The Neurobiology of Addiction: The Role of Dopamine

Cameron Sydney Crews

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The Neurobiology of Addiction: The Role of Dopamine

by

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Abstract

This paper provides a comprehensive summary of the dopaminergic pathways in the basal ganglia as well as the different dopamine receptors and their roles in reward signaling. The progression of addiction via these pathways are discussed, as well as a review of the genetic and environmental aspects of addiction with respect to several different drug classes. In addition, behaviors that are commonly called “addictive” (e.g., gambling, food, social media) are analyzed in connection with reward pathways. Lastly, a few promising treatment options are briefly reviewed.

Keywords

Basal ganglia, dopamine (DA), reward pathways, addiction
**Introduction**

Addiction is a chronic and progressively deteriorating disease that often has tragic consequences, and it is a costly issue here in the United States [8]. In 2015, 5.9% of teenagers and adults in the U.S. had an alcohol use disorder and 2.9% had an illicit drug use disorder at some point within the past year [11]. Although these are not the most imposing percentages, they correlate to 15.7 million alcoholic Americans and 7.7 million Americans with some form of illicit drug addiction [11]. Addiction is notorious for affecting not only the individual but also the lives of their loved ones. This exacerbates the saliency of this problem and brings it to the forefront of millions more lives.

The most characteristic indicator of addiction is compulsive drug use despite damages to the addict’s mind, body, and life [8]. The definition of addiction often references the 5 C’s: Continued Compulsive use despite Consequences with loss of Control and intense Cravings [8]. Addiction is most commonly to a specific substance, but it can also be with respect to a certain behavior. Gambling, digital, and food addictions develop similarly to substance use disorders (SUDs). Behavioral addiction will be discussed, compared and contrasted with SUDs in this paper.

After the development of addiction, the user is thrust into addiction’s characteristic three stage cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation [14, 19]. Addicts enter a hypo-dopaminergic neurological state that makes it difficult to gain pleasure from anything besides their drug of choice and perpetuates drug usage to return to baseline dopamine levels [8]. Addiction development is accompanied by distinct behavioral tendencies and changes to reward signaling that will be discussed further in this paper.
Body of Review

Reward Pathway Anatomy and the Basal Ganglia

The basal ganglia (BG) is largely responsible for the control and selection of behaviors and is very closely intertwined with the brain’s reward pathways [9]. Dopamine (DA) is the main neurotransmitter involved in reward signaling, and it is crucial to BG function and regulation [10]. This section will go on to elucidate how DA connects different sections of the BG to reward signaling.

The portion of the BG primarily responsible for signal input is the striatum, which is composed of GABAergic medium spiny neurons (MSNs) that are flush with various types of DA receptors to be discussed in the next section [9, 10]. The striatum can be divided into the ventral striatum, or the nucleus accumbens (NAc), and the dorsal striatum [9]. Another subsection of the BG is the substantia nigra, which is composed of the pars compacta (SNc) and the pars reticulata (SNr) [24]. The major cell type in the SNc is DA neurons, which project into the BG striatum and regulate the GABAergic neurons that make up the SNr [24]. This linkage is called the nigrostriatal pathway or the nigro-striatal-nigral loop, and it is involved in motor control and action selection [16, 24].

The SNc is one of the two primary origins of DA neurons and the neurotransmitter itself; the other is the ventral tegmental area (VTA) which links dopamine to reward processing via the mesocorticolimbic pathway [2, 16]. In this pathway, the medial forebrain bundle (MFB) sends what are theorized to be GABAergic neurons down into the VTA [8]. DA neurons in the VTA then send ascending signals to the nucleus accumbens (NAc) in the BG striatum, and areas in the prefrontal cortex (PFC) [8]. The signal is carried onward by neurons primarily regulated by GABA into the ventral pallidum (VP), which is another subsection of the BG [8]. This ascending
spiral gives dopamine signaling access to the plethora of reward recognition roles in the NAc, learning reinforcement, and the consequent regulation of motivation for further dopamine hits [16]. Both the nigrostriatal and mesocorticolimbic pathways are diagrammed in Figure 1.

In terms of dopamine transmission along these pathways, there are two complementary release techniques. Extracellular DA is generated at a low basal level all of the time by irregular and low frequency firing; this is referred to as tonic firing [2]. Additionally, burst firing occurs in response to reward situations to temporarily spike extracellular DA levels [2]. The reward signal for burst firing historically came in the form of positive stimuli such as food and sex, and helped animals be motivated to grow and reproduce. This gives dopamine its nickname of the “feel good” chemical.

Addictive drugs provide a much stronger reward signal to the brain than naturally occurring positive stimuli [8]. All drugs with addictive potential (with the exception of some hallucinogens) either directly or indirectly affect DA neuron activation in the VTA and the resulting DA release in the NAc [8, 22]. In fact, the degree to which addictive drugs elevate DA signaling is roughly matched by the intensity of the “high” that the user reports, with nicotine being the exception [8]. Opiates, barbiturates, benzodiazepines, cannabinoids, alcohol, and nicotine all target the VTA through a variety of mechanisms [8, 22]. Stimulants such as amphetamines, cocaine, and nicotine target the NAc and directly increase DA transmission [8, 22]. These attacks on the reward pathways are precisely what gives drugs their addictive potential.
Dopamine Receptors

Dopamine is transmitted along the nigro-striatal-nigral loop and the mesocorticolimbic pathways as described in the previous section, and its uptake into these neurons is mediated by two classes of receptors. All DA receptors are heterotrimeric G-protein coupled receptors (GPCRs) [2, 16]. GPCRs are composed of a transmembrane receptor and an intracellular G-protein. In this case, the G-protein has three subunits. When dopamine binds to the extracellular side of the receptor, the $G_\alpha$ subunit exchanges its bound GDP for a GTP and dissociates from the other intracellular subunits. The now activated $G_\alpha$ translocates along the membrane to adenylyl cyclase and regulates cAMP production, which serves as a second messenger to stimulate the intracellular response to DA release.

The categories of DA receptors differ in the intracellular responses they initiate. There are five different DA receptor subtypes in vertebrates, and they are categorized as D1-like or D2-like receptors because those two have the highest expression in the brain [2]. D1-like receptors (D1 and D5) are coupled to stimulatory G-proteins; they increase intracellular cAMP and overall excitability [2, 16]. D2-like receptors (D2, D3, and D4) are inhibitory GPCRs; they inhibit adenylyl cyclase and keep cAMP levels low [2,16]. D2 receptors have also been shown to activate a receptor tyrosine kinase to initiate a different signaling cascade [2].

Another difference lies in their affinity for dopamine, or the strength with which they can bind DA. D1-like receptors have a significantly lower DA affinity than D2-like receptors, which indicates that the D1-like class needs a higher concentration of DA to produce a comparable level of cellular response [2, 16]. Consequently, D1-like receptors are associated with brief, high concentration, phasic DA response to reward whereas D2-like receptors are responsible for steady uptake of low level tonically produced DA [2, 16].
MSNs in the BG striatum contain the majority of DA receptors and are divided into D1 and D2 MSNs based on which receptor class dominates [16]. About half are D1-MSNs which directly stimulate reinforcement learning, and half are D2-MSNs which indirectly inhibit it [16]. These complementary receptor types balance each other, and can cause great damage when dysregulated. For example, D2 receptor availability is reduced in obese individuals and drug addicts but elevated in the non-addicted members of alcoholic families [2]. High levels of D2 receptors could provide a high level of inhibition on reinforcement learning and addiction development, and would help correct issues with processing low levels of basal DA concentration. Low levels of D2 receptor availability could contribute to the addiction cycle.

**Addiction Progression**

The reasons and manner with which some casual drug users developed addiction while others did not was a mystery for many years. We now know that the development of addiction involves the decline from occasional reward-driven use (the “casual user”), to steady and non-addictive reward-driven use, to habit-driven use, and finally to compulsive use (the addict) [8]. Another framework for addiction is the shift from using for pleasure (positive reinforcement) to using to minimize withdrawal (negative reinforcement) [14]. What makes addiction such a tricky disease to recognize is that these stages can appear differently and progress at variable speeds for different individuals. Some who appear to be “casual users” may truly be motivated by habit or compulsion without anyone knowing.

This transition from reward-driven use to habit-driven use is accompanied by a shift in the brain locus responsible for drug intake motivation. As discussed earlier, the VTA is innervated by DA neurons that project into the NAc, which is located in the ventral striatum of
the basal ganglia [8, 22]. Reward processing in the ventral striatum is responsible for goal-directed behavior based on the estimated or actual value of the reward [22]. In turn, the DA neurons in the SNc project to the dorsal striatum, where behavior is less sensitive to actual reward value and more associated with reinforcement from repeated reward [22]. Continual repeated drug seeking behavior causes the shift from reward-driven to habit-drive behavior, which is mirrored by the shift from the dorsal striatum dominating reward-related behavior signaling to the ventral striatum [2, 8, 22]. This transition is made possible by the neurobiology of the reward pathway and the existence of the ascending spiral of the striato-nigral-striatal loop [8].

Another neurological consequence of the repeated use of addictive substances is the development of conditioning or reward prediction error. In a non-conditioned brain, DA is released right after the reward signal is received. Once repeated use has caused conditioning, DA is released before the reward is officially received; DA signaling begins to depend on the cues that are usually followed by the reward [22]. For example, a drug user typically visits a friend when they are experiencing stress and they use their drug of choice. In this instance, that friend and stress both qualify as “drug-predictive cues” [22]. Drug predictive cues can initiate DA signaling even without the presence of the drug; they can cause cravings and motivation to seek the drug all on their own.

The brain’s response to drug-predictive cues is just one of many signaling changes that occur during addiction. When DA is released early in response to the drug-predictive cues, the reward pathway begins to have reduced sensitivity to the actual reward consumption [22]. This is not only in response to the addictive substance! Other non-drug sources of reward such as food, sex, money, or positive social interactions produce a reduced activation of reward pathways in
addicts than in controls [22]. There is evidence that addicted individuals have decreased sensitivity to negative reinforcers as well [22]. In other words, addicted individuals struggle to gain pleasure from everyday stimuli and lose a healthy fear of the potential negative consequences of pursuing the addictive substance (incarceration, bankruptcy, physical danger, etc.). Addiction also impacts the frontal lobe; it can cause cognitive impairment and poor decision making that can make the disease very difficult to empathize with from the outside [23].

Enhanced cravings, decreased pleasure from natural sources, decreased sensitivity to negative reinforcement, and impaired decision all encourage the addiction cycle. These effects can remain long after the actual drug usage is stopped, which introduces the risk of relapse. The neurological circuits responsible for relapse appear to be separate from the reward pathways; the amygdala is central in drug-predictive cue related relapse and the NAc is responsible for drug and stress triggered relapse [8, 22]. The persistent risk of relapse to drug seeking behavior is precisely what makes addiction such a challenge to treat.

**Biological and Environmental Components of Addiction**

As this disease became more thoroughly researched, the classic nature vs. nurture question arose. With regards to the development of addiction, do biology and environment both play an important role or does one dominate the other? Two twin studies in particular are regarded as the first with large enough sample sizes to truly attempt to answer this question.

The first was conducted by Tsuang et al. on 3372 male twin pairs from the Vietnam Era Twin Registry and investigated the rates of abuse of marijuana, sedatives, stimulants, heroin/opiates, and psychedelics [20]. They identified a “shared or common variability factor” which displays that abuse of one drug greatly increases the risk of abusing another drug category [20]. This common vulnerability factor is affected by a combination of various biological and
environmental factors. Variances in this common vulnerability factor were used to estimate the percentage of addiction that certain factors are responsible for. They concluded that 25% of the variance came from family environmental effects, 44% from nonfamily environmental effects, and the remaining 31% from genetic effects [20]. It appears that a large portion came from environmental factors, but a significant genetic predisposition exists as well.

The second twin study was conducted by Kendler et al. on 1196 white male twin pairs from the Virginia Twin Registry and looked to corroborate the findings of Tsuang et al. [13]. They concluded that genetic and environmental factors were largely nonspecific in the drug they targeted, which agrees with Tsuang’s common vulnerability factor [13, 20]. For example, in twins with a large genetic predisposition to drug abuse, the substance classes that end up being abused are determined entirely by different environmental factors between the twins. In both studies, both genetic and family environmental factors primarily stemmed from the common vulnerability factor [13]. Additionally, there were clear biological and environmental components to addiction.

Although both studies were initially done on white male candidates, the second study was mirrored using female twins from the Virginia Twin Registry and congruent results were found [13]. That being said, more research needs to be done on non-white participants to identify any racial differences. In a similar vein, adoption studies in several countries have also displayed the biological component of addiction. A three times greater risk of alcohol use disorder (AUD) has been found in children of alcoholics even when they were adopted and raised by nonalcoholic families [19].

Overall, the biological component of addiction is widely thought to be polygenic and contributes to 40-60% of addiction risk [8, 11, 15, 19, 23]. In terms of where this biological
component of addiction is coming from, there is evidence that shows that a lack of D2 receptors and/or low basal DA levels could play a role in increased addictive potential [2]. Genome wide association studies (GWAS) have been conducted to find genetic loci associated with various diseases. GWAS have found 11 loci for smoking, eight for alcohol, and two for illicit drugs [11]. There could be many more areas in the genome that show a relationship to addiction, but this field is currently limited by the vast sample size necessary to draw statistically significant conclusions.

Multiple studies agree that risk of becoming a drug user and risk of developing an addiction to that drug are influenced by different factors, but there is not a general consensus as to what those factors are. One theory is that people who consistently pursue trying new things have increased risk of initiating drug use, whereas high impulsivity has been linked to an increased risk of transitioning from a casual drug user to an addicted individual [8]. Another theory states that initiation of drug taking is primarily related to environmental factors, while biological factors dominate addiction progression [3]. There is consensus, however, with regards to traits that confer a high risk of drug addiction in general. Novelty-seeking and impulsivity headline this list that also include antisocial conduct disorder, depression, ADHD, and undergoing stressful or traumatic events [3, 4, 8]. Depression in particular has a very strong correlation with addiction because both diseases deal with malfunctioning DA signaling.

Early life stress and trauma – such as abuse, neglect, a six month separation from either parent, and adverse social environments – are some of the strongest indicators of potential addiction development [3, 4, 22]. These environmental effects can actually cause neurological changes in youth. Children with a history of those types of adversity have been shown to have an abnormal connection between the amygdala and the PFC [22]. This linkage increases impulsivity
and addiction risk. For addicted individuals these stressors can also serve as triggers of relapse later in life. However, not all individuals who go through early life stress develop addictions even when you are looking at those with a biological predisposition to addiction. This indicates that there are some factors that protect healthy individuals from these influences that others may succumb to; these unknown factors are collectively referred to as resilience [4]. Women show greater resilience than men, and the idea of resilience is a promising developing field of research.

**Behavioral Addiction**

The word “addict” is often used lightly and erroneously. It is clear that addiction is a complex disease with neurological, physical, and behavioral symptoms. But can these symptoms be driven by factors other than drugs? A couple behaviors that are widely thought of as having addictive potential include gambling and using a smartphone and/or social media. In fact, up to 5-10% of Americans would qualify as having social media addiction, which involves excessive concern with social media, an uncontrollable urge to check it, and the disruption of other areas of life due to social media [1].

Gambling addiction is well acknowledged despite withdrawal not inducing the physical distress that drug based addiction does such as liver cirrhosis and/or stroke [18]. Therefore, the lack of physical withdrawal symptoms should not be a reason with which other behavioral addictions such as social media addiction are dismissed as trivial. Gambling, positive social stimuli, food, and other rewarding behaviors all trigger the mesocorticolimbic and nigrostriatal reward pathways that are chemically targeted by addictive drugs [2]. Thus, behaviors can induce changes in the reward system that parallel drug based addiction. Another neurological example that mirrors drug addiction is in the availability of D2 receptors. Obese people and drug addicts alike have a reduced D2 receptor expression in the striatum, which indicates decreased activation
of reward circuits [2]. This offers a potential mechanism for continual eating and/or drug use.

B.F. Skinner determined that the variable ratio reward schedule held the most addictive potential of several reward delivery systems [12]. This variable ratio reward schedule involves a reward being administered after a variable (random) number of responses; this causes individuals to participate in the behavior very frequently just to check if the reward will come [12]. Slot machines utilize this variable reward schedule to ensure gamblers keep coming back. When a reward – in this case a jackpot – is given, the reward pathways in the brain are activated in the same way that they are by addictive drugs. In this case, the association is built between reward and behavior rather than reward and substance. Every time the reward is administered due to a certain behavior, that association becomes even stronger via long-term potentiation [12].

Variable ratio reward schedules are present in our smartphones as well. For example, Instagram withholds like notifications in order to deliver them in one larger blast later on [12]. While you check your phone for notifications, the dopamine centers in your brain are being primed by the negative outcome to be hypersensitive to when a reward does come through [12]. This is called reward prediction error and it can cause individuals to enter a depressive state when the reward is not administered. Overall, behavioral addiction acts on the brain according to similar mechanisms as drug addiction does.

**Treatment Options**

There are currently four common pharmacological addiction treatments, and each act in some way through opioid receptors. Opioid receptors MOP-r and KOP-r regulate the DAergic reward system and thus can be used as treatments for more than just opioid addiction [15]. These medications fall into three categories: full agonists, partial agonists, and antagonists [23]. Agonists bind to and activate receptors just as the typical substance does, whereas antagonists
bind but do not activate the receptor and block the binding of other agonists or substances.

In the 1960s and 70s, methadone was developed as the first drug for heroin and opioid addiction management and it is still widely used and effective today [15]. Methadone is a full MOP-r agonist with some KOP-r affinity as well, which allows it to reduce powerful opioid withdrawal symptoms such as muscle ache and bone pain [23]. Additionally, in human cocaine addicts it has been shown to reduce the amount of cocaine use and help prevent cocaine-induced neuroadaptations in the reward pathways [15]. However, its full stimulation of MOP-r can cause respiratory depression and euphoria similar to actual opioid usage. Thus, buprenorphine (partial MOP-r agonist) was developed as a safer alternative that is still effective in reducing withdrawal symptoms and cocaine use in human cocaine addicts [15, 23].

Two similar antagonists are also commonly used: naltrexone and naloxone. Because they are both antagonists, they do not activate the opioid receptors as methadone and buprenorphine do. Thus, they do not cause respiratory depression and euphoria. Naltrexone is most potent against MOP-r with some KOP-r affinity, and for heroin addicts a long acting injection can continuously decrease heroin usage by reducing cravings [15, 23]. In alcoholic patients, reduced cocaine usage has also been observed, and nonalcoholic patients have reduced amphetamine usage during naltrexone treatment [15]. It is clear that naltrexone offers some resistance to many types of drug addiction.

Naloxone acts similarly as it also acts strongest on the MOP-r receptor [23]. Naloxone is commonly used to treat respiratory depression during an opioid overdose and can even be administered nasally by non-medical professionals [23]. Many efforts have been made in recent years to educate the public on how and when to administer these pharmaceuticals to treat and prevent opioid overdoses.
Beyond pharmaceuticals, there are a few other addiction therapies such as repeated transcranial magnetic stimulation (rTMS) and deep brain stimulation (DBS). rTMS is noninvasive and attempts to alter neuronal activity by stimulating specific target regions in the brain [5]. This treatment has been shown to reduce drug cravings and relapse rates in cocaine addicted individuals, but clinical trials are still ongoing to test the full effects of rTMS on those addicted to cocaine, alcohol, methamphetamines, and tobacco [5]. DBS was initially developed to treat Parkinson’s disease, and it involves surgically implanting electrodes into target brain regions [5]. Both rTMS and DBS have been shown to effectively treat other psychiatric conditions such as depression but they both need more trials to be considered an effective addiction treatment.

As the role of DA and reward signaling is investigated, new potential treatment sites are developed. Cocaine produces its effect by inhibiting reuptake of DA into the NAc so its treatment could involve the inhibition of DA transporters; additionally, most addictive drugs inhibit GABAergic MSNs in the NAc so treatment could take the form of GABAergic agonists [8]. Cannabinoids activate and regulate brain reward and relapse, so cannabinoid CB1 receptor agonists could be another interesting treatment target [8]. CRF is the neurotransmitter involved in a significant stress triggered relapse circuit; anti-CRF medication could be effective relapse prevention treatment [8]. In rodents, activation of the D2-MSNs reduces cocaine usage via D2 receptors’ inhibition of reinforcement learning and addiction progression [2, 16, 22]. Thus, D2 receptors are a promising target for future treatment.

Lastly, certain coping styles have been shown to offer significant resilience to other psychiatric disorders and that should not be overlooked when it comes to addiction [4]. While most potential treatment targets and methods mentioned in this paragraph need more extensive
research on humans and specifically related to addiction, they offer creative, promising solutions to this growing disease.

Treatment of behavioral addiction poses a contrasting challenge that is being met with very different methods. Disabling notifications and limiting usage time are two helpful ways to prevent and treat social media addiction, as well as keeping your phone screen in grayscale [12]. Overall, conscientious usage of devices will help develop a mindset and habits that confer resistance to media addiction. Therapy and support groups are common, appropriate and helpful approaches for certain behavioral addictions such as gambling. These efforts could be expanded to include the quickly rising rates of digital addiction.
Conclusion

Over the past few decades, the stigma surrounding addiction has slowly abated. With this shift has come successful treatment options and a push for addiction related research. The mesocorticolimbic and nigrostriatal reward pathways have been analyzed in conjunction with DA signaling and how drugs of abuse target and manipulate them. The types of dopamine receptors and their natural role in the regulation of DA signaling (D1-like promotion and D2-like inhibition) offers a promising avenue for addiction treatment [2, 16].

One of the greatest strides in addiction research has come from characterizing the transition from recreational use to compulsive use. Although the complete answer is still an enigma, small pieces have come together to give some semblance of an explanation. The brain region responsible for reward recognition and processing is different in casual users and addicts. As reward driven use morphs into habit driven use, the ventral striatum of the basal ganglia begins to take over reward signaling from the dorsal striatum [2, 8, 22].

Additionally, biological and environmental components both play a significant role in the development of addiction in certain individuals and not others. Two large twin studies determined that the biological component of addiction presents itself as a general risk factor for addiction of any substance rather than for one in particular; they called this the common vulnerability factor [13, 20]. Several studies have labeled genetic components as responsible for roughly 40-60% of addiction risk, with environmental factors providing the remaining risk [8, 11, 15, 19, 23]. GWAS have made some progress in determining the specific genetic loci that are responsible for the biological component of addiction, but these studies are limited by the vast sample size necessary for conclusive results. Abuse and early childhood stress are the biggest environmental indicators for addiction risk [3, 4, 8, 22].
Behavioral addiction develops very similarly to substance addiction, but it requires different treatment tactics. Pharmacological approaches such as methadone, buprenorphine, naloxone, and naltrexone have had success with the treatment of overdoses and the long term management of SUDs [15, 23]. rTMS and DBS have had success with the treatment of psychological disorders (e.g., depression, anxiety) and attempts have been made to use them for addiction treatment [5]. Behavioral addictions and SUDs are both often managed with therapy and support groups.

Although there is a plethora of information circulating on addiction and the risks of substance use, addiction still affects millions of Americans. Moving forward, the development of treatments for addiction that target the processing sites of specific drugs will help rescue more people from the grasp of this disease. The rise of personalized health care and more extensive GWAS will propel change towards a society where individuals can be notified if they have a high biological risk for addiction. While we are currently forced to focus on addiction treatments, the development of prevention methods is the future of managing the addiction epidemic.
References


Figures

Nigrostriatal Pathway

- SNC DA Neurons
- Dorsal Striatum
- SNr GABA Neurons

Involves DA in motor control and action selection

Mesocorticolimbic Pathway

- Medial Forebrain Bundle (MFB)
- Ventral Tegmental Area DA Neurons
- Nucleus Accumbens (Ventral Striatum)
- Prefrontal Cortex
- Ventral Pallidum

Involves DA in reward processing, learning reinforcement, and motivation

Figure 1: Diagram and description of the nigrostriatal and mesocorticolimbic reward pathways.