological agent in treatments for drug addiction.

The central statement of this report is that OXT could be used as a pharmacological agent in the treatment of drug addiction. To find out if this statement is true or false, it is important to find out what exactly an addiction to drugs signifies, the treatments currently available for drug addiction, the effects of OXT in the brain and periphery, and if OXT might be a new suitable therapeutic agent in drug addiction treatments.

Chapter 2 – Drug addiction

According to the DSM-5 criteria, a drug addiction (i.e., substance use disorder) is featured by "a cluster of cognitive, behavioural, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems" [7]. The diagnostic criteria for substance use disorder according to the DSM-5 are:

i. The drug of abuse is used in larger amounts or for a longer period compared to what was initially planned.
ii. The individual using the drugs shows a desire to stop or regulate the use of the drug and may have done unsuccessful attempts to stop or decrease the use.
iii. The individual spends a great amount of time getting, using or recovering from the drug.
iv. The individual suffering from a drug addiction suffers from cravings and urges for the drug. This can occur at all times but happens most often in an environment related to previous drug use.
v. Due to drug use, the individual is unable to perform obligations he/she has at a job, school or home.
vi. The individual continues to use the drug even though the effects of the drug cause problems in his/her social life.
vii. The individual gives up on social, job-related, or other activities because of drug use.
viii. The individual continues to use the drugs even though it is unsafe.
ix. The individual continues to use the drug even though knowing that the drug is likely to worsen or be the source of physical or psychological problems.
x. The individual experiences tolerance, meaning that a higher dose of the drug is necessary to get the desired effect or when taking the usual dose, a reduced effect is experienced.
xi. The individual experiences symptoms of withdrawal when the concentration of the drug in the body reduces after a long period of heavy drug use. An individual is likely to use the drug again to alleviate the symptoms of withdrawal.

When an individual is diagnosed with a mild substance use disorder, two or three of the criteria are met. Moderate substance use disorder is diagnosed when four or five criteria are met, and severe substance use disorder is diagnosed when six or more criteria are met [7].

2.1 Neurobiology of addiction

To get a better understanding of what an addiction to drugs is exactly, it is important to know a few things about the neurobiology of drug addiction. How can one go from using drugs on an occasional level to a loss of control and the development of a drug addiction? The mesolimbic pathway (also known as the dopamine reward pathway) is a system in the brain that connects the ventral tegmental area (VTA) to different areas in the brain including the nucleus accumbens (NAc) and the prefrontal cortex (PFC) (figure 1) [8]. When an individual uses a drug, dopamine (DA) is released into the NAc which is part of the ventral striatum. All drugs activate the mesolimbic pathway and thereby stimulate the release of

DA [9]. The release of DA gives the rewarding feeling when a drug is used, known as a “high”. When a drug is taken repetitively, some long-term changes occur in the mesolimbic pathway. It is expected that these changes lead to the development of a drug addiction [10]. When an individual has just started to use a certain type of drugs, an increase in response is experienced with repeated doses, this is known as sensitization. There is an increase in activation in the regions that receive input from the VTA in the mesolimbic pathway [9]. This phase is known as the “liking” phase. When the use of the drugs is continued, the mesolimbic pathway is sensitized, and it activates the nigrostriatal pathway which has DA projections from the substantia nigra to the dorsal striatum (figure 1). This system is known for the consolidation of habits that are associated with drug use. When this system is activated, not the use of the drug itself, but behaviours and cues from the environment that are associated with drug use (e.g., going to a specific place where the drug is obtained or doing a specific action before using the drugs) are rewarding and cause a release of DA [11]. After sensitization and the switch from the ventral striatum to the dorsal striatum, individuals will experience tolerance, that is, the same dose of the drug has less effect and increasingly large doses of drugs are needed to achieve the desired effect (the “high”) [12]. At this point, the positive effects of the drug of abuse and the rewarding feeling that it used to give slowly disappear as mechanisms are activated that try to maintain homeostasis and counter the effects of the drug. Because of this, negative effects are created (e.g., the baseline level of DA drops, corticotropin-releasing factor (CRF) is released which is a hormone involved in the stress response) [9,13]. When this happens, the drug is only used to relieve the negative effects (i.e., negative reinforcement). There is a switch from liking the drugs, to a state of wanting the drugs [13]. The individual does not take the drug to get “high” anymore, but only to feel normal again [12]. This means that going from occasional drug use (state of reward) to repeatedly using the drug for a long time, there is a shift in activation from the ventral striatum to the dorsal striatum, and a shift from liking to wanting the drug, people become addicted to the drug. The individual does not experience a rewarding feeling anymore and is highly dependent on the drug. The drug is used only to reduce the high level of stress (CRF) and other negative effects that the individual is experiencing when the drug is not taken for a while [13].

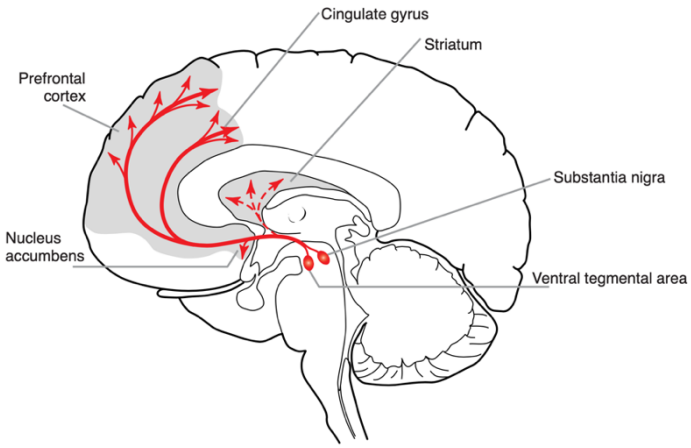

Figure 1. The mesolimbic pathway with DA projections from the VTA to the NAc and PFC, and the nigrostriatal pathway with DA projections from the substantia nigra to the dorsal striatum [11].

2.2 Addiction and stress

As a drug addiction has major consequences for an individual's health (both mentally and physically), social life and economic status, many addicted individuals would like to quit using the drugs. Unfortunately, gaining control over the disorder is not easy, it includes drug cravings (i.e., a strong desire to use the drug), withdrawal symptoms and relapses. When drug addicts try to maintain abstinence, relapse and cravings are typically induced by exposure to the drug, exposure to (environmental) cues associated with the drug, or by stress [14]. Exposure to the drug or (environmental) cues associated with the drug during abstinence cause drug-opposite effects. Because of the exposure to the drug or the cues, the brain anticipates that the drug will be used, and it takes action to counter the effects of the drug. However, during abstinence, the drug is not taken, and drug-opposite effects are experienced [15,16]. These drug-opposite effects are symptoms of withdrawal. These withdrawal symptoms cause cravings for the drug as it is needed to feel normal again. The presence of withdrawal symptoms is a prevalent reason for relapse to occur [16]. During withdrawal from chronic administration of a drug, the level of CRF in the brain is elevated, meaning that there is an increase in the level of stress that an individual is experiencing [13]. Research by Stewart, J., (2000) found that elevated levels of CRF in the brain can induce cravings and relapse, blocking the CRF receptor with an antagonist can prevent stress-induced cravings and relapse from happening [17]. The level of craving and the probability of a stress-induced relapse are high as the levels of CRF in the brain are elevated. When this happens, the drug is needed to relieve some of the stress that an individual is experiencing. The elevation in CRF levels also plays an important role in anxiety-like behaviour during abstinence from the drug [18].

2.3 Addiction and anxiety/depressive disorders

Anxiety and depression are both mental disorders that often coexist with drug addiction. Multiple studies have demonstrated that addicted individuals suffering from anxiety and/or depressive disorders may experience intense cravings and are therefore at risk of relapsing when they experience a stressful situation. An individual suffering from both an anxiety or depressive disorder and drug addiction often has worse treatment outcomes and a greater probability of relapse [19]. According to a survey by Levy, M., (2008), stressed, depressed and anxious feelings are prevalent reasons for relapse in both men and women [20]. It is suggested that the level of anxiety and depression experienced by addicted individuals are good predictors for subsequent craving ratings. It seems that individuals who experience higher levels of anxiety and/or depression, have higher levels of craving, and are consequently more likely to use drugs (relapse) [19,21–23]. The most important line of evidence is from research by Fatseas et al., (2018). This study demonstrated that individuals suffering from comorbid mood and/or anxiety disorders reported higher intensities of craving and as a consequence, these individuals used drugs more frequently [19]. 159 participants, between 18-65 years old, who met the DSM-5 criteria for substance use disorders and were just beginning treatment were qualified to participate in this experiment. 95 of these individuals were diagnosed with a current mood and/or anxiety disorder. Ecological momentary assessment (EMA) is a tool that regularly assesses behaviours and experiences of subjects in their natural environment and is used in this study [24]. EMA assessment started on the first day of treatment, that is, the target date that drug use is terminated, and lasted 14 consecutive days. In

these 14 days, patients had to bring a personal digital assistant (PDA) with them which conducted four electronic interviews per day. Additionally, participation in urine tests and alcohol breath tests were required. The Mini-International Neuropsychiatric Interview-Plus was used in the assessment of the DSM-5 diagnostic criteria for psychiatric and substance use disorders. The EMA monitoring measures consisted of two separate parts. The first part consisted of questions in which the participants were asked (1) to rate the level of craving experienced since the last assessment on a seven-point scale, and (2) if they had used the drug of abuse since the last assessment. The second part consisted of questions concerning sad and anxious moods. Participants had to rate their mood during the assessment based on a separate 7-point Likert scale. This study looked into the possible predictor abilities of craving at T0 for subsequent substance use at T1. The results demonstrate that the intensity of craving assessed at T0 is a strong predictor of substance use at T1. These results were found in the group with current comorbid mood and/or anxiety disorders ($p = 0.009$) and without current comorbid mood and/or anxiety disorders ($p = 0.002$). The association between craving intensity at T0 and substance use at T1 is shown in figure 2. The link between current anxiety and/or mood disorders, the intensity of craving, the use of the substance and the mood state during the EMA was also investigated in this experiment. The results demonstrate that when an individual is diagnosed with a current comorbid mood and/or anxiety disorder, this is linked to higher intensity cravings ($p = 0.014$), more prevalent drug use ($p = 0.003$) and higher levels of sad and anxious moods ($p < 0.001$). To conclude, the results of this study suggest that the craving intensity is a reliable predictor for subsequent drug use (relapse). In addition to the link found between craving intensity and drug use, the findings reveal that an individual suffering from a current mood and/or anxiety disorder will experience an increase in craving intensity and thus an increase in the risk of drug use and relapse [19].

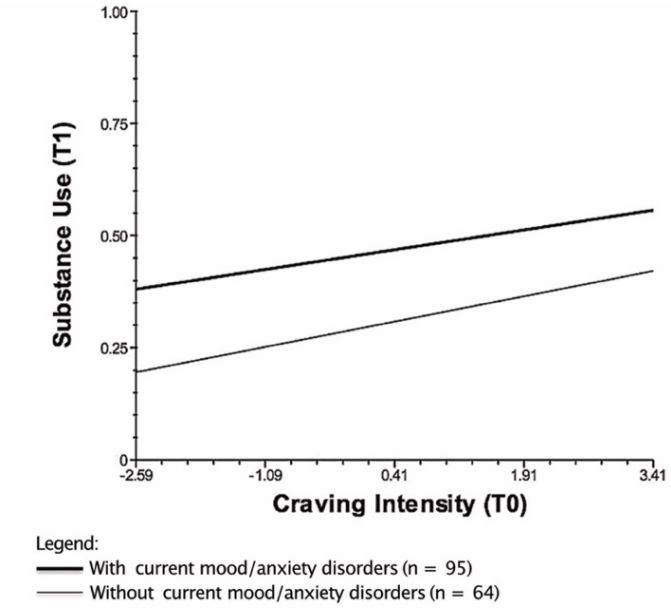

Figure 2. Substance use reported at T1 as a function of the craving intensity reported at T0 [19].

2.4 Addiction and loneliness

The majority of individuals (79%) that try to quit using drugs report feelings of loneliness. It is suggested that loneliness is common and problematic for individuals who try to kick the habit of using drugs [25]. Drug addicts often have lost their social contacts from the period before they got addicted, and the social contacts made during the period of addiction are not always helping them to stay abstinent of drugs as they are often a cue linked to drug use. Especially for female addicts, but also for male addicts, loneliness was reported as one of the main reasons for relapse to occur [20]. This suggests that a decrease in social interaction in periods of abstinence after chronic drug use, and subsequent feelings of loneliness, are associated with stronger cravings and an increased probability of relapse, especially in females [26,27]. In a study by Venirro et al., (2018) they let animals choose between self-administration of a drug and interaction with a familiar or novel member of the same species. The results demonstrate that if there is a social-reward option available (interaction with the member of the same species), this abolishes drug self-administration in addicted rats [28]. This suggests that social enrichment, e.g., social housing, might be helpful to reduce craving in addicted individuals and thereby reduce the rate of relapse [29].

To conclude, it seems that after chronic drug use, individuals experience adverse symptoms during abstinence such as high levels of stress, anxiety and loneliness. These symptoms increase the probability that drug-seeking behaviour is reinstated, and that subsequent relapse occurs to relieve the negative effects [30].

Chapter 3 – Treatment of drug addiction

Drug addiction is a chronic brain disorder characterized by relapses and long-term changes in the brain causing an individual to lose control over the drug intake. There is no cure available for drug addiction yet and long-term care is required to prevent relapse [31,32]. As drug addiction is a chronic disorder that causes long-term changes in the brain, drug addicts will be at risk of relapse and remain addicted for the rest of their life. Addicts can quit using the drugs, but drug addiction cannot be cured. This means that treatment is directed at gaining control over the drug addiction rather than curing it. There are different treatments available, examples are pharmacotherapies and behavioural therapies. Unfortunately, the current treatments are not optimal as the relapse rates are high after treatment, this a major challenge [33].

3.1 Behavioural therapies

Cognitive behavioural therapy (CBT). This form of therapy can be implemented in treatments for different mental disorders including substance use disorder. CBT is a treatment that holds the belief that drug addiction is caused by cognitive factors. The therapy aims to teach addicts how they can alter false and irrational thoughts, beliefs and behaviours they have to reduce craving and prevent relapse [4,34]. It has been shown that in a clinical setting, CBT reduces drug craving and is proven to be an effective treatment. However, not all details regarding the efficacy of this treatment over other behavioural treatments of drug addiction are clear. Currently, CBT is rarely implemented as a treatment for drug

addiction. The reason for this is that CBT has a few disadvantages. Firstly, the costs of this treatment are quite high, and a specialist is required for the therapy. The second disadvantage of CBT is that multiple cycles of treatment are necessary to protect patients from relapse [33,35]. Thus, this form of treatment is aimed at the thoughts and behaviours of addicts in moments of weakness when craving is high. It teaches individuals how their thoughts can be altered; this could protect addicts from relapse in periods of abstinence after chronic drug use.

Cue exposure therapy (CET). Similar to CBT, CET is also a form of therapy that can be used to treat many different mental disorders, including drug addiction. CET is based on classical conditioning, in which the unconditioned stimulus (US) is the drug of abuse. The consequences of the intake of the drug of abuse on body and behaviour are the unconditioned responses (UR). Cues associated with drug use will become conditioned stimuli (CS). If the CS are frequently linked to the UR, the CS will be able to generate a conditioned response (CR) which are the effects initially caused by the drug of abuse. In periods of abstinence, exposure to the US and CS can induce drug craving. In this therapy, drug-associated cues will be presented to addicted individuals, but the drug use is prevented. In this way, the therapy aims to extinguish the CR [36]. As the CR will be extinguished, cravings and drug intake will decrease as the CS do not trigger the CR anymore. Studies have shown that CET has been effective for treating other mental disorders, but the effectiveness of CET for treating drug addiction is debatable. Some studies showed positive results of CET, others showed no results, and some showed opposite results (increased craving and drug intake). The lack of effectiveness of this therapy might point out that targeting the drug-associated cues only has limited effects on the treatment of the drug addiction [33,36].

The behavioural therapies mentioned above, and other therapies directed at behaviour (e.g., contingency management interventions, family behaviour therapy) aim to help addicted individuals to recognize high craving and high-risk relapse situations. It is important to make addicts aware of these difficult moments and teach them different ways in which such situations can be handled by reducing drug craving and preventing relapse. Unfortunately, these therapies are not proven to be very successful.

3.2 Pharmacotherapies

As all drugs of abuse affect different receptors in the brain, it is not possible to have one pharmacotherapy as a treatment for all different drugs of abuse.

Dopaminergic system. It seems obvious that pharmacotherapies should target the dopaminergic system as it is activated by all drugs of abuse and plays a critical role in the development of drug addiction. However, most of the downstream molecules that transmit the DA signal also play important roles in mediating other signals in the brain. Because of this, the downstream molecules of DA are not suitable as targets of pharmacotherapies as this could result in detrimental side effects [33]. Recent studies especially focused on the DA receptors as potential targets for the treatment of drug addiction. There are different subfamilies of DA receptors. The D2-like receptors are most suitable as a target for

pharmacotherapies to treat drug addiction as they are associated with chronic drug use and relapse. Unfortunately, there is no medicine available yet that specifically targets the D2-like receptor and reduces the amount of craving. Other studies have looked into D3-like receptors as these are also considered to be suitable targets for the treatment of drug addiction. Studies investigating the effects of D3-like receptor antagonists on craving and relapse are still in the early stages [33,37]. More research is necessary to find out if the receptors of the dopaminergic system are suitable targets for treatments of drug addiction.

Stress system. As mentioned in chapter 2, an increase in CRF level is observed in the brain during the withdrawal stage after chronic administration of drugs [13]. The high levels of stress experienced can induce cravings, drug-seeking behaviour and subsequently, relapse. Different studies have investigated the role of CRF in behaviours that are linked to stress and drug use. It has been demonstrated in rodents that administration of CRF in the brain causes the activation of the stress system. Administration of a competitive CRF receptor antagonist led to the opposite effect, namely anti-stress effects [38]. A preclinical study by Koob et al., (2013) demonstrated that during drug withdrawal, a CRF receptor antagonist reduced anxiety and it reduced the amount of self-administration of drugs in an extended-access experiment of drug intake in rodents [33,38]. This suggests that a decrease in CRF level, thus a decrease in experienced stress, directly reduces drug craving. More recently, a clinical study looked into a CRF1 antagonist and the effects it has on alcohol addiction. The antagonist did reduce the stress response, but the results did not indicate that the antagonist affected stress-induced craving [33,39]. The results of the preclinical study and the clinical study are contradictory, more research is necessary to see if the CRF system in the brain could be a target for the treatment of drug addiction.

There are various other pharmacotherapies, examples for the treatment of opioid addictions are methadone, buprenorphine and naltrexone. Methadone and buprenorphine are opioid agonists used to reduce symptoms of withdrawal and to minimize drug craving. Naltrexone is an opioid antagonist; it prevents the opioids from binding to the receptors. Because of this, the desired effect of the opioid remains absent and eventually, it will reduce drug craving. Naltrexone is also used as a treatment for alcohol addiction [40]. The different pharmacotherapies mentioned come with pros and cons and the road to gaining control over a drug addiction is not easy.

To conclude, pharmacotherapy might be an effective form of treatment for drug addiction in the future. Unfortunately, the current pharmacotherapies are not able to reduce craving and prevent relapse after a period of drug abstinence. The majority of the pharmacotherapies aim to intervene with the addiction itself (opioid antagonists/agonists, dopaminergic system). A minority of the pharmacotherapies is aimed to make people aware of their weak moments with high craving and to reduce the symptoms ((e.g., stress, anxiety) that make individuals vulnerable to relapse in periods of abstinence. Pharmacotherapy in combination with behavioural therapy might increase the chances of a successful treatment for individuals struggling with drug addiction. However, research on the combination of these therapies is scarce [41]. It is important to find an effective pharmacotherapy or behavioural therapy (or a combination of both) that reduces craving and subsequently reduces the numbers of patients that relapse after a period of drug abstinence.

Chapter 4 – Oxytocin

Oxytocin (OXT) is a nonapeptide that is mainly synthesized in the magnocellular neurons of the supraoptic nucleus (SON) and the paraventricular nucleus (PVN) of the hypothalamus. The majority of OXT is released into the bloodstream by the posterior pituitary where it affects peripheral processes [30,42–44]. In the periphery, OXT is known to play an important role in uterine contractions throughout labour and delivery and it controls milk ejection [44,45]. The focus of this chapter will be on the role of OXT in the central nervous system as a neurotransmitter. Some of the oxytocinergic neurons originating in the PVN of the hypothalamus have projections to several other brain regions, including the NAc, amygdala, and VTA [30,44,45]. At these brain regions, OXT binds to its only receptor, the oxytocin receptor (OXTR) [44].

4.1 Oxytocin and dopamine

In chapter 2 it was mentioned that the VTA and the NAc are critical brain regions of the mesolimbic pathway. The cell bodies of dopaminergic neurons are located in the VTA and project to the NAc. These brain areas play an important role in the regulation of drug reward and drug relapse. OXT is released from the PVN of the hypothalamus and is projected to other brain regions where OXTR are expressed, including the VTA and the NAc (figure 3). Oxytocinergic neurons projecting to the VTA might modify the activity of dopaminergic neurons located in the VTA projecting to the NAc [46]. A study by Melis, M. et al., (2007) demonstrated elevated levels of extracellular DA in the NAc and the PVN after administration of OXT into the VTA in male rats [47]. This data indicates that there might exist a neural circuitry in the brain in which the mesolimbic pathway and the oxytocinergic system interact. A possible explanation could be that OXT binding to the OXTR in the VTA has an impact on DA signalling to the NAc, this might then impact drug reward and relapse [48]. Further research is necessary to see if this is true or if there is something else happening in the VTA as a consequence of OXT binding to the OXTR that affects dopaminergic signalling.

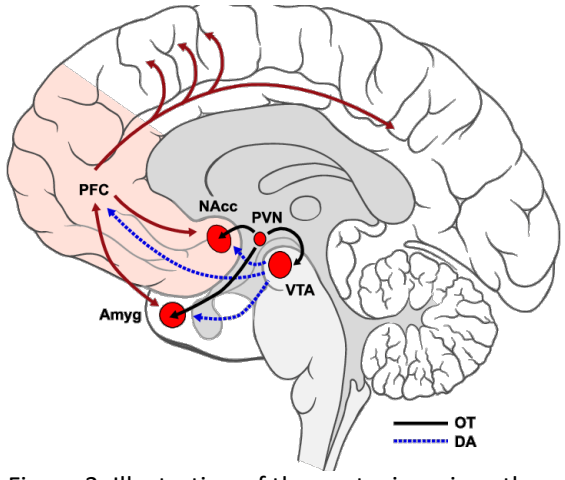

Figure 3. Illustration of the oxytocinergic pathway in black. OXT is released from the PVN and projected to various brain regions including the VTA and NAc. The mesolimbic pathway is represented by the dashed blue lines. DA is synthesized in the VTA and projected to, amongst others, the NAc and the PFC

4.2 The role of oxytocin in different behaviours

OXT is popularly known as the “cuddle hormone” or the “love drug”, however, a lot of research has looked into the effects of the neurotransmitter, and it seems that OXT is important in many different behaviours [49]. Firstly, several animal studies have shown that OXT can induce bonding between a mother and her offspring. Secondly, different studies in both animals and humans have investigated the role of OXT in the formation of social bonds. Studies focusing on the prairie vole established that OXT can induce pair-bonding behaviour. This is measured by the amount of time that a prairie vole spends near a partner compared to the amount of time spent near an unfamiliar conspecific. If the prairie vole spends the majority of the time with a partner, this suggests that a pair bond is established [50–52]. It has been demonstrated that intracerebroventricular (icv) injection of OXT can give rise to pair-bonding behaviour, i.e., more time is spent with the partner. An injection of an OXTR antagonist in the NAc and the PFC can prevent pair-bonding behaviour [50]. Thirdly, several studies have demonstrated that intranasal OXT administration can give rise to an increase in trust between human beings, indicating that OXT affects trust [53,54]. Lastly, recent studies linked deficits in OXT pathways of the brain to autism spectrum disorder (ASD) [45]. ASD is characterized by deficits in social functioning, communication, recognition of emotions and a reduced attentional preference for faces [55]. Studies have shown that nasal administration of OXT enhances social behaviour in individuals suffering from ASD. After OXT was intranasally administered, improvements were observed in the ability to recognize emotions and in attention directed towards faces [55,56]. These different studies suggest that OXT plays a major role in the social functioning of both animals and humans.

4.3 Oxytocin and anxiety

In addition to the well-known functions of OXT in social- and reproductive behaviours, OXT is also linked to other important behaviours. Firstly, it has been demonstrated in several studies that OXT plays an important role in several mental disorders, such as anxiety disorders [57]. A study has shown that there is a negative correlation between feelings of anxiety and plasma OXT levels, suggesting a link between OXT plasma levels and anxiety levels [58]. Different animal studies have revealed that OXT administration can reduce levels of anxiety, indicating that OXT has anxiolytic effects [59–63]. The most important piece of evidence comes from a study by Slattery and Neumann (2009), in which it was demonstrated that by manipulation of the OXT-system in the brain in selectively bred Wistar rats, a state of high anxiety can be attenuated. In this study, selectively bred adult female and male Wistar high anxiety-related behaviour (HAB) and low anxiety-related behaviour (LAB) rats and female Wistar rats that were not selected for anxiety-related behaviour (NAB) were used. The testing for high- or low anxiety-related behaviour was done using the elevated plus maze (EPM). In the EPM, the amount of time spent in the open arms is determined by an observer, this is an indicator of anxiety level. For the assessment of the effects of acute manipulation of the oxytocinergic system on anxiety-related behaviour, an indwelling icv guide cannula was implemented in the rats. In the acute study, either vehicle, OXT, or an OXT antagonist (OXT-A) was infused into the rats. In the chronic study, osmotic minipumps were implemented in the rats for the assessment of the effects of chronic manipulation of the oxytocinergic system on anxiety-related behaviour. The minipump was filled with either the vehicle, OXT, or OXT-A. The behavioural experiment used in the assessment of anxiety-related behaviour in this

study is the light-dark box (LDB). In the LDB, the amount of time spent in the light compartment, entries into the light compartment and latency were measured and are indicators of the level of anxiety. No effect of acute icv OXT and OXT-A on anxiety-related behaviour tested in the LDB was observed in male or female LAB and HAB rats. In contrast to the results of acute icv OXT and OXT-A, chronic icv OXT infusion in HAB female rats resulted in attenuations of anxiety-related behaviour. The amount of time spent in the light compartment of the box was increased compared to the vehicle group (figure 4A), also, these rats entered the light compartment more often. These results demonstrate that chronic icv OXT infusion has anxiolytic effects. Chronic OXT-A infusion in LAB female rats resulted in a decreased time spent in the lightbox in comparison to the vehicle group (figure 4A) and a decreased number of entries into the lightbox in comparison to the vehicle and OXT treated groups. This suggests that chronic OXT-A infusion has an anxiogenic effect. The anxiolytic results found in HAB female rats after chronic icv OXT infusion and the anxiogenic results in LAB female rats after chronic OXT-A infusion were not found in male HAB or LAB rats (figure 4B). These results demonstrate an anxiolytic effect of chronic administration of synthetic OXT in HAB female rats while chronically administered OXT-A led to anxiogenic effects in LAB female rats. These results indicate the potential of OXT as an anxiolytic drug in individuals with extreme levels of anxiety [59]. In addition to animal studies, several clinical studies have demonstrated that OXT attenuates anxious behaviours in humans [50]. These results suggest that OXT might be a potential therapeutic agent for the treatment of anxiety disorders in humans.

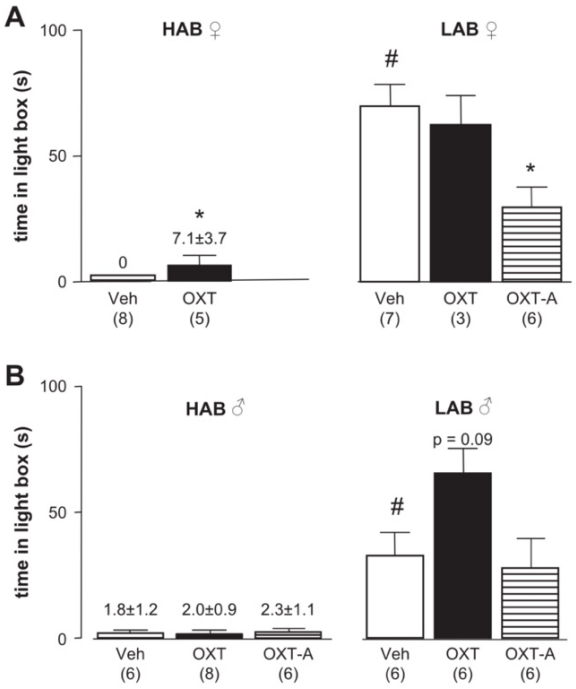

Figure 4. Illustration of the amount of time spent in the light compartment of the box after chronic icv administration of OXT, OXT-A or vehicle in HAB and LAB male and female rats. (A) There is a significant increase in the amount of time spent in the lightbox after chronic icv OXT infusion in HAB female rats. Chronic OXT-A infusion decreased the amount of time spent in the lightbox compared to the vehicle rats in LAB female rats. (B) No significant results were found in HAB or LAB male rats [59].

4.4 Oxytocin and stress

Secondly, it is suggested that there is an interaction between the oxytocinergic system and the stress system of the brain. When an individual is exposed to a stressor, CRF and OXT are released in the brain. The majority of oxytocinergic neurons originating in the hypothalamus have projections to the posterior pituitary from which OXT is released into the periphery. A minority of the oxytocinergic neurons originating in the hypothalamus have projections to other regions in the brain, including regions that are sensitive to stress [43]. Different animal studies have demonstrated that chronic or acute administration of OXT in the brain attenuates the stress response, suggesting that OXT has anti-stress effects [43,62,64]. The most important line of evidence is from research by Windle et al., (1997). Study 1 of this experiment is the most relevant for this section of the report as they looked into the effects of central OXT administration on the release of stress-induced corticosterone in rats. Female Sprague-Dawley rats were used in the experiments of this study. All animals were ovariectomized and treated with oestradiol to prevent variations in ovarian steroid from influencing the results. Osmotic minipumps were implemented in the rats for the delivery of OXT, vasopressin or saline to the brain. To assess the specificity of the corticosterone response to OXT, some rats received vasopressin infusion. A SILASTIC-tipped right jugular venous cannula was implanted in all rats for the collection of blood samples. In study 1, saline, different infusion rates of OXT (1, 10 or 100 ng/h) and vasopressin (10 or 100 ng/h) were centrally administered and the stress response to a stressor was assessed via blood samples. The stressor was a white noise generator, the animals were exposed to 114 decibels for 10 min. The reversibility of the effect of OXT was also assessed in some rats. These rats were subjected to the blood sampling and stressor twice, once when OXT was delivered and once after the termination of OXT delivery. Plasma corticosterone concentrations were assessed as an indicator of the stress response. In the control animals who received saline infusion, there is a large increase in plasma corticosterone concentrations observed after exposure to 10 min of noise stress (figure 5A). In the rats who received OXT infusion at a rate of 10 or 100 ng/h for 5 days, a significant and dose-dependent decrease in plasma corticosterone by OXT is observed (figure 5C and D). For the reversibility assessment of the effect of OXT, the rats were exposed to a second white noise after the termination of OXT delivery. There were no differences observed between the control rats and the rats that were previously infused with OXT. The different doses of vasopressin treatment had no significant effects on the corticosterone response after exposure to the stressor. In this study, they also looked at the effects of OXT infusion on the behavioural responses of the rats to the stressor. The number of rearings was measured, this is an indicator of stress level. After administration of OXT (infusion rates 10 and 100 ng/h), the number of rearings significantly decreased compared to the control group 0-10 min after exposure to the stressor (figure 6). The results of this study reveal that central infusion of OXT significantly reduces the corticosterone response to a white noise stressor. This suggests that OXT might be able to attenuate the stress response [62].

Besides the effects of OXT on stress-induced release of corticosterone, study 2 examined the effect of OXT on anxiety-related behaviour. The results of this study support the results of the study by Slattery and Neumann (2009) described above [59]. In this study, rats were infused with either saline or OXT and anxiety-related behaviour was assessed using the EPM. The animals were either tested in a familiar environment or an unfamiliar environment. The results reported no significant differences

between the saline-infused rats and the OXT infused rats in the total maze exploration in a familiar environment (figure 7A, C, E, G). However, when the animals were mildly stressed because of testing in an unfamiliar environment, the OXT-treated rats spent significantly more time in the open arms and entered the open arms significantly more compared to the control rats (figure 7B, D, F, H). These results are in line with the results of the study by Slattery and Neumann (2009), suggesting that OXT has anxiolytic effects [62]. The effect of OXT on the activation of the stress system has also been investigated in humans. In response to stressful situations, OXT is released, and it exhibits anti-stress effects, i.e., the stress response is dampened [65].

4.5 Oxytocin and loneliness

Lastly, many individuals, both young and old, live in social isolation and experience loneliness. It is known that there are detrimental effects of social isolation and subsequent feelings of loneliness on both physical and mental health [66]. It is crucial to see if there might be interventions that diminish loneliness or the negative consequences that are caused by loneliness. A report by Cacioppo et al., (2016) mentioned OXT as a potential treatment for loneliness. Experiments with prairie voles demonstrated that OXT buffers the detrimental effects caused by a separation from a partner. An exogenous administration of OXT in the prairie voles diminished the negative effects of social isolation and attenuated loneliness [67]. In humans, it has been shown that OXT administration stimulates social behaviour, communication and trust [53]. As OXT attenuates loneliness, buffers the negative effects of loneliness, and promotes social behaviour, OXT might be an effective pharmacological treatment for loneliness [67,68]

To conclude, both clinical and preclinical studies have examined the role of OXT in different behaviours. A study in rats suggests a possible direct link between the dopaminergic- and oxytocinergic-system. Results of other experiments suggest that OXT is anxiolytic, exhibits anti-stress effects, and attenuates loneliness. As mentioned in chapter 2, anxiety, stress and loneliness are very common adverse symptoms during drug abstinence that cause intense drug cravings and relapse. As there are many connections between the symptoms of drug withdrawal and the effects of OXT in the brain, OXT might be an effective therapeutic agent in pharmacological treatments of drug addiction.

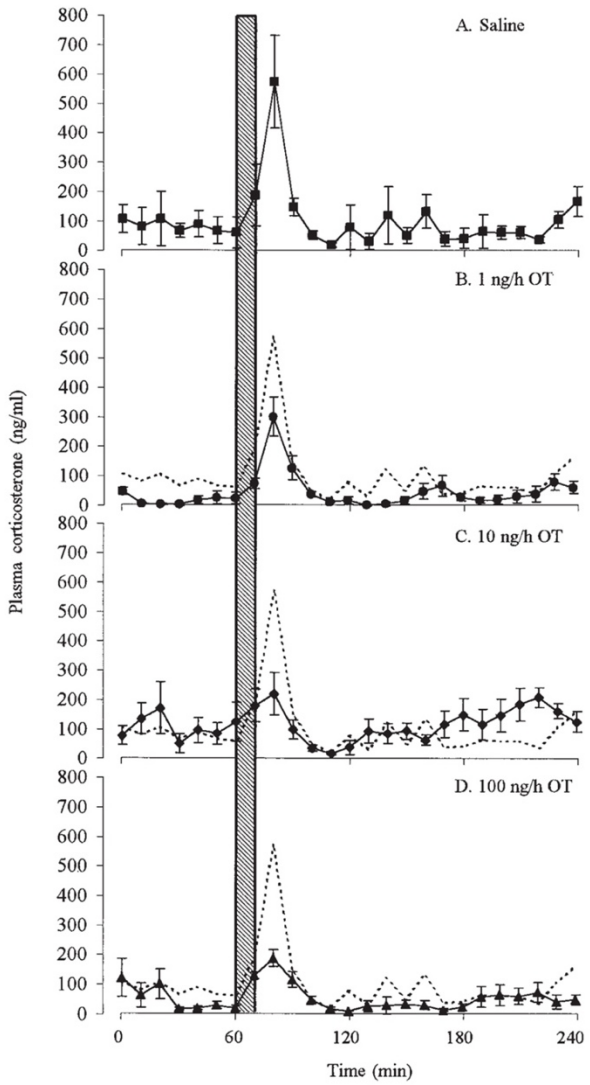

Figure 5. The effect of a white noise stressor (114 DB for 10 min) represented by the hatched bar, on the level of plasma corticosterone concentrations in female rats infused with saline or OXT at different rates (1 ng/h, 10 ng/h or 100 ng/h). The control value shown in A is shown in B-D by the broken line. (A) A large increase in plasma corticosterone concentrations is observed after 10 min of white noise stress in saline infused rats. (B) No significant difference is observed in plasma corticosterone concentration after 10 min of white noise stress in rats infused with OXT at 1 ng/h. (C and D) Significant differences are observed in plasma corticosterone concentrations after 10 min of white noise stress in rats infused with OXT at 10 ng/h and 100 ng/h [62].

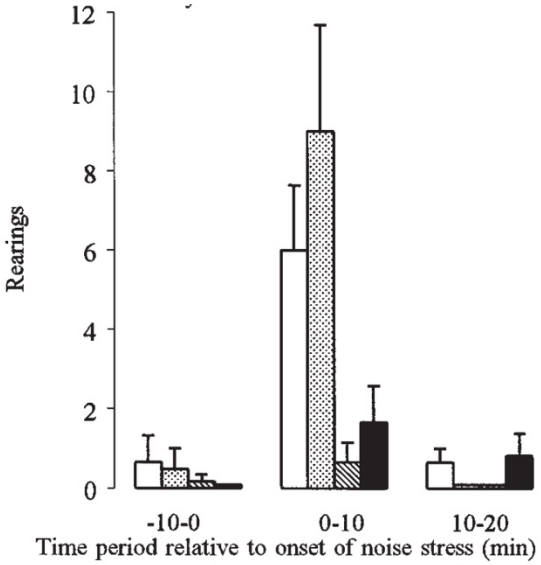

Figure 6. Illustration of the effect of a white noise stressor (114 dB, 10 min) on the number of rearings in rats centrally infused with OXT. Open bars represent the control rats infused with saline. Stippled bars represent OXT infusion at a rate of 1 ng/h, hatched bars represent OXT infusion at a rate of 10 ng/h, filled bars represent infusion rate of 100 ng/h. The number of rearings significantly decreased in the OXT infused rats (10 and 100ng/h) 0-10 min after exposure to the stressor [62].

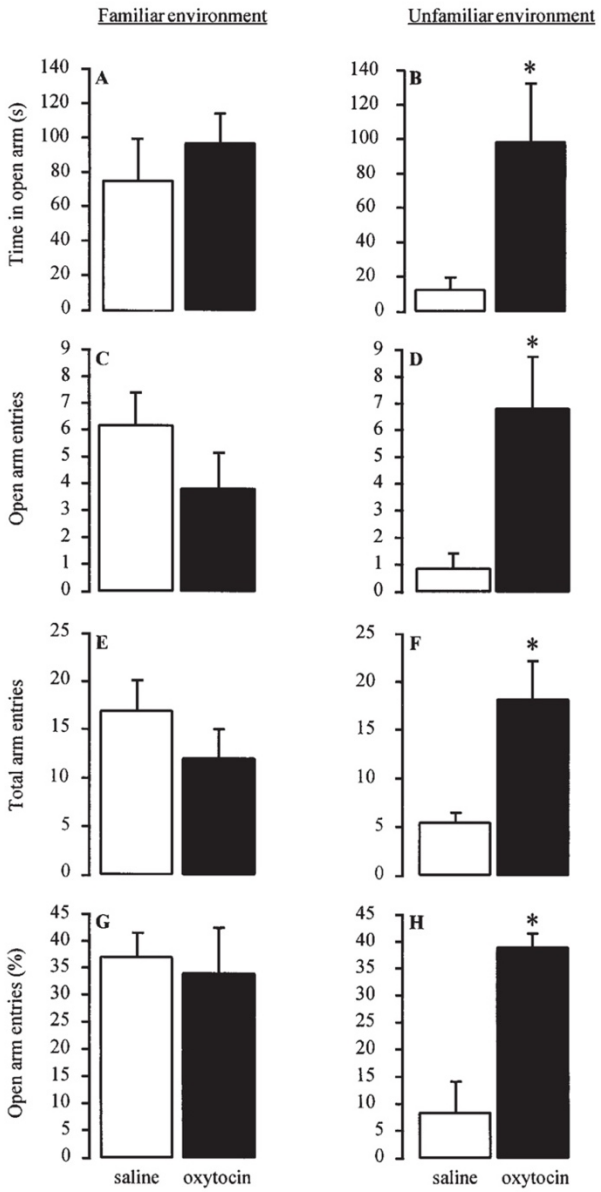

Figure 7. Performance on the elevated plus maze. Open bars represent the group of rats that received central saline infusion. Closed bars represent rats that received central infusion of OXT at 100 ng/h. Graph A and B illustrate the time spent in the open arm, graph C and D illustrate the open arm entries, graph E and F illustrate the total arm entries, and graph G and H illustrate the open arm entries as a percentage of total arm entries. Graph A, C, E, and G report that in a familiar environment, no significant differences between the rats are reported. Graph B, D, F and H report that in an unfamiliar environment, the OXT-treated rats spent significantly more time in the open arms of the maze and entered the open arms significantly more compared to the saline infused rats [62].

Chapter 5 – Treatment of drug addiction with OXT

Considering OXT as a therapeutic agent in pharmacological treatments is not a novel idea. A few years ago, OXT was already suggested as a potential drug treatment for the core symptoms of ASD. The core symptoms are mainly deficits in social functioning and communication. Some of the studies looking into the effects of OXT on social functions have investigated single-dose administrations, others have looked into the effects of multiple-dose administrations. Both forms of treatment reported significant clinical improvements in social functioning in young children and adults with ASD [56,69–72]. In a systematic review of the negative effects of long-term nasal OXT administration in individuals suffering from ASD, the results support that long-term intranasal OXT administration was well tolerated and can safely be used in treatments [73]. As a consequence of OXT administration, ASD patients exhibit more proper social behaviours and respond stronger to other individuals. The results of these studies suggest that OXT has therapeutic potential in treatments for ASD [70].

OXT is not only considered as a therapeutic agent for ASD, there is also evidence for the therapeutic potential of OXT in eating disorders. OXT is thought to be involved in the regulation of food intake and metabolic processes [74]. A study in normal weight and obese mice showed that administration of OXT in the brain attenuated food intake and caused a reduction in body weight in both types of mice [75]. In humans, intranasal administration of OXT decreased reward-driven food intake (e.g., the consumption of snacks) [76]. These results suggest a potential therapeutic use of OXT in treatments for eating disorders.

Furthermore, several clinical studies have looked into the potential therapeutic role of OXT in treatments for anxiety and personality disorders such as schizophrenia and borderline personality disorder. These studies are still in the early stages and the efficacy of OXT as a drug treatment for these mental disorders is not clear yet. Further clinical studies are needed to see if there might be a potential therapeutic role for OXT in treatments for these mental disorders [57,77,78].

Recently, there is a growing interest in OXT as a potential therapeutic agent in treatments for drug addiction as there are so many connections between the effects of OXT in the brain and the adverse symptoms that drug addicts experience when they quit using drugs. As discussed in chapter 2, the most common adverse symptoms of withdrawal after chronic use of different drugs of abuse are elevated CRF levels in the brain and high levels of anxiety. Besides these symptoms of withdrawal, individuals who try to maintain abstinence from drugs are often socially isolated and experience loneliness. These different factors (stress, anxiety and loneliness) make it difficult for individuals to maintain abstinence, as they cause intense drug cravings and make individuals vulnerable to relapse. Thus, when individuals try to quit using drugs after chronic use, an increase in stress level, feelings of anxiety and loneliness increase the likelihood that drug-seeking behaviour is reinstated, and that relapse occurs [30].

As mentioned in chapter 4, OXT is known to be anxiolytic, it exhibits anti-stress effects, attenuates loneliness and promotes social behaviour. This suggests that OXT buffers exactly those factors that cause an increase in drug craving and a higher probability of relapse in drug addicts that try to maintain

abstinence. In addition to the indirect effects that OXT has on drug craving through its anxiolytic, anti-stress and social effects, it is suggested that there is also a direct effect of OXT on drug addiction. It has been demonstrated in rats that following OXT administration into the VTA, elevated levels of extracellular DA in the NAc and PVN are observed. An increased extracellular DA level in the NAc is an important neurobiological substrate for the addictive features of all drugs [79]. As drug addicts crave for the release of DA that is a consequence of drug use, and OXT increases the extracellular DA in the NAc, this might mean that administration of OXT can already be rewarding and it might reduce craving and relapse behaviour. This suggests that OXT is an appealing candidate for treatments of drug addiction because of the direct and indirect effects of OXT that infer with the processes that keep up the addictive behaviours.

Recent clinical and preclinical studies have investigated OXT as a potential treatment for drug addiction. Leong et al., (2019) reported that intranasal OXT administration decreases stress-induced craving and reduces levels of anxiety in individuals dependent on cannabis. Furthermore, OXT treatment also decreased symptoms of withdrawal in individuals addicted to alcohol and it reduced anxiety following the termination of drinking [48]. Another study by Ferrer-Pérez et al., (2021) reported that clinical and preclinical studies have shown that acute administration of OXT can reduce withdrawal symptoms such as anxiety-like behaviour during abstinence from different drugs of abuse [30]. In mice, it has been demonstrated that OXT administration reduces stress-induced reinstatement of alcohol-seeking behaviour [80]. Thus, studies investigating the potential of OXT treatment for drug addiction are still in the early stages, but the results of the first studies are promising.

To conclude, OXT treatment might be a potential drug for pharmacological treatments of drug addiction as it reduces anxiety, stress and loneliness. These are exactly the factors that cause intense drug cravings when individuals try to maintain abstinence after chronic drug abuse. Through its anxiolytic, anti-stress and prosocial features, OXT attenuates craving and reduces the number of individuals that relapse during periods of drug abstinence.

Chapter 6 – Conclusion

When addicted individuals try to quit using drugs, they are likely to experience various symptoms of withdrawal. One of these symptoms is an increase in stress caused by elevated CRF level in the brain. At moments when the experienced stress is high, the individuals crave for the drug of abuse to alleviate the stress. In these moments during abstinence when the craving is high, the probability of relapse is also very high. To prevent relapse, it is necessary to reduce the level of stress. As mentioned in chapter 4, there is a link between the oxytocinergic system and the stress system of the brain. OXT attenuates the stress response through its effects on brain regions sensitive to stress. Thus, stress is a common symptom of withdrawal and OXT has anti-stress effects. This suggests that OXT treatment could be used to alleviate stress symptoms and therefore reduce drug craving and prevent relapse.

Anxiety disorders are common to co-exist with drug addiction. Individuals suffering from both disorders are more vulnerable to craving and have a higher risk of relapse when they are in anxiety-inducing

situations. Anxiety has turned out to be a good predictor for craving and therefore it is important to reduce the level of anxiety and thereby prevent relapse. Studies have demonstrated that OXT has anxiolytic effects, thus it reduces feelings of anxiety. As anxiety is reduced in drug-addicted individuals, there will be a decrease in craving for the drug of abuse, and therefore relapse might be prevented. This suggests that the anxiolytic effects of OXT are of critical importance in the treatment of drug addiction as it reduces drug craving and prevents relapse.

Thus, anxiety and stress give rise to difficult situations in which individuals experience cravings for the drug of abuse and are more likely to relapse compared to other situations. In addition to these two factors, it has been discussed in chapter 2 that loneliness is also reported as one of the most prevalent reasons for men and women to relapse. Social isolation and subsequent feelings of loneliness are linked to stronger cravings and higher chances of relapse, suggesting the importance of attenuating loneliness. There are multiple solutions to tackle the problems of social isolation and loneliness. One of the solutions might be that drug-addicted individuals who try to quit using drugs are socially housed. In this way, social isolation and therefore, drug craving might be reduced. An alternative solution is OXT as a potential drug treatment for loneliness. As mentioned in chapter 4, different animal studies have shown that OXT has prosocial effects, it can attenuate loneliness and reduce the adverse effects of loneliness. This data indicates that OXT treatment might be used to attenuate loneliness, and as a consequence, reduce drug craving and prevent relapse.

Unfortunately, there is no cure for drug addiction found yet. There are treatments available that are directed at helping individuals to gain control over their addiction. There are behavioural therapies such as CBT and CET, and pharmacotherapies directed at, for example, the dopaminergic system or the stress system. The behavioural therapies are quite costly, and the efficacy of both treatments are not entirely clear as the results gained from experiments are contradictory. Regarding the pharmacotherapies, medicine targeting DA receptors are not available yet and the studies examining CRF receptor antagonists are conflicting. There are other pharmacotherapies such as methadone, buprenorphine and naltrexone which are used nowadays. However, these therapies do come with pros and cons (such as adverse side effects) and the current relapse percentage is still very high, indicating that the therapies currently available are not optimal yet. Since drug addiction is a major public health issue, it is of critical importance that an effective treatment is found.

The findings of this report present circumstantial evidence that OXT could be used as a pharmacological agent in the treatment of drug addiction through its direct and indirect actions. Through its indirect actions, OXT helps to attenuate feelings of anxiety, stress and loneliness and thereby it reduces drug craving and prevents relapse. There is also a direct link between OXT and DA as it has been proven that centrally administered OXT into the VTA elevates levels of extracellular DA in the NAc and the VTA and thereby OXT might reduce DA craving. OXT does not replace the drug of abuse, but it is a tool that can be used in treatment to help addicted individuals to reduce the risk factors that cause drug craving and relapse. OXT exhibits both direct and indirect effects, but the majority is indirect. OXT helps addicted individuals through difficult times in total abstinence by reducing drug craving and preventing relapse.

Epilogue

It seems that OXT might be a suitable pharmacological agent in the treatment of drug addiction. However, some potential disadvantages have to be taken into account when considering using OXT in drug addiction treatments. Firstly, the blood-brain barrier (BBB) is a semi-permeable membrane that functions to protect the brain and facilitate selective transport [81]. The BBB can prevent some drugs from entering the central nervous system and therefore it has been investigated a lot if there are routes of drug delivery to the brain that might bypass the BBB [82,83]. In most experiments that link OXT to addiction in humans, OXT is administered nasally in the form of a spray. In the last decades, this route of drug delivery to the brain has been widely investigated as it might bypass the BBB. From a review of 12 studies that examined if nasal drug administration can bypass the BBB, only two studies reported results that indicated a direct transport route from the nose to the brain in rats [83]. However, a recent experiment in rhesus macaques demonstrated that intranasally administered OXT can circumvent the BBB and reach the brain where it can exhibit its actions [84]. In humans, there are promising results of intranasally administered OXT in treatments of, for example, ASD [69] and eating disorders [76]. However, the results of the efficacy of intranasal administration of OXT are conflicting [85,86]. To establish if intranasal OXT treatment in humans is of therapeutic value, a better understanding of this route of drug delivery is necessary and future research should focus on the optimal way to administer OXT to the brain.

Secondly, OXT can also be administered via intravenous injection, this is commonly used to induce labour and the adverse side effects of the intravenous administration are well established. Frequently reported side effects of intravenous OXT injections in the mother to induce childbirth are nausea, anaphylactic reaction, vomiting and arrhythmia [73]. It is unclear if these adverse side effects will also be present after intranasal administration of OXT. Future research should look into possible adverse side effects of intranasal OXT spray.

There are many connections between the effects of OXT and the symptoms of withdrawal that drug-addicted individuals experience in periods of abstinence. This suggests that OXT might be a suitable therapeutic agent in pharmacological treatments of drug addiction as it attenuates difficult moments when loneliness and high levels of anxiety and stress are experienced. Additionally, OXT directly affects DA release in the NAc which might also be helpful to reduce drug craving and prevent relapse. Future research directions should focus on the indirect link between OXT and drug craving and the direct link between OXT and DA in humans.

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