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REVIEW ARTICLE

The relation between the dopaminergic system, drug addiction, and brain structures related to reward behaviors and decision-making

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Abstract

Drug addiction is a serious global health problem that affects the brain, behavior, and decision-making of people, leading to an inability to control drug use. The pharmacological effects of drugs, experienced as a reward, are driven by a variety of genetic, environmental, developmental, and psychosocial factors and are mainly regulated by the dopaminergic system in the reward circuit, with the ventral tegmental area and nucleus accumbens being the most important. Dopamine, the main neurotransmitter, is responsible for regulating physiological functions, including reward-related behaviors. When substance abuse occurs, dopamine is released in greater quantities, forming a connection between the substance and the feeling of reward, thus creating a desire for more pleasurable effects. Dopamine receptors also play a direct role in generating intracellular signals related to pleasure and rewards. Drugs with addictive potential can downregulate the activity and expression of dopamine receptors in the brain. This review focuses on understanding the role of dopamine, the dopaminergic system, and brain structures related to rewards and associated behaviors in drug addiction.

Keywords: *Addiction. Drugs. Reward. Decision-making. Dopamine.*

La relación entre el sistema dopaminérgico, la drogadicción y las estructuras cerebrales relacionadas con las conductas de recompensa y la toma de decisiones

Resumen

La drogadicción es un grave problema de salud global que afecta al cerebro, la conducta y la toma de decisiones de las personas, lo que lleva a una incapacidad para controlar el consumo de sustancias. Los efectos farmacológicos de las drogas, experimentados como una recompensa, están impulsados por una variedad de factores genéticos, ambientales, del desarrollo y psicosociales, y están regulados principalmente por el sistema dopaminérgico en el circuito de recompensa, siendo el área tegmental ventral y el núcleo accumbens las regiones más importantes. La dopamina, el principal neurotransmisor, es responsable de regular funciones fisiológicas, incluidas las conductas relacionadas con la recompensa. Cuando se produce el consumo de sustancias, se libera dopamina en mayores cantidades, formando una conexión entre la sustancia y la sensación de recompensa, lo que genera el deseo de experimentar nuevamente esos efectos placenteros. Los

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receptores de dopamina también desempeñan un papel directo en la generación de señales intracelulares relacionadas con el placer y la recompensa. Las drogas con potencial adictivo pueden disminuir la actividad y la expresión de los receptores de dopamina en el cerebro. Esta revisión se centra en comprender el papel de la dopamina, el sistema dopaminérgico y las estructuras cerebrales relacionadas con la recompensa y las conductas asociadas en la adicción a las drogas.

Palabras clave: *Adicción. Drogas. Recompensa. Toma de decisiones. Dopamina.*

Introduction

The use and consumption of psychoactive substances dates back to prehistoric times. Archeological data suggest that the use of such substances, mostly plants, has been around for at least 10,000 years, and there is historical evidence of their cultural use for the past 5,000 years[1]. A clear example is the chewing of coca leaves, which dates back more than 8,000 years in Peruvian society.

Psychoactive substances are natural or synthetic compounds that, when introduced by any route (e.g., buccal, nasal, oral, and intravenous) and passing into the bloodstream, have a direct effect on the central nervous system (CNS), causing specific changes in its functions. The CNS is a target for many types of drugs of abuse as well as specific prescribed medications. These drugs affect the brain by binding to receptors, resulting in changes in neuronal activity. The effects of drugs vary, depending on the drug, its concentration, and the type of receptor to which it binds. Drug use is driven by the pharmacological effects of drugs in the CNS, which are experienced as rewards and influenced by genetic, developmental, and psychosocial factors that mediate access to the drug, social norms, and support systems[2]. All drugs of abuse modulate gene expression involved in neuroplasticity through epigenetic and, possibly, transcriptional modifications, leading to addictive behaviors as a result of allostatic maladaptation of neuronal circuits[3]. These modifications disrupt intracellular signaling mechanisms and neural circuits, the dysfunction of which has been implicated in the long-lasting changes associated with addiction.

This review presents a synthesis of the existing literature on the relationship between the dopaminergic system, drug addiction, and brain structures related to reward behavior and decision-making. It was conducted as a narrative review, an approach that allows for the exploration of the breadth and complexity of the topic, identification of the key trends, and provision of a descriptive overview. This narrative review is characterized by a thematic organization of the information, synthesizing study findings in a descriptive manner to provide a comprehensive understanding of the topic.

Drug addiction is a chronic, recurrent, progressive, and sometimes fatal condition that manifests in various mental and physical states throughout the addiction cycle, from craving to drug intake, intoxication, withdrawal, and remission (preoccupation/anticipation, binge/intoxication, and negative affect/withdrawal). It worsens over time and involves changes in brain's reward and stress systems[4]. Structures considered to be part of these reward systems are located along the primary dopaminergic pathway of the brain. When exposed to rewarding stimuli, the brain responds by releasing increased amounts of dopamine, the main neurotransmitter associated with rewards and pleasure during addiction states[5]. Other behavioral and cognitive disturbances, such as impulsivity or impairments in learning, conditioning, reward processes, and executive function, are thought to play a role in the development and maintenance of addiction[6]. Addiction can cause long-lasting changes in brain circuits related to reward, stress, and self-control, even after a person has stopped taking a drug[7]. The current data suggest that most drugs of abuse initially reinforce their effects by activating reward circuits in the brain and that drug experimentation is largely voluntary. Chronic drug use impairs brain function by interfering with a person's ability to self-control addictive drug-using behaviors, making the brain more sensitive to stress and negative moods[8]. This is why drug abuse can have rewarding effects and why it is consumed by humans or self-administered by laboratory animals. Brain imaging studies of people with addiction show physical changes in areas of the brain that are critical for judgment, decision-making, learning, memory, and behavior control. Imaging studies such as positron emission tomography (PET) provide new ways to investigate and understand how individual biological factors integrate with one another and relate to behavior, as well as how biological and environmental variables interact during drug addiction[9]. Most PET studies on drug addiction have focused on the dopaminergic system of the brain, as this system is believed to be through which most drugs of abuse exert their reinforcing effects[10]. Dopamine lies at the core of drug reward and pleasure and is involved

in all stages of drug addiction, from induction to maintenance to relapse after a period of withdrawal[11]. All drugs of abuse, directly or indirectly, affect the brain's reward system, causing a release of high amounts of dopamine a neurotransmitter found in various regions of the brain that modulates movement, emotions, cognition, motivation, and feelings of pleasure.

Process addiction, also known as behavioral addiction, is characterized by an overwhelming impulse to engage in a certain behavior, despite the negative consequences that may result. Upon engaging in said behavior, the individual often experiences an elevated mood, followed by a sense of shame or guilt upon its completion. Common process addictions include shopping, gambling, sexual activity, pornography, eating disorders, internet use, exercise, work, and compulsive criminal behavior. These addictions can harm the individual's physical and emotional health, damage interpersonal relationships, and may even lead to legal or financial problems. Process addiction should not be confused with an addiction to drugs or alcohol. Although process addiction and addiction to drugs are distinct disorders, they often co-occur, a phenomenon referred to as dual diagnosis. All addictions share similar characteristics, such as the inability of the addicted person to stop or limit compulsive behavior, even when it has a negative impact on many aspects of their life[12].

The reward system and mesolimbic pathway

Rewards are a natural process in which the brain associates various stimuli – such as substances of abuse, situations, events, or activities – with positive or pleasant outcomes, causing adjustments in an individual's behavior, also known as appetitive or preparatory and consummatory behavior, ultimately leading them to seek out that particular positive stimulus again and again[13]. Dopamine has been extensively implicated in the processing of all types of rewards at a cerebral level, including the valence of food, drink, sex, social interaction, and substance abuse[14].

The mesolimbic system is a key component of the reward system, playing an important role in motivating behavior and providing positive reinforcement. This system is mainly composed of the ventral tegmental area (VTA) and nucleus accumbens (NAc), along with their afferent and efferent connections. The mesolimbic system is a CNS circuit in which dopamine inputs from the VTA innervate brain regions involved in executive, affective, and motivational functions, including the prefrontal cortex (PFC), amygdala, and NAc[15]. This circuitry is crucial for establishing the relationship between rewards and stimuli, thereby guiding behavior. Changes in dopamine mesolimbic neurotransmission modify behavioral responses to various environmental stimuli associated with reward behaviors. Psychostimulants, drugs of abuse, and natural rewards such as food and sex can cause substantial synaptic changes in the dopaminergic mesolimbic system[16].

The reward system is primarily composed of the VTA and consists of dopaminergic projections to the NAc and other brain targets, including PFC, amygdala, and hippocampus[17]. The VTA, located in the midbrain, is a small region that is an important source of dopamine, particularly in the limbic regions. This region is composed of dopaminergic, gamma-aminobutyric acid neurons, and glutamate neurons, with the dopaminergic neurons being the most abundant (up to 60%)[8]. The VTA is a heterogeneous structure in the midbrain and plays an important role in reinforcement, reward, learning, motivation, cognition, aversion, and addictive behavior[18]. In the VTA, drugs of abuse directly influence the release of dopamine in this area, leading to addiction and associated behaviors compared to those of non-addicted individuals. Dopaminergic neurons in the VTA (VTA-DA neurons) project to the NAc, a central hub of the reward circuit and a major driver of goal-directed actions that are sensitive to the current salience (estimated value) of an associated goal[19]. Furthermore, these neurons project to the amygdala and hippocampus, mediating memory and emotional associations, as well as to PFC regions, which mediate salience attribution and self-regulation. Collectively, these regions contribute to reinforcement and conditioning that follow chronic drug consumption[20]. The activity of VTA-DA neurons is linked to all reward-predicting processes, including the psychostimulatory effect of rewards. Addictive drugs, such as cocaine, amphetamine, morphine, nicotine, and ethanol, induce characteristic changes in synaptic plasticity in VTA-DA neurons within 24 h of acute exposure. VTA is an anatomical site critical for behavioral sensitization following repetitive drug administration[19]. Therefore, VTA-DA neurons have been an interesting topic and are considered the main therapeutic target for treating reward and pleasure-related disorders, such as drug addiction and mood disorders, owing to their key role in directing reward-related responses[21].

The NAc is located in the rostral region of the basal forebrain, below the ventral striatum. It consists of two parts: the NAc shell and the NAc core. This structure

is responsible for regulating an individual's reward circuit, with the NAc shell receiving information from the limbic system and the NAc core mainly receiving information from the motor system[22]. The NAc acts as a functional interface between these two systems, converting motivation into action. It is also responsible for modulating the response to reward-related signals, which are encoded through projections to and from the amygdala, thalamic nuclei, and PFC[23]. The VTA-NAc circuit is the primary reward pathway in the brain, in which drugs of abuse have important effects on the release and increase of dopamine concentrations. Rewarding stimuli primarily stimulate VTA-DA neurons to release dopamine into the NAc, thereby driving the activity of medium spiny neurons (MSNs) and subsequent reward-seeking behaviors[22,23]. In the NAc, MSNs make up 90-95% of all neurons[23]. These, along with cholinergic interneurons, have been shown to be the two main groups of neurons in this structure that are important for studying addiction comorbidity[24]. The NAc plays a crucial role in various forms of adaptive and pathologically motivated behavior. Several studies have demonstrated a strong association between this structure and a range of neurological and psychiatric disorders, including depression, obsessive-compulsive disorder, bipolar disorder, anxiety disorders, Parkinson's disease, Alzheimer's disease, Huntington's disease, obesity, drug abuse, and addiction[24,25].

The habenula is another important brain structure in reward circuitry; it receives information from the limbic system, sends signals to the VTA, regulates dopamine levels in the striatal region, and plays a role in modulating reward and reward-associated learning[26]. However, the ventral striatum, including the NAc, is the major structure involved in reward processing.

The dorsal striatum is critically involved in action selection and initiation components of decision-making, and it also appears to mediate feedback properties such as valence and magnitude in habitual behavior control and addiction[27,28]. Therefore, both the ventral and dorsal regions of the striatum play collaborative roles in mediating rewards[27].

Recent studies have shown that reward is subjective and highly influenced by the chemistry of the individual, homeostatic state, genetics, and epigenetics[29]. The main function of the reward system is to determine the valence of a stimulus, signal whether it should be avoided or approached and assign priority to one stimulus over another. Substances of abuse, whether illicit (e.g., cocaine and heroin) or licit (e.g., alcohol, nicotine), hijack the mesolimbic system by offering a reward with no obvious biological function. However, the pleasure and reward attached to the initial substance use are later lost through abuse, leading to a vicious cycle of addiction. All drugs of abuse acutely lower reward thresholds at the brain level, thereby increasing or facilitating rewards[30].

Addiction is a complex process that involves multiple networks in the brain, with one of the most important being the VTA. It is now widely accepted that repeated exposure to addictive substances leads to adaptive changes at the molecular and cellular levels in the mesolimbic dopamine pathway, which is responsible for regulating motivational behavior and organizing emotional and contextual behaviors[31]. These modifications in the mesolimbic pathway led to drug dependence, a chronic relapsing disorder characterized by compulsive drug-seeking and drug-use behaviors that persist despite the severe negative consequences of the drugs[32] (Fig. 1). Animal models of addiction and depression have chosen the NAc as a primary research target because of experimental evidence showing that addictive drugs increase dopamine release or alter synaptic plasticity in this structure, while non-addictive drugs generally do not affect basal dopamine release or plasticity[33,34]. Neurons in this structure are activated by stimuli that produce rewarding experiences, such as drugs of abuse, exercise, food, sex, and music. Alterations in dopaminergic signaling are common mechanisms in several motivational and reward disorders, including addiction. Drugs of abuse, while sharing the common effect of increasing dopamine levels in the NAc, achieve this through diverse mechanisms. Some drugs, such as cocaine, directly block dopamine reuptake, while others like opioids indirectly increase dopamine release by disinhibiting dopaminergic neurons in the VTA[35-37]. These increases in dopamine contribute to the reinforcing that promotes drug-taking behavior. In humans, functional imaging studies have shown that environmental cues associated with addictive drugs can release dopamine into the NAc region[38]. Thus, alterations in dopaminergic signaling play a critical role in the development and maintenance of addiction.

The dopaminergic system

The dopaminergic system undergoes late maturation in the brain, suggesting its essential role in stabilizing and integrating functions in neural circuits throughout the lifespan, such as motivation, motor control, and reward processing. Shortly after its identification, the roles of dopamine in reward theory and addiction were

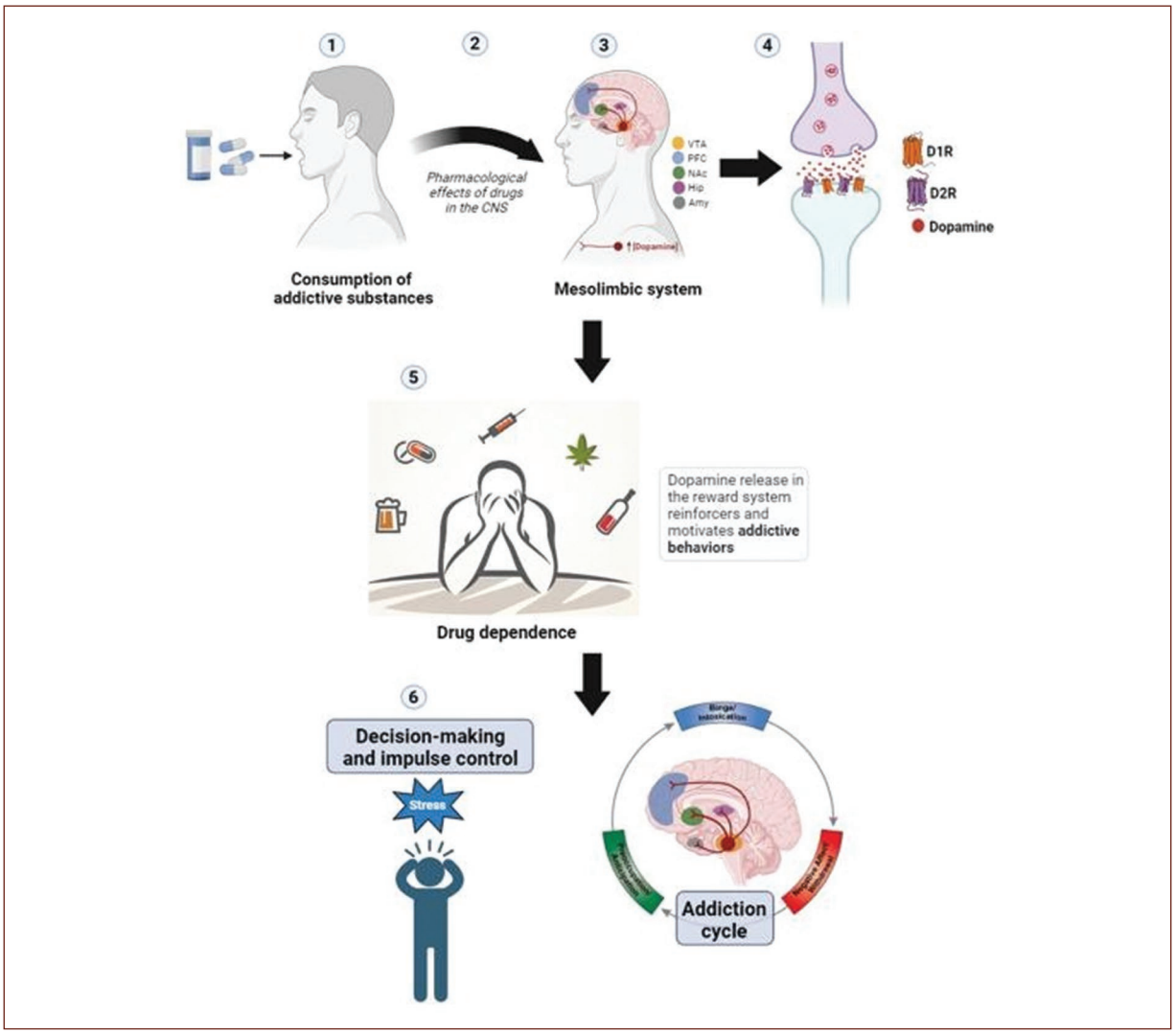

Figure 1. Behavioral addictions to drugs. (1) Psychoactive substances are natural or synthetic compounds that, when introduced into the bloodstream by any route, directly affect the CNS, causing specific changes in its functions. (2) Drug use is driven by the pharmacological effects of drugs in the CNS, which are experienced as rewards or relief from pain. The effects of drugs vary, depending on the drug, its concentration, and the type of receptor to which it binds. (3) The mesolimbic system is a key component of the reward system, mainly composed of the ventral tegmental area (VTA) and nucleus accumbens (NAc), along with their afferent and efferent connections. When exposed to rewarding stimuli, the brain releases increased amounts of dopamine, the main neurotransmitter associated with rewards and pleasure during addiction states. (4) The release of dopamine causes the stimulation of specific receptors, the dopamine receptors (DARs). D1R and D2R are the most abundantly expressed DAR in the brain and G-protein-coupled integral membrane receptors. D1R and D2R contribute to distinct rewarding and addictive behaviors. (5) Modifications to the mesolimbic pathway led to drug dependence, a chronic relapsing disorder characterized by compulsive drug-seeking and drug-use behaviors that persist despite the severe negative consequences of the drugs' effects. (6) Alterations in prefrontal cortex (PFC) function can result in the loss of inhibitory control, leading to compulsiveness and drug-seeking despite severe negative consequences in substance use disorders. Craving is a major challenge in overcoming addiction. This figure was created using BioRender.com.

established, based on anatomical and pharmacological evidence[2,14]. The dopaminergic system is activated by three types of external stimuli: rewards, punishments, and novel stimuli. When activated by rewards or punishments, parts of the dopamine system are activated in bursts that can last up to several seconds, whereas other portions are inhibited in response to negative reinforcement[39].

Dopaminergic neurons fire either in stable, tonic mode (1-8 Hz), which is important for momentary sensitivity to external stimuli and setting the background dopaminergic tone for behavior, or in transient, high-frequency phasic mode (> 15 Hz). Under normal conditions, DA neurons contain a pool of dopamine that is insensitive to stimulation, and more than half of the synaptic dopamine release sites are functionally silent when stimulated[40].

The release of dopamine causes the stimulation of specific receptors, the dopamine receptors (DAR), which are G-protein-coupled integral membrane receptors. The dopaminergic system sends signals through five DAR subtypes, divided into two main subclasses: D1-like (D1R and D5R) and D2-like (D2R, D3R, and D4R) receptors[41]. The role of DAR in different neuronal populations of the striatum illustrates their complexity. Neurons expressing D1R and D2R contribute to distinct rewarding and addictive behaviors. D1R responds primarily to dopamine burst signals, while optogenetic studies have shown that the effect of dopamine burst firing on D2R is not occluded by the presence of a background dopamine tone, suggesting that D2R can respond to a broader range of stimuli. Tonic activation of dopamine leads to the release of dopamine from extra-synaptic release sites, where it binds to high-affinity dopamine D2R and is linked to motivational arousal in response to external stimuli[41,42]. Phasic activation of dopamine causes high extracellular concentrations of dopamine, which activates low-affinity D1R and are linked to conditioning to positive and negative reinforces. This phasic pattern of dopamine activity has been observed in association with drug and reward-seeking behaviors[42].

All drugs of abuse with addictive potential increase dopamine levels, either directly or indirectly affecting dopaminergic neurons in the VTA, resulting in the release of dopamine in the NAc[4]. People with drug addiction show a significant reduction in the function of D2R in the striatum, including in the NAc[41]. This reduction of striatal D2R, which modulates the indirect striatocortical pathway, has been implicated in impulsive and compulsive behaviors[40-42]. The activation of D1R by different stimuli, such as food and drugs, fulfills a reinforcing action, which consolidates the memory traces of the reception of the reward and the events that preceded it. In animal models, the activation of the D1R, through exposure to a reinforcer or predictor (for example, food and drugs of abuse), causes the animal to remember more (in subsequent trials) about the associated internal and external stimulus conditions, leading to the progressive identification of earlier predictive stimuli.

Decision-making and drug use: the role of prefrontal cortex

Decision-making is a complex process that requires the coordination of multiple brain regions, with the PFC playing a major role. This region of the brain is responsible for controlling emotions, forming judgments, and making decisions based on available information[43]. Adolescents are particularly vulnerable to the effects of drug abuse because of the ongoing neurodevelopmental process, particularly in regions such as the PFC, which is crucial for decision-making and impulse control. Imaging studies have shown that the adolescent brain undergoes significant changes in dopamine pathways and PFC development that may increase vulnerability to addiction[6,36,37,43-50]. Alterations in PFC function can result in the loss of inhibitory control, leading to compulsiveness and drug-seeking despite severe negative consequences in substance use disorders. Reward-sensitive processes occur in three key subdivisions of the PFC: the anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC)[44,45]. Craving is a major challenge in overcoming addiction and is associated with activation of the ACC, vmPFC, OFC, striatal areas, and insula. Neuroimaging studies in individuals with addiction problems have shown overactivation of the ACC and OFC during drug-related signaling activities, including craving, and hypoarousal during cognitive tasks with neutral valence[45,46].

The OFC in primates and humans is a key for emotion, representing the values of reward and non-reward. It has been established as a critical brain region in adaptive decision-making when the expected reward fails to occur[44]. This structure has been implicated in the pathology of drug and behavioral addiction. Disruptions in OFC function may explain decision-making impairments in some substance-dependent individuals. The vmPFC is involved in various social, cognitive, and affective functions commonly disrupted during mental illness. It is connected to other brain regions implicated in drug abuse behaviors related to impulsive consumption[46].

Amygdala: role in emotional processing, conditioning, and craving

The amygdala, a structure located in the temporal lobe of the mammalian brain, is associated with the

experience of fear and anxiety. It is composed of different nuclei and has traditionally been related to emotional responses, which has been supported by various studies using fear conditioning paradigms. These studies have demonstrated that damage to the amygdala results in deficits in learning and memory of emotionally relevant stimuli[47]. The amygdala is a highly conserved structure of the temporal lobe limbic system, composed of basolateral (BLA), central (CeA), and medial (MeA) subcomponents[47,48]. It interacts with both the cortex and striatum to influence motivated behavior. The BLA, the primary input region of the amygdaloid complex, receives inputs from across the brain, including the hippocampus, NAc, PFC, thalamus, and other amygdala nuclei. Furthermore, the BLA has been found to mediate conditioned drug-seeking behavior for cocaine, alcohol, and heroin[47].

In addition, research has shown that both the BLA and CeA nuclei play different roles in representing the value of primary and conditioned rewards[49].

The amygdala projects to the mesolimbic system in a similar manner to that by which the NAc is activated when cravings occur in cocaine addicts[48,49]. It is suggested that the NAc translates drug-related motivation into drug-seeking actions, and the amygdala is thought to mediate the emotional impact associated with the craving[49]. The BLA encodes Pavlovian incentive associations, and through its projections to the NAc, it underlies the performance of prolonged drug-seeking sequences reinforced by drug-associated conditioned stimuli, which act as conditioned and delayed drug-seeking behaviors. Recent studies have found that low functional connectivity between the amygdala and OFC circuits is associated with greater weekly alcohol intake in binge-drinking young adults and is predictive of future alcohol use, suggesting that this circuit mediates drug use susceptibility[50].

Material and methods

A literature review was conducted using a methodological search strategy in the PubMed database, part of the National Library of Medicine (NIH), to identify relevant studies published between 2000 and 2023. The search strategy used a combination of keywords including “addiction,” “behavior and rewards,” “brain reward system,” “dopamine,” “limbic system,” “dopaminergic system,” “drug abuse,” “decision-making,” “prefrontal cortex,” and “drug addiction”. Boolean operators (AND, OR, NOT) were used to refine the results. Search terms were adapted to the specific syntax of the PubMed database to ensure comprehensive retrieval.

The inclusion criteria were human studies, animal studies, reviews, and meta-analyses without language restrictions. Studies in any language were included to minimize the risk of bias in the review; gray literature (such as dissertations and unpublished reports), and non-peer-reviewed sources were excluded. The selection process included a review of titles, abstracts, and where necessary, full texts of articles to determine their relevance to the review.

Results

The literature review demonstrates that drug addiction remains a prevalent global health issue, with a notable rise in the number of individuals using illicit drugs in the last two decades. Chronic drug use impacts behavior and decision-making, leading to a loss of control over drug consumption. The pharmacological effects of drugs cause structural and neurobiological alterations in crucial brain circuits, particularly those related to reward and pleasure. The dopaminergic system is crucial in modulating these effects.

Dopamine, the primary neurotransmitter involved in reward, regulates various physiological functions, including reward-related behaviors. Drugs of abuse increase the release of dopamine in the brain, strengthening the association between the substance and pleasure and promoting the desire to use the drug more. Dopamine receptors are also directly involved in generating intracellular signals related to pleasure and reward. However, chronic drug use can lead to a downregulation of dopamine receptor activity and expression in the brain.

Several brain structures are involved in addiction, including the VTA and NAc, which are key components of the reward circuitry. The VTA is a major source of dopamine and plays a role in reward, learning, motivation, and addictive behavior. The NAc is a central structure in the reward circuitry that receives information from other brain areas and translates motivation into action. Other brain structures involved in addiction are the PFC and the amygdala. The PFC is critical for decision-making, judgment, and emotional control, while the amygdala processes emotions and is involved in the conditioning associated with drug use.

Repeated exposure to drugs of abuse induces adaptive changes at the molecular and cellular levels in the mesolimbic dopaminergic system, a circuit crucial for motivation, emotion, and reward. These changes, which occur in response to addictive substances, alter the

Table 1. Key studies on brain structures and neurobiology of addiction

Study/Reference	Study design	Study focus	Key findings
Volkow et al.[10]	Human neuroimaging study (PET)	Function of the dopaminergic system in cocaine addiction	Cocaine addicts show a decrease in D2 receptor availability in the striatum, which increases compulsivity in drug use.
Di Chiara and Bassareo[11]	Theoretical review	Role of dopamine in reward and addiction	Dopamine is involved in all stages of addiction, from induction to maintenance and relapse.
Nestler and Carlezon Jr.[15]	Theoretical review	Mesolimbic dopaminergic system in depression and addiction	Modifications in the mesolimbic dopaminergic pathway play a crucial role in drug dependence.
Lüscher and Malenka[19]	Theoretical review	Drug-evoked synaptic plasticity in addiction	Exposure to drugs of abuse induces adaptive changes in the synapses of dopaminergic neurons.
Koob and Volkow[4]	Review	Neurocircuitry análisis of addiction	Addiction involves changes in brain's reward and stress system.
Schultz[5]	Physiological review	Neuronal reward and decision signals	Dopamine has been extensively implicated in the processing of all types of rewards at a cerebral level.
Volkow et al.[2]	Physiological review	Neuroscience of drug reward and addiction	The review discusses the neuroscience of drug reward and addiction.

normal function of this system and contribute to the development of addiction, a chronic, relapsing disorder characterized by compulsive drug seeking and use.

At the molecular level, drugs of abuse modulate gene expression and intracellular signaling in dopaminergic system neurons. These modifications can affect the synthesis, release, reuptake, and metabolism of dopamine, as well as the expression and function of dopamine receptors and other proteins involved in synaptic transmission. At the cellular level, drugs of abuse can induce changes in synaptic plasticity, that is, in the strength and efficacy of connections between neurons. These changes can strengthen connections between neurons involved in reward and motivation processing, leading to increased sensitivity to drug-related stimuli and a higher probability of relapse. Furthermore, drugs can alter the morphology and function of neurons, as well as communication between different brain regions.

To more clearly illustrate the relationship between dopaminergic pathways, brain structures, and addiction, the following table summarizes the key findings from relevant studies in this area (Table 1)[2,4,5,10,11,15,19].

Discussion

Drug addiction alters brain structure and function, leading to maladaptive and potentially harmful behaviors. These behaviors, caused by excessive drug use, lead to changes in the brain circuits related to pleasure and reward. The reward circuit plays a fundamental role in the development and maintenance of addiction, as it is responsible for regulating pleasant and rewarding sensations, facilitating learning, and memorizing contextual stimuli which can serve as triggers for the repetition of addictive behaviors. The dopaminergic system modulates the reward system associated with addictive behavior; this system is a crucial element in addictive disorders and behaviors, and its implications and importance have been confirmed by numerous animal and human studies. Dopamine, a key brain-reward neurotransmitter, is activated by addictive drugs, and its dopamine receptors play a critical role in the development of addiction and are associated with sensitization induced by chronic drug use.

The phenomenon of addiction must be explained in a complex system of interrelated subsystems, at least including the biomedical, sociocultural, and psychological. In particular, neuroscience stands out in its relevance to the circuits involved in addiction (Fig. 2). Therefore, it is essential to continue investigating the consequences and effects of drugs on reward circuits at the behavioral level, which cause addiction. In the

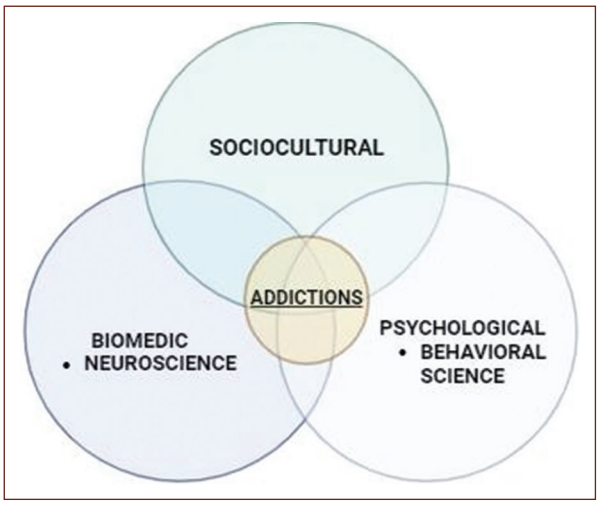

Figure 2. Complex diagram of interrelated subsystems for understanding the phenomenon of addictions.

future, it will be possible to study and analyze potential treatments to avoid these aggravating circumstances.

While this review highlights the common neurobiological pathways involved in drug addiction, there are still gaps in our understanding, particularly regarding the differences between substance addiction and behavioral addiction. Although both share the involvement of the reward system, the specific neurobiological mechanism may differ. For example, the degree of involvement of certain neurotransmitters or the specific patterns of brain activation may differ between these types of addiction. More research is needed to clarify these differences and their implications for treatment.

Emerging therapies offer promising avenues for the treatment of addiction. For instance, deep brain stimulation has shown potential in modulating brain circuits involved in addiction[51], particularly in severe cases refractory to conventional treatments. In addition, research on the modulation of dopamine receptors, such as through targeted pharmacological interventions, may lead to the development of more effective treatments for addiction. Future research should also explore other promising areas, such as gene therapy and treatment of addiction.

Conclusion

The review highlights the significant impact of addictive drugs on the dopaminergic system, the reward circuitry, and decision-making processes, ultimately leading to altered behavior. These findings have important clinical and transnational implications. A deeper understanding of the neurobiological mechanisms underlying addiction can inform the development of more targeted interventions, such as pharmacological therapies aimed at modulating dopaminergic activity or behavioral therapies designed to counteract maladaptive reward learning. In addition, this knowledge can contribute to public health strategies aimed at preventing drug use, particularly among vulnerable populations such as adolescents, who are particularly susceptible to the long-lasting effects of drugs on the developing brain. By translating research findings into clinical practice and public health initiatives, we can strive to mitigate the devastating consequences of addiction for individuals and society.

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Conflicts of interest

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Ethical disclosures

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Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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