

Chapter 2

Neurobiology of Substance Abuse

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Introduction

Drug dependence is understood as a complex disorder associated with biological, emotional, and social factors. Consequently, an individual might develop dependence as a result of the interaction of those factors or even one of them alone, which favors the repetitive use that leads to dependence.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), the disorders caused by substance use are characterized by a pattern of use which entails severe clinical damage that might be physical, psychological, or social, and have significant impact on the life of the users and those around them. Among the clinical diagnoses for dependence of the DSM-V are: failure to control use; social damage; recurring use even in situations that imply in physical danger, or pharmacological criteria (presence of tolerance or abstinence).

Concerning the neurobiological bases of drugs of abuse, the first fundamental hypothesis about drugs of abuse, which attempted to explain the action of drugs on the brain, was formulated in the 1980s. Supported by several previous studies, this theory has been enhanced and many efforts have been devoted, and still are, for

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researchers to understand the neurobiological effects of drugs, mainly those associated with dependence. By studying the central nervous system (CNS), neurobiology aims at understanding and identifying the areas involved in the behavior of continuous drug use. This understanding will allow therapeutic strategies to be developed, shed light on the etiology of dependence, and promote the perception of drug dependence as a health-related disorder rather than a moral issue.

Therefore, the objective of the present chapter is to describe the main neurobiological aspects involved in the dependence on drugs of abuse, hence help understand the etiology of this dependence.

Basic Concepts: Psychopharmacology and Neuroanatomy

The brain of an adult human has approximately 170 billion cells, out of which 86 billion cells are neurons (Azevedo et al. 2009). Neurons are the main cells of the CNS responsible for the transmission of information. One of their particular characteristics is their form. They comprise a *cell body*, which processes all the basic activities of a cell and the region where the nucleus of the cell lies; the *dendrites*, which are ramifications that receive most of the information from other neurons; and the *axon*, a slender projection of a nerve cell, responsible for conducting the nervous impulse to the other neurons. Once a given stimulus reaches a neuron, this can activate it and promote the transmission of the information received, forwarding it to different brain regions. For example, when an individual sees a cake or a drug, the neuron that receives this sensory information may trigger it to other neurons that in turn might evoke a memory of how tasty that cake is or how pleasant the use of a certain substance.

Additionally, most of the neurons do not touch physically; hence, the communication among them is permeated by *synapses*. A synapse is composed by a set of two neurons (pre- and post-synaptic) and a gap between them (synaptic cleft). The information is transmitted by chemical signals from the neurotransmitters (NTs) which interact with their respective receptors. Once an electrical signal reaches the end of a neuron, called axon terminal, NTs are released into the *synaptic cleft*, allowing them to bind with their *receptors*. The binding between NTs and receptors takes place through the chemical attraction among the molecules. In a specific way, an NT can only bind with a compatible receptor. The best analogy to explain the interaction between NTs and receptors is the relation between a key and its lock. A key can only open the lock it was designed for, not working for other models. In the same way, a dopamine molecule (DA), a type of neurotransmitter, can only bind with specific dopamine receptors. Once coupled to its binding site, the NT may activate or inhibit the receptors, spreading or interrupting the transmission of information to the post-synaptic neuron.

Similarly to the NTs, drugs of abuse are chemical substances that alter the functioning of the CNS directly or indirectly. Such alterations may lead to changes in the basal activity of the brain. For example, some drugs may increase the amount

of NTs released into the synaptic cleft or even increase the time they are available in the cleft. There are several physiological mechanisms that allow drugs to perform their modulations in the brain. Drugs of abuse may act by hindering the *reuptake* of NTs (their removal from the synaptic cleft); binding directly to receptors and acting independently of the presence of NTs; binding to receptors in different sites from those of the NTs (allosteric sites), modulating the action of NTs; inhibiting the degradation of NTs by binding to enzymes that are specific for this function; taking the place of NTs in the *synaptic vesicles* (site where NTs are stored); or binding directly to the membrane of the pre-synaptic neuron, promoting the release of NTs.

Neurobiology and Behavioral Aspects

According to the neurobiological theory of drug dependence, the behavior of continuously seeking for the substance or its specific effects (euphoria, relaxation, motor alterations, sleepiness, etc.) results in alterations the drugs promote in the brain activity by changing, for instance, the amount of time of action of the NTs in the synaptic cleft. The study of the neurobiology of drugs of abuse is directly related to the study of behavior. From the neurobiological perspective, the behavior of continuous consumption of drugs might be understood as a learning process in which the drug acts as reinforcement. Therefore, basic concepts of behaviorism such as stimulus, response, operant conditioning, punishment, and positive and negative reinforcements are important for the understanding of the neurobiological basis of drug use. A *stimulus* might be defined as an event or something that might cause a specific reaction, known as *response*. Responses can be of biological, psychological, or behavioral nature. Using the example we already mentioned, a cake and drugs are considered *stimuli* that might trigger a *response*: The memory of how tasty the food or how pleasant the use of the drug can be. When a *stimulus* **increases** the frequency of a *response*, it is called *reinforcement* or *reinforcing stimulus*. *Punishment*, on the other hand, **decreases** the frequency of the *response*. *Reinforcement* can be of two types: *positive* or *negative*. It is considered *positive* when its **presence** increases the frequency of a response, and *negative* when its **withdrawal** or **absence** promotes the increase in the frequency of a response.

If an individual uses the drug (stimulus) and presents a sensation of well-being (response), which enhances the chances of that behavior being repeated, the drug will be considered a *positive reinforcement*. In a negative situation, when individuals are experiencing a negative state, as in the withdrawal syndrome, they will feel relaxed and well (*response*) when they use the drug (*stimulus*), the drug will be a *negative reinforcement*, since it increases the frequency of drug-using behavior in order to relieve the discomfort of a withdrawal syndrome. Therefore, a *stimulus* does not necessarily trigger a response. When that is the case, it is called a *neutral stimulus*. However, it may start to trigger a response once the person is conditioned to produce that response. This learning process is called *conditioning*. There are two basic types of conditioning: *classic* and *operant*. In the *classic conditioning*, a

neutral stimulus is associated with an *unconditioned stimulus* (a stimulus that produces an innate response, such as a type of food that makes one's mouth water). After repeated pairing of the *neutral stimulus* with the *unconditioned stimulus*, a type of learning occurs in which the *neutral stimulus* begins to elicit the response. It is then called *conditioned stimulus*. The other type of conditioning, called *operant*, postulates that learning takes place through reinforcement and punishment. In that case, unlike in the *classic* conditioning, the *operant* conditioning is based on the fact that there is an **increase** or a **decrease** of the chances of a response depending on the consequences associated with the behavior. An important aspect of the *operant conditioning* is that it deals with *voluntary* behaviors, such as eating a piece of cake or using a drug. Conversely, the classic conditioning is frequently based on involuntary responses, such as physiological responses (e.g., pain, salivation, and sweating).

Common Action of Drugs of Abuse: The Brain Reward System

Considering the basic behavioral aspects associated with substance use that have been presented, now we can better understand which are the neurobiological basis of the drugs of abuse. In this section, we will discuss the similarities regarding the brain functioning when there is drug use, and how this use changes the transmission of information in the brain. Later on we will discuss some particularities of the action of each drug of abuse, better explaining how the different effects are generated by each class of drug (depressant, stimulant, and hallucinogenic). Drug use may range from one single use in life to a frequent and daily use. In other words, not every initial use of drugs will evolve into a condition of dependence. In fact, only a small proportion of individuals who have already used some type of drug develop dependence. As an example we can mention the use of alcohol by the adult Brazilian population: while 74 % drink, only, approximately 12 % fulfill the diagnostic criteria for dependence (Carlini et al. 2007). The way individuals consume a drug (sniffed/snorted, inhaled/smoked, intravenous, oral, etc.) will also interfere in the odds of their evolving to a more severe pattern of use, and the pattern itself might increase or decrease their odds of becoming dependent.

Every psychoactive drug needs to reach the brain to produce its effect. The different routes of administration have a direct effect on the time the substance takes to reach the brain. Some routes provide a fast access of the substance to the bloodstream, quickly increasing its levels in the blood. As a result, it reaches the brain almost immediately, causing faster effects. On the other hand, the faster the drug reaches the brain, the faster its effects wear off. Due to the characteristics of the lungs, the substance reaches the bloodstream very fast. Thereafter the blood, already containing the substance, reaches the heart, being directly pumped to the whole body, including the brain. A large concentration of the drug will soon be available to reach the brain quickly, causing fast yet transient effects. A study

comparing equivalent doses of cocaine in different routes of administration (smoked, sniffed/snorted, and injected) concluded that the alterations resulting from some physiological reactions (increased blood pressure, increased heart rate, and mydriasis) happen in a similar way for the smoked or injected route. Cognitive-behavioral effects (euphoria, pleasure, and perception of the intensity of effect), however, are stronger in the smoked use. In the use of snorted cocaine (cocaine chlorhydrate), the cognitive-behavioral effects have a slower onset, and the physiological effects take place in a more slowly and less intense manner than in the smoked or intravenous use. Taken together, these data point to a higher potential for cocaine abuse and dependence in its smoked (crack) and injected route when compared to the snorted route (cocaine chlorhydrate) (Cone 1995).

Dependence on any drug of abuse cannot and should not be diagnosed based on one single use of the substance. As discussed before, there are diagnostic criteria that should be met, as the examples present in the DSM-V (American Psychiatric Association 2013), in order for dependence to be characterized. All of them are related to the recurring or continuous use of the drug (use for long periods; unsuccessful attempts to quit or cut down on use; continuous use even in situations that involve physical, psychological, or social damage to oneself or others; tolerance; withdrawal syndrome; and craving). Moreover, the severity of symptoms, characterized by the number of criteria met, reflects the increase or decrease in the frequency or number of doses used. Hence, independently of the route of administration of the substance, it is not possible to characterize dependence in an individual who has used drugs only once.

Since there should be a repetitive behavior of drug use to characterize dependence, the study of the neurobiological bases of drugs is strongly related to behavioral aspects. Several studies, especially those with animals, were conducted in order to determine which are the brain regions involved in dependence. Even though there are numerous animal models to study it, one of the main ones is the paradigm of *self-administration*. In this paradigm, an animal is placed in a box with access to a lever (Skinner box). By pressing the lever, the animal can receive a number of rewards as food and water, and also drugs of abuse. Animals deprived of food and water initially explore the environment and, over time, learn that they receive the reward by pressing the lever. When they are presented with two levers, one that supplies water and the other that supplies some drug, many animals choose to press the lever that provides the drug rather than the one that provides the natural rewards. Once this happens, one may assume that substance is passible of self-administration. Variations of this model include the injection of drugs directly in the circulation, in brain regions, and even the electric stimulation in specific brain regions. Using a variation of the traditional self-administration model through the use of electrodes that promoted electric stimulation of the brain, Olds and Milner (1954) published a study that aimed at detecting the reinforcing characteristics of electric stimulation of some brain areas of rats. The authors observed that when a certain region was stimulated (septal area), the animal pressed the lever several times, similarly to what happened with natural reinforcing stimuli (food and water). Therefore, they assumed they had detected a brain system responsible for the

reinforcing effect of behaviors. In the following years, until the 1960s, several studies were conducted that identified other regions associated with the reinforcing effects and the data of Olds and Milner (1991). Among those regions were the *ventral tegmental area* (VTA), the *nucleus accumbens* (Nacc), regions of the *do pre-frontal cortex* (PFC), and the *amygdala* (Wise 1996). Those regions stood out initially in the study of a pathway called “*reinforcement pathway*” or “*pleasure pathway*,” exactly the one that would explain the reinforcing effect of behaviors.

The reinforcement pathway consists of two pathways of dopaminergic neurons, the *mesolimbic* and the *mesocortical pathways*, known as the *mesocorticolimbic system* when taken together. The pathway of neurons that goes from the VTA into the Nacc is called *mesolimbic pathway*. Other regions of the limbic system are also part of the mesolimbic pathway, as the amygdala, which is associated with the reinforcement and pleasure generated by drugs of abuse, in addition to the memories associated with the use and conditioned responses (Koob and Bloom 1988) (see *conditioned stimuli* in the section “*Neurobiology and Behavioral Aspects*”). The neurons that go from the VTA into the PFC form the *mesocortical pathway*. This pathway seems to be associated with the compulsive behavior of drug use, low inhibitory control, and the emotional valence of the drug (Volkow and Fowler 2000). The reinforcement pathway is activated by natural reinforcing stimuli as food, water, and sex, as well as by artificial stimuli as drugs of abuse. Every time it is activated it promotes the release of an important component to understand the neurobiological bases of dependence: the neurotransmitter *dopamine* (DA). When any of the reinforcers is presented, there is the release of DA into the Nacc, generating a feeling of pleasure. In fact, once DA is released into the Nacc, the response to the stimulus is facilitated, giving it more salience. When this happens, the behavior tends to be repetitive, enhancing associative learning. This condition attaches excessive value to the stimulus or to the contexts associated with the use of the drug (Di Chiara and Bassareo 2007; Di Chiara et al. 1999). Dopamine is released into the PFC as well. In that case, the release is involved with cognitive processes, as the regulation of attention, memory, motivation, and executive functions (Seamans and Yang 2004).

Some substances as cocaine and amphetamines promote the release of DA directly into the Nacc as a result of their direct action in that region. Other drugs, on the other hand, promote the release of DA into the Nacc by activating the neurons of the mesolimbic pathway in the VTA (Koob and Volkow 2010). The release of DA into the Nacc seems to be important for the feeling of pleasure caused by the use of drugs, the compulsive behavior, and the motivation to search for the substance. When the *mesolimbic pathway* is stimulated, there might be release of DA into the *amygdala*, in addition to the release of that neurotransmitter into the Nacc (Weiss et al. 2000), since the amygdala is involved in the learning of memories associated with the use of drugs. An example is the pleasant memories caused by the use of the substance. Moreover, the amygdala might be activated when something associated with the drug is close, as the view of a place where the drug is usually used. Hence, the amygdala plays a fundamental role in the learning of clues

associated with the drug and the evoking of some memory associated with its use (Stahl 2010).

Some regions of the PFC are believed to be involved in drug dependence, namely the portions of the *ventromedial pre-frontal cortex*, associated with emotions and affective states; *dorsolateral frontal cortex*, related to memory and decision making, and the *orbitofrontal cortex*, associated with the inhibition of responses (Noël et al. 2006). Broadly speaking, these PFC regions seem to regulate the decision making toward or away from the use of substances. In short, different information seems to be integrated into the PFC, allowing the modulation of responses by means of their efferent connections (Volkow and Fowler 2000). Another interesting point is that the *orbitofrontal cortex* is activated in individuals in different phases of dependence, as intoxication, craving, and abuse, while it is deactivated during abstinence. In that case, the activation would be associated with motivation, tracking, modulation, and updating of salience of a reinforcing stimulus, as drugs, according to context, control abilities and inhibition of associated responses (Goldstein and Volkow 2002). When this happens, stimuli associated with the use of drug might evoke pleasant memories associated with the use, hence favoring the reuse of the substance. At the same time, the PFC regions may also be activated and evoke negative memories associated with use. As the PFC is related to decision making and response inhibition, the behavior might be suppressed, preventing a future use of the drug (Bechara 2005; Noël et al. 2006).

As discussed above, both natural and artificial reinforcing stimuli can promote the release of DA into the pleasure pathway. Those reinforcers, however, seem to act differently in the brain from the natural ones (basic activities of survival, as feeding and reproduction). Such stimuli are innate and unconditioned, evoking behaviors of search or flight, depending on their characteristics (Di Chiara 2002; Glickman and Schiff 1967). After repeated exposure to a reinforcing stimulus, one might reach an adaptive stage called *habituation*, in which the responses to the stimulus are reduced or paralyzed. Conversely, behaviors associated with non-natural reinforcers, such as drugs of abuse, might get around this adaptive mechanism. This would, in turn, lead to an excessive motivation of the stimuli conditioned to the drug, favoring the onset of dependence (Di Chiara and Bassareo 2007). Another relevant aspect is that the response resulting from the use of drugs might promote a high increase in the amount of extracellular DA in the Nacc, higher than that generated by food, sex, or other reinforcers (Fibiger 1993). Moreover, even though both the natural and the non-natural stimuli promote the release of DA into the Nacc, the action of those two different types of reinforcers is different regarding the neurobiological regions affected. While natural reinforcers release DA into the portion known as *core* of the Nacc, non-natural reinforcers release DA into the portion *shell* of the Nacc (Di Chiara and Bassareo 2007).

The release of DA into the Nacc might happen both when the reinforcing stimulus is presented and when one is about to receive the reinforcer. Behaviors associated with reinforcing stimuli can be subdivided into *preparatory* (related to the anticipation of the behavior, working as encouragement that promotes approaching the reward and facilitates the production of a response) and *consummatory* (immediately after the behavior, as orgasm after intercourse, or chewing

after the contact with food). Both of them promote the release of DA into the Nacc. As a result, anticipatory signals to the use of substances lead to the release of DA into the Nacc (Blackburn et al. 1989), favoring the repetition of the behavior.

Different Action of the Drugs in the Brain Reward System

Drugs of abuse share the same action in the brain, causing the release of DA into the Nacc and promoting the feeling of pleasure, which makes the body perceive this eliciting stimuli as more salient. The DA release into the Nacc might happen in different ways, be it directly, as in the case of cocaine and amphetamine, or indirectly, through its action in different brain regions (see below).

Drugs of abuse have different effects depending on their class, the main ones being *depressant*, *stimulant*, and *hallucinogenic*. Depressant drugs work by reducing the brain activity and causing slowing down of the CNS. Some examples are alcohol, opioids, and benzodiazepines. Stimulant drugs act in the opposite way, increasing the activity of the CNS. Some examples of this class of drugs are cocaine/crack, amphetamine, and tobacco. Hallucinogenic drugs are those that affect the working of the CNS in a qualitative way, changing the perception of the individual, as in the case of marijuana.

From the neurobiological viewpoint, what makes those substances cause such different effects is the type of neurotransmission system involved, its mechanisms of action, and the brain areas the substance acts on. Therefore, although cocaine and heroin cause release of DA into the Nacc, these drugs have particular effects. In the case of cocaine, the effects are clearly stimulant. In the case of heroin, however, the effects are depressors of the CNS.

Alcohol

The acute effects of alcohol on the CNS are mediated especially by the potentialization of the inhibitory action of GABA (main inhibitory neurotransmitter of the CNS) and the reduction of the stimulant action of glutamate (main excitatory neurotransmitter of the CNS). In the chronic use of alcohol, there seems to be an inversion, in which there is an increase in the activity of glutamate receptors and a reduction in the function of the GABA receptors (Samson and Harris 1992). The use of alcohol increases the concentration of DA in the Nacc through the activation of neurons in the VTA. This release seems to be associated with both the action of alcohol on GABA receptors and of glutamate receptors. The activation of GABA inhibits the GABAergic interneurons that communicate with the VTA. As GABA is the main inhibitory neurotransmitter of the CNS, this reaction causes the disinhibition of the DA neurons of the VTA, releasing DA in the Nacc. At the same time, alcohol might inhibit glutamatergic receptors, decreasing its stimulant action on the

same GABAergic interneurons, which will once again reduce the inhibitory effect of GABA on the VTA (Gilpin and Koob 2008; Tabakoff and Hoffman 2013). The reinforcing actions of alcohol also seem to affect the endogenous opioid system. As discussed above, GABA interneurons in the VTA keep the release of dopamine into the Nacc inhibited. Opioid receptors inhibit GABA interneurons, disinhibiting the release of DA into the Nacc (Herz 1997). The activation of opioid receptors might occur by the action of both β -endorphins and enkephalins (released by neurons from the arcuate nucleus, for example). Alcohol seems to act stimulating the release of those substances (Gianoulakis 1996; Stahl 2010).

Cocaine and Crack

Cocaine and crack are the same substances concerning their action on the CNS. Their main differences lie in the process of production of the drug and their most common routes of administration. Their action on the CNS is stimulant and happens through the blockade of monoamine transporters (dopamine, serotonin, and norepinephrine), especially by blocking DA transporters. Hence, the blockade of the latter, responsible for removing the neurotransmitter from the synaptic cleft, causes an increase in the amount and length of time in which DA is available in the synaptic cleft. As a result, there are higher chances that DA binds with post-synaptic receptors, potentializing the normal effects of DA. This increased DA availability favors the learning of associations among the subjective and physiologic effects of the use of cocaine/crack and environmental and behavioral stimuli (Kalivas 2007).

The stimulant effects of cocaine/crack, as euphoria, are a consequence of their effects on different brain regions, as the VTA, the Nacc, the amygdala, the hippocampus, and the frontal cortex. Particularly the Nacc seems to be of utmost importance in the repetitive behavior of cocaine/crack use, since the amount of DA released into that region is very large, outweighing the physiological levels associated with natural activities as sex (Nestler 2005). Consequently, greater salience is conferred to the drug when compared with other natural reinforcements (Kalivas 2007). Another significant aspect is that cocaine/crack, due to their mechanism of action, might stimulate the release of DA directly into the dopaminergic terminals of the Nacc (Koob and Le Moal 2005a).

Amphetamines

The group of drugs classified as amphetamines includes substances as ephedrine, methamphetamine, and methylphenidate, among others. Those substances might be of natural or synthetic origin, licit, or illicit. They share the characteristic of stimulating the CNS, just as cocaine/crack. Amphetamines are similar to cocaine/crack not only in relation to their effects on the CNS, but also regarding the blockade of

noradrenaline, DA, and serotonin (Koob and Le Moal 2005a). Nevertheless, they use other mechanisms, acting as inhibitors of monoamine oxidase (enzyme responsible for the degradation of monoamines), to promote a greater availability of DA (Robinson 1985) and the displacement of DA to outside the synaptic vesicles, taking its place inside the vesicle. As a result, the intracellular concentration of DA increases, releasing it into the synaptic cleft (Stahl 2010). The action of amphetamine is mediated by mesolimbic and mesocortical dopaminergic pathways, and the release of DA might happen into both the Nacc and the amygdala (Koob and Le Moal 2005a).

Opioids

This class of substances includes heroin, codeine, morphine, and opium, among many others. Some opioid drugs can be obtained directly from the poppy flower (*Papaver somniferum*) or be produced in laboratories. Their main effects are depressor and include analgesia, sedation, respiratory depression, and sensation of euphoria. The same way as amphetamines, the class of opioids includes both licit (morphine and codeine) and illicit (heroin) drugs.

The action of opioids on the CNS is mediated by different types of opioid receptors. Their main effect on the CNS is the dopaminergic stimulation in the VTA and the increase of DA release into the Nacc. Those receptors are involved in the effects of exogenous opioids (drugs) as well as the endogenous opioids (substances naturally present in the CNS, with similar action to that of drugs of abuse; World Health Organization 2004). Hence, opioids activate their receptors in the VTA, Nacc, and amygdala, and promote the release of DA into the Nacc by means of the action of the VTA or the Nacc itself (Koob and Le Moal 2005a).

Benzodiazepines

Benzodiazepines (BZD) are medications used in the treatment of anxiety, convulsions, and sleep induction. They appeared as an alternative to the use of barbiturates for being safer from the therapeutic point of view. The main mechanism of action of BZDs happens through their binding to GABA receptors. By binding to the receptor, BZDs modulate the functioning of the neuron, potentializing and prolonging the GABA effects, activating the chloride channels, increasing the GABA capacity of allowing chloride ions to enter the neuron, and inhibiting the neuron. BZD actions require less GABA to open the ion channel (World Health Organization 2004; Petursson and Lader 1981).

The potential of BZDs to cause dependence is extensively discussed in the literature. Among the clear clinical aspects, we can mention the fast development of tolerance to some of their effects and the withdrawal syndrome (Ashton 2005; World

Health Organization 2004; Owen and Tyrer 1983; Petursson and Lader 1981). However, few studies point to the capacity of BZDs to bring about the sensation of pleasure associated with the use of drugs as amphetamines and cocaine.

Marijuana

Marijuana is a natural drug of abuse that produces hallucinogenic effects on the CNS. There are other synthetic compounds, as the synthetic marijuana, that produce similar effects to those of that plant. Even though marijuana contains dozens of psychoactive substances known as cannabinoids, its main hallucinogenic effects result from the delta-9-tetrahydrocannabinol. The compounds of this class are not found exclusively in plants. The endogenous version (produced in our body) of cannabinoids is called endocannabinoids, and their main example is the anandamide. Cannabinoids and endocannabinoids bind to specific receptors, the two main ones being CB1, present predominantly in the CNS, and CB2, present in peripheral tissues and the immune system (Gong et al. 2006; Wang and Ueda 2008). Cannabinoid receptors are present in several regions associated with the reinforcement of drugs of abuse, including the PFC, the Nacc, and the VTA. The reinforcing action of cannabinoids seems to happen through the increase in the activity of dopaminergic neurons of the mesolimbic pathway, even though cannabinoid receptors are not directly present in those neurons. The action happens by means of their activity on GABA and glutamate neurons (Fattore et al. 2008; Maldonado et al. 2006).

The activation of cannabinoid receptors in the VTA seems to promote the release of DA through the inhibition of GABA neurons. In the Nacc, the cannabinoid receptors present in the glutamate neurons (from the PFC) inhibit the release of glutamate. Such inhibition makes the GABA neurons that project from the Nacc to the VTA be inhibited as well, which will result in the release of DA into the Nacc through the mesolimbic pathway (Maldonado et al. 2006).

Tobacco

The action of tobacco in any of its forms (cigarettes, cigars, snuff, etc.) is mediated in the CNS by nicotine. This activity happens in a series of receptors spread over several brain regions. Nicotine is a stimulant of the CNS and reaches the brain very quickly when smoked in the form of cigarettes (see route of administration in the section “[Common action of drugs of abuse: the brain reward system](#)”). Moreover, large amounts of nicotine are made available in the body after each cigarette puff.

Nicotine acts in acetylcholine nicotine receptors. Nicotine dependence seems to be primarily associated with its reinforcing properties that result from the action in the receptors of dopaminergic neurons in the VTA. Therefore, its action promotes

the direct or indirect release of DA into the Nacc, a crucial aspect for the behavioral effects associated with reinforcing properties (World Health Organization 2004). In a direct way, nicotine acts on dopaminergic receptors present in the post-synaptic neurons in the VTA; in an indirect way, the action happens by means of the desensitization of the GABAergic interneurons in the VTA, reducing the release of GABA that acts inhibiting the dopaminergic neurons.

Main Neurobiological Theories on Drug Dependence

Even though several studies raise the hypothesis that the use of drugs of abuse activates brain regions related to the reward system (mesolimbic and mesocortical pathways), there is no complete definition of all the mechanisms of action of drugs on the human brain. This is so especially because of methodological restrictions or techniques that limit the studies. Consequently, the assertions are based on scientific information that was tested and replicated over decades, and corroborate the hypotheses formulated.

Below we present two important neurobiological theories on drug dependence.

Dependence, Dopamine, and the Mesolimbic Pathway

The first significant neurobiological theory about drugs of abuse was presented in 1980 by Roy Wise, researcher in the Department of Psychology at Concordia University in Montreal, Canada (Wise 1980). His hypothesis was that several types of reinforcement, including drugs of abuse, would activate the reinforcement pathway (related to the dopaminergic system) at least partially. This system would be directly activated by drugs as cocaine and amphetamine (the direct action of opioids was still uncertain then). Other drugs, on the other hand, would act not by the direct activation of the dopaminergic fibers of the reinforcement pathway, but rather by the excitation or inhibition of the dopaminergic system by means of its afferences. Such drugs would include opioids, benzodiazepines, ethanol, and barbiturates (Wise 1980). In 1987, in another work in which he shared the authorship with Michael Bozarth, Wise further suggested that all the drugs with a potential to cause dependence had the ability of psychomotor stimulation (Wise and Bozarth 1987). According to this theory, every positive reinforcement would share the same biological mechanism involving dopaminergic pathways. This time Wise stated that opioids would have a common action with cocaine and amphetamine, that is, promoting the psychomotor activity directly in the reinforcement pathway. The psychostimulant action of nicotine, caffeine, barbiturates, benzodiazepines, marijuana, and phencyclidine, on the other hand, would result from the direct stimulation of the dopaminergic fibers of the reinforcement pathway or by means of circuits associated with it (Wise and Bozarth 1987). In short, in this new phase of

their theory, Wise and Bozarth declare that all drugs of abuse have a stimulant action on the psychomotor activity, mediated by dopaminergic neurons of the reinforcement pathway and its connections with other systems.

Over 20 years later, another study was published with much information added to the original theory of 1980 and enlarged in 1987. In that version, more recent and complete, Wise points the dopaminergic mesolimbic pathway as the key point of the brain circuitry in the reinforcement of drugs of abuse (Wise 2002). Cocaine and amphetamine would be reinforcers for releasing dopamine into the Nacc. The action of nicotine would be a result of actions in the cholinergic receptors present mainly in the VTA, and its activation would also promote the release of DA into the Nacc. Heroin and morphine, both opioids, would act in two ways: one by inhibiting the GABA neurons, which normally keep the mesolimbic pathway inhibited, disinhibiting it; the other by inhibiting the neurons that come out of the Nacc. Marijuana and alcohol seem to act by unknown mechanisms, increasing the triggering of the mesolimbic dopaminergic neurons. Caffeine seems to have a reinforcing effect by means of an independent circuit. Finally, benzodiazepines and barbiturates seem to activate one or more circuits of GABAergic neurons, not necessarily associated with the dopaminergic system, thus activating their habit-generating effects (Wise 2002). A noteworthy point in this new version of Wise's theory is that the mesolimbic system could be activated both by the direct message of the reinforcement that is present and by sensory stimuli that pointed to the closeness of a reinforcer. Consequently, the drug does not necessarily have to be present for the mesolimbic pathway to be activated, and it only takes signals that the drug is near.

Dependence as a Disorder Associated with Stress

George Koob is another eminent researcher who proposed a theory to explain the common action of drugs on the brain. His theory was based on the perspective of the reinforcement and the pleasure produced by drugs on the brain. He suggests that the brain reinforcing pathway is associated with several neuropharmacological elements that have neuroanatomic elements in common (Koob 1992). Three key neurotransmission systems are thought to be involved in the reinforcing capacity of drugs: the opioid, the GABAergic, and the dopaminergic systems. Initially, Koob's theory addressed opioids, hypnotic/sedative substances, cocaine, and amphetamine. All those drugs would have a significant action on the mesocorticolimbic system (mesolimbic and mesocortical pathways).

DA appears to be critical in the reinforcing properties of cocaine and amphetamine, though not so strong in the case of opioids and hypnotic/sedative substances. In those situations, DA would contribute to the reinforcing properties, but not in an essential way. As for opioids, Koob suggests that their receptors in the Nacc and VTA would be critical for reinforcement. In the case of hypnotic/sedative substances, mainly alcohol, the GABA receptors would be the initial sites of the reinforcing action, especially those present in the Nacc and amygdala (Koob 1992).

The hypothesis Koob proposes differs considerably from the theory proposed by Wise (1980), since for Koob DA does not play a critical role in the reinforcing action of all the drugs, as suggested by Wise.

In 1997, Koob and Le Moal (1997) published a review on the use of drugs in which they proposed that the vulnerability to dependence would not only involve a spiraling sequence triggered by the acute use of drugs (binge/intoxication pattern), but also involve stages of withdrawal/negative feelings and concern/anticipation. Consequently, the authors concluded that the cycle of dependence cannot be explained only by the association to responses that result from the initial drug use (Koob and Le Moal 1997). Therefore, according to the theory proposed by Koob as regards drug dependence, that condition is characterized by a chronic disorder that involves relapse and comprises three specific stages: (1) compulsion for the search and use of the drug; (2) loss of control in limiting the use; and (3) presence of negative emotional states such as dysphoria, anxiety, and irritability when the access to the drug is limited (Koob and Volkow 2010). This view places particular importance on strategies of *negative* reinforcement in the maintenance of dependence, not limiting it only to *positive reinforcement* (pleasure generated by the use of the substance). Even if the first use is promoted by the pleasure generated by the substance (positive reinforcement), the maintenance of use would happen as an attempt to relieve the negative consequences (physical and emotional) of the lack of drug (negative reinforcement; Kreek and Koob 1998). This leads to another important point in the difference between the theories of Wise and Koob, since the hypothesis of Wise is based mainly on the positive reinforcement aspect of the drug, while to Koob it may act as a negative reinforcement as well, especially in the cases of drug dependence.

During the intoxication phase (acute), the reinforcing effects of drugs make the reward system favor the creation of habits through the activation of the reinforcement systems, which would involve both the action of dopamine and the opioid system in the Nacc and the dorsal striatum (related to the learning process and habit formation; Koob and Volkow 2010). However, due to the excessive stimulation of the reward system (by means of positive reinforcements that would lead to the release of opioid peptides), there would be the activation of dynorphin (an endogenous opioid) in the Nacc and VTA, suppressing the release of DA. As a consequence, this decrease in the release of DA would favor negative states after the withdrawal of the drug (Koob et al. 2014).

Several studies by Koob and other researchers give consideration to the role of the regulatory system of stress in the pathway of reinforcement and maintenance of dependence (Koob and Le Moal 1997; Kreek and Koob 1998; Piazza and Le Moal 1996, 1998). According to George Koob, drug use activates the brain system of stress (Koob et al. 2014; Kreek and Koob 1998). He believes that both the system of stress and that of dependence are associated with a series of neuroadaptations that result from the prolonged use of drugs. The use of drugs, initially motivated by social reasons and the search for reinforcement in an acute way, might lead to the development of a compulsive pattern of use in some individuals, and eventually to dependence (Koob and Le Moal 2005a). During this process of transition from

social use to dependence, there would be excessive and prolonged stimulation of the mechanisms of stress regulation (Koob et al. 2014). In that way, the use of drugs in the long term would promote alterations in the pleasure pathway and in the brain system of stress, connected to important changes in the motivation to use. In the view of Koob and Le Moal, this would be the “dark side” of drug use, known as the antireinforcement system (Koob and Le Moal 2005b, 2008). In the second phase of the spiral proposed by Koob, the stress mechanism seems to act promoting negative emotional states. His hypothesis is that by the activation of the brain system of stress during drug withdrawal there would be a sensitization through the release of corticotropin, noradrenaline, and dynorphin that would promote such negative states. One of the associated regions would be the amygdala (Koob et al. 2014; Koob and Volkow 2010).

Finally, the phase of concern/anticipation, or the craving stage, has been pointed out as a key element in relapse. This stage would involve the processing of conditioned reinforcement in the amygdala, of contextual information in the hippocampus, and the executive control dependent on the PFC, which would include the representation of contingencies and outcomes associated with the drug, in addition to the value attributed to the drug and the subjective states related to it (Koob and Volkow 2010).

Final Considerations

The study of the neurobiology of drugs allowed the identification of several brain regions associated with substance use and, consequently, considered as possible therapeutic targets. Moreover, the neurobiological view of dependence is fundamental for a better understanding of this process as a health disorder rather than a moral issue. The main drugs of abuse have already been pointed as important in the mediation of the response to a given stimulus, giving it special value and providing higher chances for the behavior to be repeated. From the neurobiological view, this is possible through the release of dopamine into the Nacc. On the other hand, the way through which the drugs promote the release of that neurotransmitter is highly variable- that is, it might take place in a direct way or through associated pathways, as the mesolimbic and the mesocortical pathways. The different ways drugs act on the brain allow the understanding of their different cognitive, behavioral and physiological effects.

As important as the study of the neurobiological bases of dependence, it is noteworthy that substance use should always be considered a multifactor disorder of biopsychosocial nature. This means that once any of those aspects is neglected, the attention to the substance-dependent individual will be faulty or at least incomplete. Even though neurobiological factors might be determining in the development of dependence in certain individuals, this alone should not be considered the factor responsible for the whole dependence process.

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