Potential Treatment for Substance Abuse: Pharmacological Agents Targeting the Orexin System

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Abstract

Substance abuse or substance use disorder (SUD) is a form of addiction, a compulsive brain disorder associated with the continual craving for a substance. It is characterized by persistent use of this substance, despite the negative consequences regarding health and social life. These negative consequences include illness, accidents, overdoses, and sometimes even result in death. The worldwide prevalence of SUD and the resulting amount of deaths are currently increasing. Existing behavioral and pharmacological treatments are not sufficient as 40-60 percent of individuals with substance abuse still encounter relapse, even after many years of abstinence.

Relapse is the result of recurring cravings for the rewarding substance. Cravings are induced by the drug itself, stress, withdrawal symptoms, and drug-associated stimuli. The latter results in cravings due to the process of Pavlovian conditioning. Neuronal changes in the brain are the basis for this associative conditioning, including changes in the dopaminergic and glutamatergic pathways. A system involved in these pathways is the orexin/hypocretin system. By altering the dopaminergic and glutamatergic systems, the orexin/hypocretin system plays a role in eliciting cravings and regulating drug-seeking behavior in several types of substance abuse. Therefore, an upcoming potential treatment could use pharmacological agents that target the orexin/hypocretin system in the brain.

Orexin, also known as hypocretin, is a neuropeptide that was originally discovered to play a role in the regulation of sleep-wake rhythms and food-seeking behavior. More recently, researchers found out that orexin increases cravings for rewarding substances. Orexin increases dopamine transmission, by altering both glutamatergic and dopaminergic systems. This increased dopamine transmission results in cravings and increased drug-seeking behavior, which increases the chance of relapse.

Pharmacological agents like orexin antagonists prevent the binding of orexin to its receptor, and thereby block the effect of orexin. This means that an orexin antagonist could reduce craving and thereby prevent relapse. How orexin plays a role in addiction differs for each type of substance abuse. In this thesis, the focus lies on three commonly abused substances, cocaine, nicotine, and alcohol. Different types of orexin receptor antagonists can be used. A selective orexin receptor antagonist for the OX1 receptor (1-SORA) is effective in reducing cravings in cocaine addiction. A dual orexin receptor antagonist (DORA) is effective in reducing cravings for alcohol addiction. Literature about the effects of orexin antagonists on nicotine addiction is ambivalent and remains unclear.

Altogether, orexin antagonists are effective in preventing relapse by reducing cravings for cocaine and alcohol addiction, and maybe other types of substance abuse as well. These effects are all examined in rodents, and no research about the effects of orexin antagonists on addiction is done in humans. Nevertheless, the orexin system in humans plays a similar role in addiction to that in rodents, so orexin antagonists are a potential treatment for substance abuse.

Keywords: addiction, substance abuse, craving, reward system, mesolimbic pathway, dopamine, glutamate, orexin, hypocretin, antagonist

Table of contents

Chapter 1 - Introduction

Addiction is a brain disorder associated with a constant compulsive need for a certain substance or activity. Addiction to substance use is also known as substance use disorder (SUD) or substance abuse and is characterized by persistent use of this substance despite its negative consequences regarding health and social life (Hyman et al., 2006). Even after many years of abstinence, the urge to take drugs is recurring (Koob & Volkow, 2009). This thesis will focus on addiction in the form of substance abuse. The most commonly abused substances are alcohol, nicotine, and cocaine (Carlson & Birkett, 2016). Therefore, this thesis will mainly focus on addiction to these substances. The consequences of substance abuse are problematic and include overdoses, accidents, suicides, violence, and illness. The prevalence of SUD and the number of deaths resulting from it are currently increasing (Global Burden of Disease, 2015). Therefore, intervention is needed to prevent and treat SUD. There are several behavioral and therapeutical interventions for addiction but are not very effective since 40-60 percent of individuals still relapse after treatment or therapy (NIDA, 2020).

A potential target for pharmacotherapy could be the orexin system. This system seems to play a role in inducing craving and drug-seeking behavior. Orexin enhances the glutamatergic and dopaminergic systems, which leads to increased dopamine transmission. This contributes to increased craving and reward-seeking (Mahler et al., 2013). Therefore, a pharmacological agent that blocks orexin binding should reduce dopamine transmission and reward-seeking. This leads to the question of this thesis, *to what extend is the administration of an orexin antagonist effective in treating substance abuse?* The hypothesis is that an orexin antagonist reduces dopamine transmission and thereby decreases cravings and reward-seeking in several types of addiction. If literature confirms this hypothesis, orexin antagonists would be a potential treatment for individuals with substance abuse.

The next chapter of this thesis, chapter two, will describe the characteristics of addiction and the behavioral model explaining how addiction comes about and persists. The third chapter supports this model by explaining the underlying neural mechanisms. Chapter four explains the cravings that are associated with addiction and relapse, and what stimuli elicit cravings. Chapter five will discuss the orexin system, and how it is related to these cravings in addiction. Chapter six describes current treatments and the potential of pharmacological agents targeting the orexin system. The last chapter contains the conclusion and will discuss the implications and limitations of these findings.

Chapter 2: Addiction/substance use disorder

Addiction is a compulsive brain disorder associated with the constant need for a certain activity or substance. Addiction tends to persist, despite the attempts to control it (Hyman et al., 2006). Substance abuse is characterized by persistent use of a substance regardless of the harmful consequences to self or others (Koob & Volkow, 2009). Commonly abused substances are intoxicants such as alcohol, nicotine, and cocaine, also known as recreational drugs. Different drugs lead to different patterns of addiction (Carlson & Birkett, 2016). Eleven criteria

of SUD, see table 1, are outlined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013).

Table 1. Criteria of substance use disorder outlined by DSM-5

1. Taking the substance in larger amounts than meant to
2. Not managing to stop using the substance even if wanted to
3. Large amount of time spent on seeking or using the substance, or recovering from its effects
4. Craving for the substance
5. Not managing to do what you should do at home, work or school because of substance abuse
6. Continued use of the substance despite problems at work, school, or with social interactions
7. Giving up of activities because of substance abuse
8. Continued use even when the use of the substance puts you in danger
9. Continued use even when the substance worsens physical or psychological problems
10. Tolerance occurs; needing more of the substance to get the desired effect
11. Development of withdrawal symptoms, which are relieved when taking the substance

Adapted from NIDA, 2020

2.1 Risk factors

Not every person is as vulnerable to develop substance abuse, there are certain risk factors involved. Adolescents are most vulnerable to addiction since their prefrontal cortex (PFC) is still developing (Volkow et al., 2016). The PFC is part of the frontal lobe of the brain and is important for certain executive functions, including inhibitory control. Therefore, the underdevelopment of the PFC causes adolescents to be more susceptible to experiment with drugs (Carlson & Birket, 2016).

Not only age is a risk factor, but also heredity and environmental factors play a role in the vulnerability to substance abuse (Carlson & Birkett, 2016). Environmental factors play a role in that exposure to high-risk environments, like socially stressful environments combined with easy excess to drugs, increase vulnerability to addiction (Volkow et al., 2016). Environment plays a strong role in influencing a person to experiment with drug and perhaps continue to use them recreationally. On the other hand, genetics play a role in determining whether occasional drug use develops into the dependence on the drug (Carlson & Birkett, 2016).

How genetics play a role differs for each type of drug. For alcohol abuse, variability in the genes responsible for the production of alcohol-metabolizing enzymes plays a role in susceptibility. For nicotine abuse, increased susceptibility is associated with a particular allele of the gene responsible for the production of an acetylcholine receptor. Genes that produce proteins that play important regulatory roles in cells, affect the likelihood of cocaine abuse (Carlson & Birkett, 2016).

2.2 Prevalence & consequences

In 2017 the prevalence of SUD was 2 percent of the total world population (Global Burden of Disease, 2015). This is problematic since substance use disorder has major negative consequences regarding health. Consequences of alcohol abuse include Korsakoff's syndrome, increased risk of heart disease, stroke, and liver cirrhosis. Nicotine abuse increases the risk of lung cancer, heart disease, and stroke. Cocaine abuse can lead to brain damage, psychotic behavior, and overdose may even lead to death (Carlson & Birkett, 2016). SUD is, directly and indirectly, responsible for approximately 12 million deaths a year worldwide. Direct deaths include overdoses, and indirect deaths include deaths as a result of accidents, suicides, violence, and illness. SUD resulted in 307,400 deaths in 2015, this amount has almost doubled since 1990 (Global Burden of Disease, 2015). Thus, addiction is an increasing problem in the current world and intervention is needed. Substance abuse does not only lead to health problems, other negative consequences such as failure in certain life roles and engagement in criminality are common (Hyman et al., 2006).

2.3 Behavioral model of addiction

Why do people still use intoxicants in excess, despite the abundant negative consequences? This can be explained by a form of learning, better known as Pavlovian conditioning (Woods & Ramsay, 2000). Drugs increase the release of dopamine in the brain and thereby activating the reward system. The reward system is responsible for reward-related cognition, regulated by certain neural pathways (Carlson & Birkett, 2016). Consumption of rewards initiates learning processes. In these learning processes experiencing the rewarding goal as pleasurable will consolidate. Also, the environmental cues that predict the consumption of the reward will be reinforced (Heyman et al., 2006). Consequently, after repeated experience with a rewarding drug, the reward becomes associated with the environmental stimuli that anticipate them. For example, the rewarding effect of heroin becomes associated with a syringe. Now, the environmental cues related to the drug, trigger the reward system and dopamine release (Volkow et al., 2016).

Drugs are reinforcing, meaning that behavior aimed at taking the drug tends to strengthen with experience (Heyman et al., 2006). Positive reinforcement occurs when a certain type of behavior leads to a desirable stimulus. For example, the drug-taking causes a euphoric feeling. Negative reinforcement is induced when a certain type of behavior causes an aversive stimulus. For example, the drug-taking diminishes a dysphoric feeling. Both types of reinforcement result in the maintenance of the behavior, in this case, drug abuse (Carlson & Birkett, 2016).

As a result of conditioning, individuals with substance use disorder show symptoms of tolerance and withdrawal and become physically dependent. Tolerance means that an individual becomes less sensitive to a substance when used continuously. As a result, the user must take larger amounts of the substance to gain the desired effect. Researchers explain tolerance as a compensatory mechanism for disturbed homeostasis as a result of the presence of the drug in the body (Carlson & Birkett, 2016).

As a result of these compensatory mechanisms, withdrawal symptoms occur. Withdrawal symptoms are often the opposite effects of the drug itself and occur when the addict stops taking the drug. For example, alcohol administration causes hypothermia. When an alcohol addict stops taking the drug, the body tries to anticipate the drug effects by compensating the body temperature. As a result, withdrawal symptoms of alcohol include hyperthermia (Woods & Ramsay, 2000). Withdrawal could lead to serious health problems, withdrawal from alcohol could even lead to seizures (Hyman et al., 2006). Withdrawal symptoms are unpleasant and disappear when the person takes the drug again, leading to negative reinforcement. This then contributes to the persistent use of the drug (Carlson & Birkett, 2016).

Not all continuous drug use leads to tolerance, sometimes an opposite effect occurs, i.e. sensitization. Sensitization means that the body needs less of the drug to gain a similar effect after repeated exposure. This causes an increased quality of reward, which increases motivation for drug-seeking and thereby contributes to relapse (Tzschentke & Schmidt, 2003). Tolerance often occurs when dosing is constant, whereas sensitization is more likely when dosing is intermittent. Both mechanisms increase cravings in addiction (Hyman et al., 2006).

Chapter 3: Neural mechanisms of addiction

The reward-learning process of addiction can be explained by its underlying neural mechanisms. Drugs take advantage of brain mechanisms that originally help us adapt to the environment, through conditioned learning. When an organism learns the appearance of novel salient stimuli, it will recognize the stimuli when it is encountered again. This is advantageous to predict hazardous situations, for example, encountering a dangerous animal (Kalivas & Volkow, 2005).

The most important system that plays a role in the development of addiction is the dopaminergic system. Additionally, the glutamatergic system is critical in the maintenance of an addiction. Both systems will be described in the following paragraphs.

3.1 Dopaminergic system

Reinforcement is stimulated by an appetitive stimulus or so-called cravings. Fulfilling these cravings by taking the drug, triggers dopamine release in the nucleus accumbens (NAc). The NAc is the major component of the ventral striatum, a brain region that plays a role in the mesolimbic dopaminergic pathway. This pathway is also known as the reward pathway, depicted in figure 1. The NAc projects dopamine to the Ventral Tegmental Area (VTA), as well as to the amygdala, hippocampus, and PFC (Hyman et al., 2006). All these brain regions are involved in the reward system. The increased level of synaptic dopamine within the NAc as a result of drug consumption is stimulated by all addictive drugs, although the mechanism differs per drug (Carlson & Birkett, 2016). Cocaine enhances dopamine actions in the NAc, while heroin and nicotine stimulate dopamine release in the VTA, which can be seen in figure 2 (Bear et al., 2020). The VTA is a brain region connected to projecting dopamine to the forebrain and the lateral hypothalamus (LH). The latter region is part of the hypothalamus, the brain region that plays a critical role in maintaining homeostasis (Carlson & Birkett, 2016).

A mice study by Saal et al. (2003) discovered that administration of a drug induces neural changes in the VTA, by means of increased strength of excitatory synapses on dopaminergic neurons. These plastic changes are the neural basis for learning processes. This is the case for many drugs, including cocaine, amphetamine, morphine, alcohol, and nicotine. Changes in the VTA result in increased activation of the striatum, a region where dopaminergic neurons of the VTA project to. The striatum consists of the ventral striatum (including NAc) and the dorsal striatum (including putamen and caudate nucleus). As a result of neural changes in the VTA, changes in the dorsal striatum occur. These changes are the basis for many forms of learning, among which associative learning. In addiction the NAc is no longer required to activate the reward system, activation of the dorsal striatum only is sufficient (Hyman et al., 2006). Drug-taking behavior is encouraged by changes in the ventral striatum and changes in the dorsal striatum cause the behavior to become habitual (Carlson & Birkett, 2016). This makes it more difficult to treat addiction since it is a challenge to reverse these neural changes that result in habitual drug-taking (Hyman et al., 2006).

Results of a study by Vanderschuren et al. (2005) show that interactions between the ventral and dorsal striatum contribute to the compelling drug-taking behavior. These interactions are mediated by the dopaminergic connections between these regions and the VTA. In individuals who abuse drugs, stimuli that are associated with the drug taking (e.g. environmental stimuli) trigger dopamine release in the dorsal striatum, not the drug taking itself. This contributes to the consolidation that drug-related cues elicit cravings and not just the drug itself (Carlson & Birkett. 2016).

The process of drug tolerance is also mediated by the dopaminergic pathway. Chronic overstimulation of the reward system causes downregulation of the dopamine system, which is a compensatory response to maintain homeostasis. Many drugs affect the brain by binding to a receptor and activating it. One way in which the body attempts to compensate is via decreased effectiveness of the drug binding to the receptor. Another compensatory mechanism works via decreased effectiveness in the coupling process of receptors to ion channels. Due to this decreased effectiveness of the drug binding, dopaminergic activity is downregulated (Bear et al., 2020). Additionally, sensitization is also mediated by the dopamine system. In contrast to tolerance, sensitization is associated with an increased dopamine release as a result of a drug of drug related cues. Thereby, it strengthens the consolidation of drug-related associations (Hyman et al., 2006).

In short, dopamine plays a role in reward-related learning, through neural changes in the VTA and dorsal striatum. Next to that, dopamine is required for motivation for reward-seeking behavior (Hyman et al., 2006).

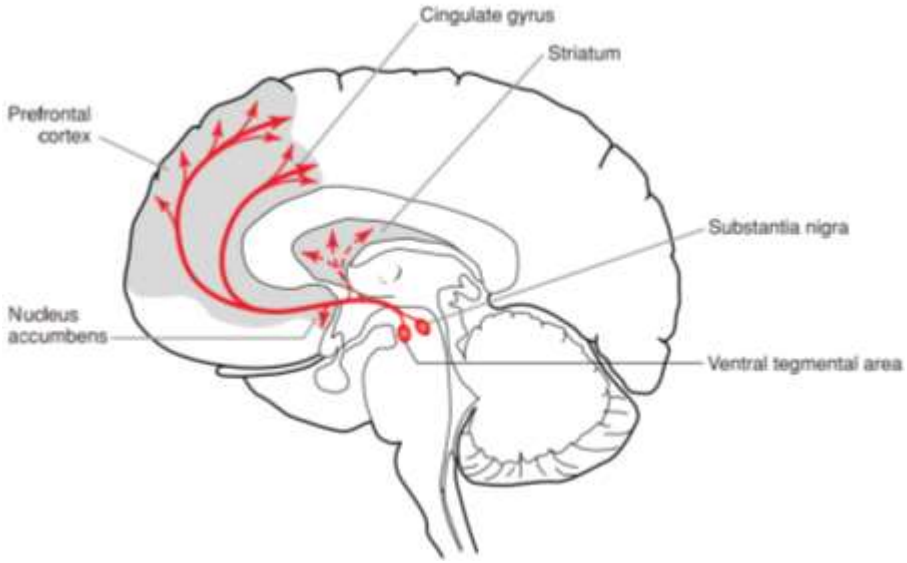

Figure 1. The mesolimbic dopaminergic system. Arrows resemble dopamine projections from the VTA to the NAc, PFC and dorsal striatum (Hyman et al., 2006).

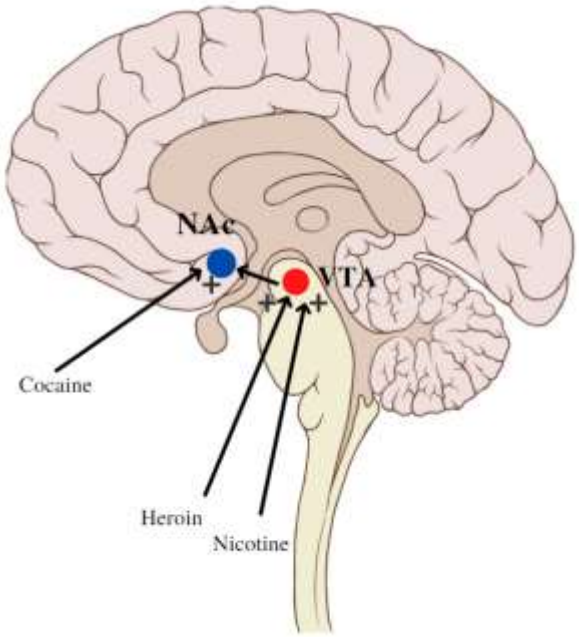

Figure 2. Addictive drugs (cocaine, heroin and nicotine) act on the dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Adjusted from Bear at al. (Bear et al., 2020).

3.2 Glutamatergic system

Not only the dopaminergic system plays a critical role in addiction, but also the glutamatergic system seems to be of importance. Glutamate, an amino acid, is the most important excitatory neurotransmitter in the brain. It is used by nerve cells to send signals to other cells (Carlson & Birkett, 2016). First of all, glutamate plays a role in the reward-learning process of addiction. The plastic changes in the VTA, by means of increased strength of excitatory synapses on dopaminergic neurons, are the result of glutamatergic mechanisms. The dopamine release in the NAc as a result of a reward is triggered by glutamatergic input to the VTA. This process is

mediated by AMPA receptors, i.e. receptors for glutamate that control sodium channels (Tzschentke & Schmidt, 2003).

The glutamatergic system also plays a role in inducing cravings. Glutamatergic projections from the PFC to the NAc induce drug-seeking behavior. The PFC activates glutamate synapses that in turn activate dopaminergic neurons in the VTA, this increases the amount of dopamine release in the NAc (Carlson & Birkett, 2016). Via the PFC, goal-directed behavior is activated. This contributes to the last step in becoming addicted since increased goal-directed behavior is characterized by excessive drug seeking-behavior (Kalivas & Volkow, 2005).

To summarize, the neural changes in the brain that contribute to increased dopamine transmission in learning processes, are the result of glutamatergic input to the VTA. Also, glutamatergic input from the PFC to the NAc is important, as it activates goal-directed behavior.

Chapter 4: Cravings

Craving is the strong desire to consume a substance and is often associated with relapse in addiction (Ray & Roche, 2018). A person with substance abuse will experience cravings or appetite for the drug, after taking a small dose. Just like food, a small taste of it increases the appetite (Carlson & Birkett, 2016). Not only the drug itself can evoke cravings, also stimuli associated with the drug taking behavior can elicit cravings. Due to associative learning, drug-associated cues can induce cravings even when the drug is absent. These drug-associated clues could be anything, for example, the smell or sight of the location where the drug was used before (James et al., 2017).

Another potent stimulus to induce cravings is stress, mediated by the stress hormone called corticotrophin-releasing hormone (CRH). Administration of CRH increases cravings and drug-seeking behavior. Especially the VTA seems to play a critical role here (Carlson & Birkett, 2016).

Furthermore, withdrawal-related distress can increase cravings. Negative reinforcement drives the individual with drug abuse to relieve the negative withdrawal symptoms by taking the drug again, contributing to relapse (Carlson & Birkett, 2016). Figure 3 shows a schematic overview of all stimuli that trigger cravings.

Even after years of abstinence, individuals can experience acute and intense cravings due to neuroadaptations. Cravings increase the motivation of drug-seeking behavior which increases the chance of relapse. Additionally, a craving state is associated with impaired cognitive functions (Ray & Roche, 2018). Craving is a predictor of relapse and therefore an important target for treatment (Kober & Mell, 2015). A potential target could be the orexin system since cravings induced by environmental stimuli and stressors are mediated by this system. The orexin system will be more extensively described in the next chapter.

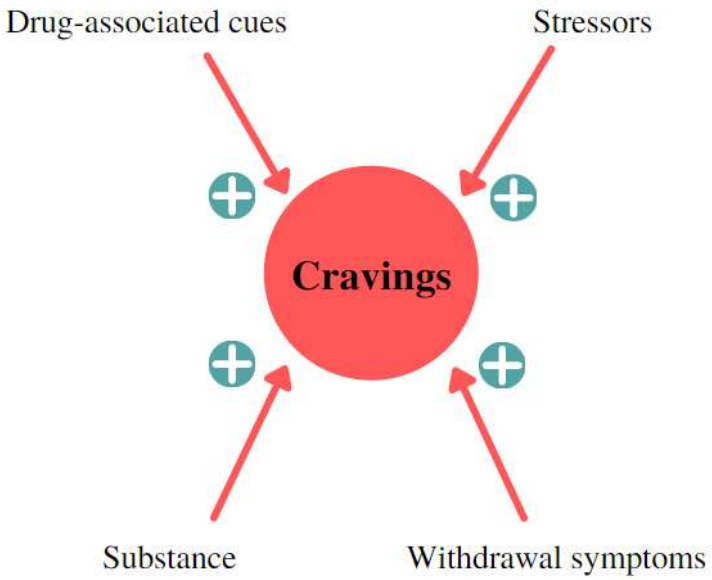

Figure 3. Schematic overview of stimuli that elicit cravings in substance abuse

Chapter 5: Orexin/hypocretin

Orexin, also known as hypocretin, is a neuropeptide synthesized by neurons in the hypothalamus. There are two types of orexin peptides, orexin A and orexin B, that target neurons located throughout the central nervous system via two G-protein-coupled receptors called OX1 receptor and OX2 receptor (Mahler et al., 2013). The difference between the two peptides is their structure. Orexin-producing neurons are located in the LH, the perifornical area (PFA), and the dorsomedial hypothalamic nucleus (DMH) (Perrey & Zhang, 2020).

Orexin was originally found to play a role in the control of sleep stages and food-seeking behavior. The first function was discovered in animals with narcolepsy since this disorder involves a decreased ability to regulate sleep-wake cycles and is associated with a dysfunction in the orexin system (Aston-Jones et al., 2009). The name ‘orexin’, meaning appetite stimulants, originates from the discovery that administration of orexins into the LH produced feeding in rats (Sakurai et al., 1998).

Box 5.1 Orexin or hypocretin?

Orexin is also known as hypocretin since the discovery of the peptide was reported by two different groups independently. Orexin was discovered by Sakurai et al. (1998), whereas hypocretin was simultaneously discovered by de Lecea et al. (1998). De Lecea and colleges called the peptide hypocretin because it is similar to the peptide secretin and located in the hypothalamus (de Lecea et al., 1998) Sakurai and colleges discovered that orexins produces appetitive behavior and therefore derived the peptide name from the Greek word *orexis*, meaning appetite (Sakurai et al., 1998). The debate about which term to use is still ongoing, so scientists refer to the peptide using both terms (Goodrick, 2015). This thesis will use the term orexin.

5.1 Orexin and cravings

The fact that orexin administration produced feeding in rats, leads to the speculation that orexin increases appetite for rewarding substances. Indeed, a study of 2005 demonstrated that orexin neurons in the LH contribute to reward processing and drug abuse (Harris et al., 2005). As described in the behavioral model of addiction, drug-seeking behavior is driven by environmental cues associated with the drug use, even when the drug is not present. This seems to be altered by the orexin system, as reward-associated stimuli activate orexin neurons in the LH, which leads to increased cravings and motivation for drug-seeking behavior. Orexin transmission does not play a role in reinforcing effects, but does regulates cravings by strengthening motivation for drug-seeking (Boutrel et al., 2013).

Orexin neurons located in the DMH and the PFA are not associated with reward functions, only orexin neurons in the LH are critical here. Research suggests a dichotomous role of OX1 and OX2 receptors. Reward is particularly associated with activation of the OX1 receptor, while activation of the OX2 receptor is associated with the regulation of sleep-wake cycles (Perrey & Zhang, 2020).

Orexin is released in the VTA, NAc, and dorsal striatum, which are all regions involved in the reinforcement of drugs (Carlson & Birkett, 2016). The VTA is the region most prominent involved with the reward-related effects of orexin. VTA orexin increases reward-seeking by increasing dopamine transmission in the forebrain. Orexin can directly trigger dopamine neurons in the VTA, but also via enhancing glutamatergic synaptic strength on dopamine neurons (Mahler et al., 2013).

Not only do drug-associated cues activate orexin neurons, also various stressors enhance the orexin system, by activating orexin neurons. Orexin neurons have bidirectional connections with regions related to stress, including the medial prefrontal cortex (mPFC), the central amygdala (CeA), the paraventricular nucleus of the hypothalamus (PVN), and the bed

nucleus of the stria terminalis (BNST). Via activating these regions, orexin might increase cravings and can lead to relapse (Mahler et al., 2013).

Because orexin increases cravings and drug-seeking behavior, researchers started to speculate that pharmacological agents targeting the orexin system could reduce reinstatement of substances, motivation for drug-seeking behavior, and cravings. For example, an orexin antagonist blocks orexin receptors and thereby prevents binding of orexin to the receptor. Consequently, the administration of an orexin antagonist may be a potential treatment for substance abuse.

Chapter 6: Treatment for addiction

6.1 Current treatments

Despite the profound and abundant research about addiction, there is no solution yet for the high incidence of substance abuse. However, researchers developed several therapeutic interventions to treat and prevent substance abuse (Carlson & Birkett, 2016). Some of these therapeutic interventions are based on medication that prevents withdrawal symptoms to occur. For example, treatment for opiate abuse uses opiate agonists to reduce withdrawal symptoms and thereby diminish cravings (Volkow et al., 2016). Also, opiate antagonists are used in treatment to prevent opioid intoxication. For nicotine and stimulant abuse (cocaine and amphetamines) development of antibodies may prevent the entry of these drugs into the brain. This would lead to immunity against substance abuse. However, this method is not yet used and is still being developing (Carlson & Birkett, 2016).

Another potential method used to treat addictions is deep brain stimulation (DBS). Especially DBS of the NAc seems promising in treating addictions. Although this method is effective, it is very invasive. DBS involves brain surgery, which could lead to complications like infections or hemorrhages (Carlson & Birkett, 2016). Another less invasive potential treatment for substance abuse is transcranial magnetic stimulation (TMS), but this only temporarily treats addiction.

Next to therapeutical interventions, behavioral interventions are used to treat addictions. There are several strategies to treat addictions. One strategy is to promote natural stimuli that cause reward, to compete with the drug cravings. Another strategy is to focus on relieving stress, thereby diminishing drug cravings. Also improving executive functions, particularly inhibitory control, could help a person in resisting the drugs. Lastly, drug-associated environmental cues could be avoided to reduce conditioned cravings (Volkow et al., 2016). Common types of behavioral interventions are listed in table 2.

The most successful treatments include a combination of pharmacological and behavioral interventions. Unfortunately still 40-60 percent of individuals with substance abuse relapse after treatment (NIDA, 2020). Therefore, further research is needed to develop a solution for this problem, which opens the door for orexin-antagonists as a treatment for substance abuse.

Table 2. A list of common behavioral interventions, their general approach and type of substance it is used for.

Behavioral interventions	General approach	Type of substance
Cognitive behavioral therapy (CBT)	Developing skills to cope with cravings and avoid situations associated with drug use	Alcohol, cocaine, methamphetamine, marijuana, nicotine
Contingency management	Giving patients rewards to reinforce positive behaviors (e.g. abstinence)	Alcohol, stimulants, opioids, marijuana, nicotine
Motivational enhancement therapy (MET)	Using motivational interviews to gain motivation for the recovery process	Alcohol, opiates, marijuana
The matrix model	Combines all above therapies; patients receive support and education from therapist and family	Stimulants
Community reinforcement approach (CRA)	Developing a lifestyle without drugs, which is more rewarding than with substance abuse, by using recreational and social reinforcers	Alcohol, cocaine, opioids
12-step facilitation therapy	12 steps in which the abuser learns to accept, surrender, and actively engage to promote abstinence	Alcohol, opiates, stimulants
Family behavior therapy	Engagement of individual's social networks	All substances

Adjusted from NIDA, 2020; Donohue et al., 2000; Carroll & Onken, 2005.

6. 2 Orexin-antagonist as potential treatment

Since orexin increases cravings and thereby causes relapse, targeting the orexin system could be a potential treatment for reducing cravings. Several studies examined the effects of an orexin antagonist on different types of addiction in rodents. There are two types of antagonists studied, dual orexin receptor antagonist (DORA) and selective orexin receptor antagonist (SORA). The latter can be selective for OX1 receptor (1-SORA) or for OX2 receptor (2-SORA). Each type of substance abuse shows a different addiction pattern, and orexin plays a different role in each. A review by Mahler et al. (2013) summarizes the role of orexin in different types of substance abuse, and whether orexin antagonists could help in treating that kind of addiction. The role of orexin (antagonist) in the most commonly abused substances (cocaine, nicotine, alcohol) is described next.

In cocaine addiction, orexin is required for cue-induced drug-seeking behavior, but not necessary for the reinforcement of cocaine. This leads to the finding that orexin antagonists do not reduce cocaine self-administration. However, orexin antagonists do help in preventing relapse elicited by drug-associated stimuli (Smith et al., 2009). 1-SORAs reduce the effect of cocaine on dopamine signaling, and thereby decrease the motivation to take cocaine (Perrey & Zhang, 2020).

In contrast to cocaine addiction, orexin does play a role in reinforcement of nicotine addiction. Additionally, orexin plays a role in the withdrawal of nicotine addiction. Administration of orexin antagonist reduces nicotine self-administration and withdrawal symptoms (Mahler et al., 2013). However, a study by Khoo et al (2017), showed that administration of a dual orexin receptor antagonist does not affect reinstatement of nicotine-seeking. Studies show contradictory results regarding the effect of an orexin antagonist on the prevention of relapse.

In alcohol addiction, orexin is required for cue- and stress-induced drug-seeking. Next to that, activation of OX1 receptor is required for alcohol self-administration (Mahler et al., 2013). Blockade of the OX1 receptor by 1-SORA decreased alcohol taking and reduces cue-induced reinstatement of alcohol. Also, 2-SORA reduces self-administration of alcohol, although it has no impact on cue-induced reinstatement. This proves that both OX1 and OX2 receptors play a role in reducing drug-seeking. Thus, DORAs are most effective in reducing cravings for alcohol addiction (Perrey & Zhang, 2020).

Although most patterns in different substances vary, there is one common theme associated with all substances. Orexin modulates motivation in drug-seeking behavior in all substances, mainly when triggered by environmental stimuli (Mahler et al., 2013). 1-SORAs are more successful in reducing cravings in cocaine addiction, whereas DORAs are more effective in reducing cravings in alcohol addiction (Perrey & Zhang, 2020).

An example of a DORA is suvorexant, used as a medication for insomnia. This medication was approved by the Food and Drug Administration (FDA) in 2015. Nevertheless, there are some side effects associated with suvorexant usage, including drowsiness, dizziness, and headache (Deoras & Moul, 2017).

Chapter 7: Discussion

Because the prevalence of substance abuse is high, and the consequences are problematic, the development of more effective treatment is essential. Orexin plays a role in the reward system and substance abuse and is, therefore, a potential target for treatment. The hypothesis was that pharmacological agents that target the orexin system could reduce cravings in various types of addiction.

Recently, several studies examined the effects of orexin antagonists on different types of substance abuse. For cocaine addiction, 1-SORAs are effective in reducing cravings for cocaine via decreasing dopamine signaling. Therefore, variations of 1-SORA could be effective in treating cocaine addiction. For alcohol addiction, DORAs are more successful in reducing drug-seeking behavior. Thus, variations of DORA could be effective in treating alcohol addiction. The effect of orexin antagonists on nicotine addiction remains unclear. Literature is ambivalent and it is unclear whether orexin antagonists increase or decrease drug-seeking

behavior. However, orexin increases the reinforcement and withdrawal of nicotine. Therefore, you would expect that an orexin antagonist would be useful in reducing these effects and thereby prevent relapse. Further research is needed on the effects of orexin antagonists on nicotine addiction.

Since evident literature already proved the effectiveness of orexin antagonists in addiction, the following question arises. Why are orexin antagonists not already used as a treatment for addiction? The answer lies with the complications that come with administration of orexin antagonists into the brain. Since VTA orexin increases reward-seeking, orexin antagonists need to reach the VTA to be effective as pharmacotherapy for substance abuse. In order to get to the VTA, they need to be administered into the cerebral ventricles or microinjected into brain regions since they have a poor permeability of the blood-brain barrier. This includes surgery and is not possible for humans. Fortunately, intranasal administration of orexins can be effective as well, which is more accessible for humans (Perrey & Zhang, 2020).

All research about the effects of orexin antagonists on addiction is done in rodents. Although there is no research yet about the effects of orexin antagonists on addiction in humans, rodent studies may serve as a translational model for humans. There is one approved orexin antagonist on the market for humans, namely suvorexant. However, this DORA is not used as a medication for addiction, but to treat insomnia. Since it can be used orally, it is not clear whether this is suitable as pharmacotherapy for substance abuse. There are some side effects, but these are minor compared to the consequences of persistent substance use. Suvorexant is not yet used to treat substance abuse but is potential and further research could examine its effectiveness.

To conclude, orexins antagonists are effective in reducing cravings in alcohol and cocaine addiction and thereby preventing relapse. Thus, orexin antagonists are potential treatments for substance abuse. A combination of pharmacological agents targeting the orexin system with behavioral therapy might even be more effective.

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