



From Sugar to Fentanyl: Common Pathways, Different Levels of Addiction

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1. Introduction

In modern society, people are exposed to many substances and activities that can affect the brain's reward system. These include not only illegal drugs but also common substances such as sugar and caffeine, as well as tobacco, alcohol, marijuana, and prescription opioids. Certain activities, such as gambling and using social media, can also activate the brain's reward system. Although these substances and activities are very different from one another, many of them affect similar pathways in the brain that are involved in reward, motivation, and repeated behavior (Volkow and Baler).

The increasing availability of such rewarding stimuli has made addiction one of the major public health challenges of the twenty-first century. As reported by the World Health Organization, alcohol consumption causes approximately 2.6 million deaths around the world each year, and psychoactive drug use contributes to approximately 600,000 deaths annually worldwide, with about 400 million people suffering from alcohol use disorders around the world (World Health Organization). In the United States, the economic cost of such problems is just as high. The cost of excessive alcohol consumption in America is about \$249 billion a year. Smoking of cigarettes is estimated to be responsible for more than \$240 billion of health care costs annually, whereas obesity and other chronic diseases linked to excessive consumption of foods, which provide extremely high reward value, account for hundreds of billions of additional dollars in annual medical expenditures (Centers for Disease Control and Prevention). Furthermore, the economic burden of the opioid crisis—including opioid use disorder, overdose, and lost productivity—has been estimated to exceed \$1 trillion annually in the United States (Centers for Disease Control and Prevention). These figures show that addiction is both a medical issue and a major economic and public burden.

Though these substances have distinct pharmacology and levels of social acceptance, they share very similar behaviors such as craving, compulsion to take, tolerance, withdrawal, and relapse. This raises a basic biological question: Why do chemically unrelated compounds produce similar behavioral phenotypes? This question is especially relevant because the brain circuits involved in substance addiction appear to overlap with those involved in emerging behavioral addictions such as use of social media, short video clips, and online gaming.

Although our study in this review primarily focuses on substance addictions, these behavioral addictions also suggest that similar reward-related mechanisms may cause seemingly different forms of obsessive behavior. Since the adolescent brain continues to develop throughout the teenage years, understanding these shared mechanisms is especially relevant.

There is extensive literature concerning the addictive nature of individual addictive substances like nicotine, alcohol, cannabis, opiates, and cocaine. There are also many studies that have explored the neurobiological impact of legal substances like sugar and caffeine. However, relatively few studies have compared these categories of substances within a single conceptual framework to explain why some primarily produce physiological dependence while others are more likely to result in Substance Use Disorder (SUD).

In the present review, we classify addictive substances into three different groups based on their addictive potential and neurobiology rather than on their legality. The first group includes sugar

and caffeine; they lead mainly to the development of addiction-like behavior, but they are not able to cause a SUD based on the criteria set by DSM-5. The second group involves tobacco, alcohol, and marijuana, which can induce both dependence and SUDs. Finally, the third group is focused on fentanyl and cocaine, two substances associated with particularly high addiction liability because of their strong neurobiological effects and high risk of compulsive use. We also review behavioral addictions related to digital media and compare them with substance addiction.

This literature review includes peer-reviewed studies, including clinical research, epidemiological studies, and neurobiology studies published in medical and neuroscience journals. Studies were selected based on their pertinence to four important factors of addiction: (1) the pharmacology of addictive drugs, (2) neurobiological changes due to repeated drug exposure, (3) the processes involved in reward-based learning, and (4) factors from the environment and development that make one susceptible to addiction. By comparing evidence across these four domains, this review examines why chemically different substances produce different degrees of dependence and addiction despite engaging overlapping neural reward circuits.

This review shows that the addiction process cannot be explained solely by the rewarding properties of a substance. Instead, addiction emerges from the interaction of pharmacological actions, neurobiological plasticity, behavioral reinforcement, and environmental vulnerability. Understanding these common mechanisms may improve our understanding of substance use disorders and provide insight into emerging behavioral addictions among adolescents.

2. Biological Framework of Addiction

First, we investigate the biological mechanisms that addictive substances share. Although addictive substances differ in their chemical structures and pharmacological effects, they affect many of the same neural circuits involved in reward, motivation, learning, memory, and decision making (Volkow and Baler). Addiction therefore comprises changes across multiple connected brain systems rather than a single neurotransmitter or brain region. The mesolimbic dopamine system plays an important role in addiction (Volkow et al.). Dopamine is a neurotransmitter that helps the brain recognize rewards and motivates a person to repeat rewarding behaviors (Volkow et al., "Addiction: Beyond Dopamine Reward Circuitry"). Addictive substances can increase dopamine activity between the ventral tegmental area (VTA) and the nucleus accumbens (NAc), two important parts of the brain's reward system (Thomas et al.). This is able to reinforce drug-related behaviors and encourage repeated use. However, dopamine alone cannot fully explain addiction. Repeated drug use also affects brain systems involved in stress, memory, emotions, and behavioral control (Volkow et al., "Addiction: Beyond Dopamine Reward Circuitry"). Other neurotransmitters, including glutamate, GABA, endogenous opioids, and stress-related signaling molecules such as CRF, add to these processes (Kalivas and Volkow; Koob and Volkow). This suggests that addiction results from complex interactions among multiple neurotransmission systems rather than from dopamine alone.

The incentive-sensitization theory distinguishes between "liking" and "wanting." While the pleasurable effects of a drug may decrease with repeated use, the desire for the drug can be stronger when a person is exposed to drug-related cues. As a result, an individual may continue to want a drug even when it becomes less pleasurable (Berridge and Robinson). Koob and Volkow similarly describe addiction as a cycle of binge/intoxication, withdrawal/negative affect,

and preoccupation/anticipation. Changes in reward, stress, and executive-control systems across these stages contribute to continued drug use and relapses. Together, addiction includes not only the pharmacological effects of a drug but also changes in brain function and behavior. Environmental and developmental factors can additionally influence an individual's vulnerability to addiction (Nunes and Volkow). Based on this understanding, the present review compares addictive substances using four main factors: drug pharmacology, changes in brain function after repeated use, behavioral reinforcement and learning, and environmental and developmental influences.

Addictive substances can enter the body through various routes, including oral, intravenous, transdermal, and inhalational administration. Oral drugs are absorbed through the gastrointestinal tract and usually pass through the liver before entering systemic circulation (National Institute of Diabetes and Digestive and Kidney Diseases; Open RN). Liver metabolism can reduce the amount of active drug reaching the bloodstream, a process known as the first-pass effect (Kirby et al.; Open RN). Oral administration can also produce slower effects because the drug must first be absorbed through the gastrointestinal tract. In contrast, intravenous (IV), transdermal, and inhaled drugs can enter systemic circulation without first passing through the liver (Open RN). IV administration delivers a drug directly into the bloodstream, producing rapid effects and complete bioavailability. However, it carries risks such as infection, and the administered dose cannot be easily removed once injected. Transdermal administration delivers drugs through the skin and can provide a steady release over time (Open RN). However, only certain drugs can effectively cross the skin barrier. Inhalational administration allows substances to enter the bloodstream through the lungs and can produce rapid effects. However, the amount absorbed can vary depending on how the substance is inhaled, and some inhaled substances can irritate or damage the respiratory system. After entering the bloodstream, addictive substances that act on the central nervous system must reach the brain. To do so, they must cross the blood-brain barrier (BBB), which limits the entry of many substances into the brain (Figure 1). Most addictive substances discussed in this review, including caffeine, nicotine, alcohol, THC, fentanyl, and cocaine, can cross the BBB, although their rates and mechanisms of entry differ. These differences, together with the route of administration, can influence how rapidly a substance affects the brain.

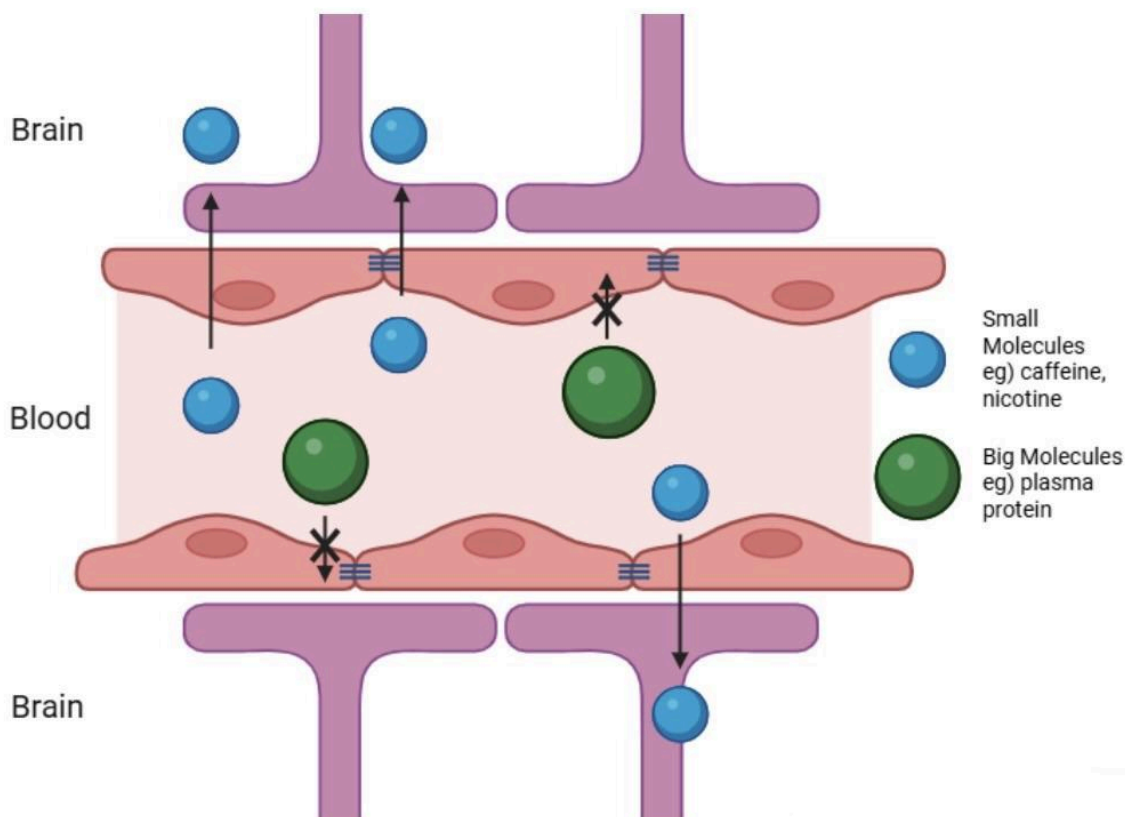


Figure 1. Routes of drug administration and passage through the blood-brain barrier (BBB) While small molecules such as caffeine and nicotine molecules can go through the blood-brain barrier, big molecules such as plasma protein cannot.

3. Sugar and Caffeine: Rewarding Substances That Primarily Produce Dependence

Sugar and caffeine are widely consumed and socially accepted substances. Although they are not generally considered addictive in the same way as nicotine, cocaine, or opioids, repeated consumption can affect brain reward systems and produce dependence-related behaviors (Avena et al.; Juliano and Griffiths). However, it is important to distinguish dependence from substance use disorder (SUD). Dependence occurs when the body adapts to repeated exposure to a substance, resulting in tolerance or withdrawal when use is reduced or stopped. In contrast, SUD involves continued and often compulsive substance use regardless of harmful consequences. Physical dependence can occur without addiction, making this distinction particularly important when comparing substances with different addictive potential.

3.1 Sugar

Sugar influences the reward system through different mechanisms. Sugar does not directly bind to specific receptors associated with addictive drugs. Instead, sugar activates taste and metabolic pathways that can increase dopamine activity in the brain's reward system, particularly in the NAc (Avena et al.; Qin et al.). Under normal conditions, this system helps reinforce food-seeking behavior. However, animal studies suggest that excessive and

intermittent sugar consumption can produce prolonged dopamine release and changes in the endogenous opioid system (Avena et al.; Colantuoni et al.). Rats exposed to intermittent sugar intake have shown binge-like eating, withdrawal-related anxiety, and behaviors resembling tolerance and craving (Colantuoni et al.; Avena et al., Figure 2). Nevertheless, evidence for sugar addiction in humans remains limited, and human eating behavior is influenced by many factors beyond the pharmacological effects of sugar (Westwater et al.).

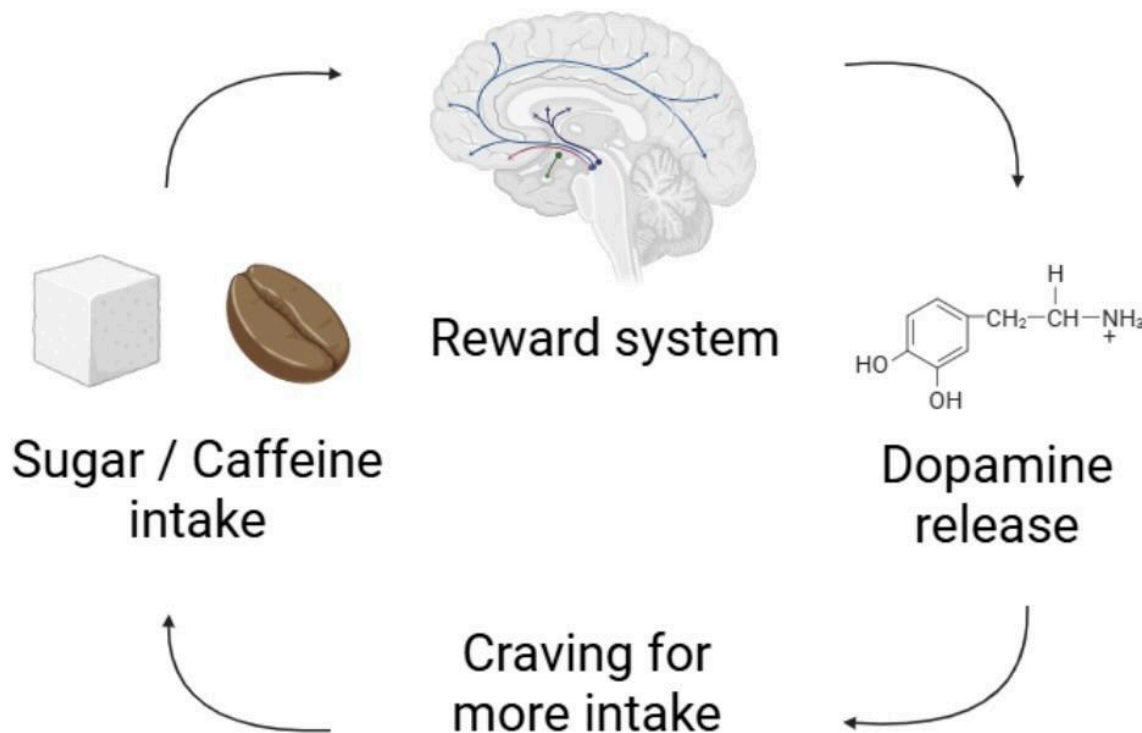


Figure 2. Sugar-induced reward pathway and behavioral outcomes.

When sugar is absorbed into the body, it activates pathways that signal the reward system to release dopamine. The prolonged exposure to dopamine leads to behaviors such as binge eating and craving. When Caffeine gets absorbed and reaches the brain, it blocks adenosine receptors. Since adenosine signaling interacts with the dopamine system and reward system, it ultimately influences a person to consume more caffeine.

3.2 Caffeine

Caffeine works through a different mechanism. It reaches the brain easily, where it mainly blocks adenosine A1 and A2A receptors (Fredholm et al.). Adenosine is a chemical in the brain that builds up during the day and slows down brain activity, making a person feel tired and sleepy (Fredholm et al.; Temple et al.). By blocking adenosine receptors, caffeine reduces these effects and increases alertness. Because adenosine signaling also interacts with the dopamine system, repeated caffeine consumption can indirectly affect the brain reward system (Figure 3).

Unlike substances such as cocaine, however, caffeine does not produce its main effects by directly causing a large increase in dopamine signaling.

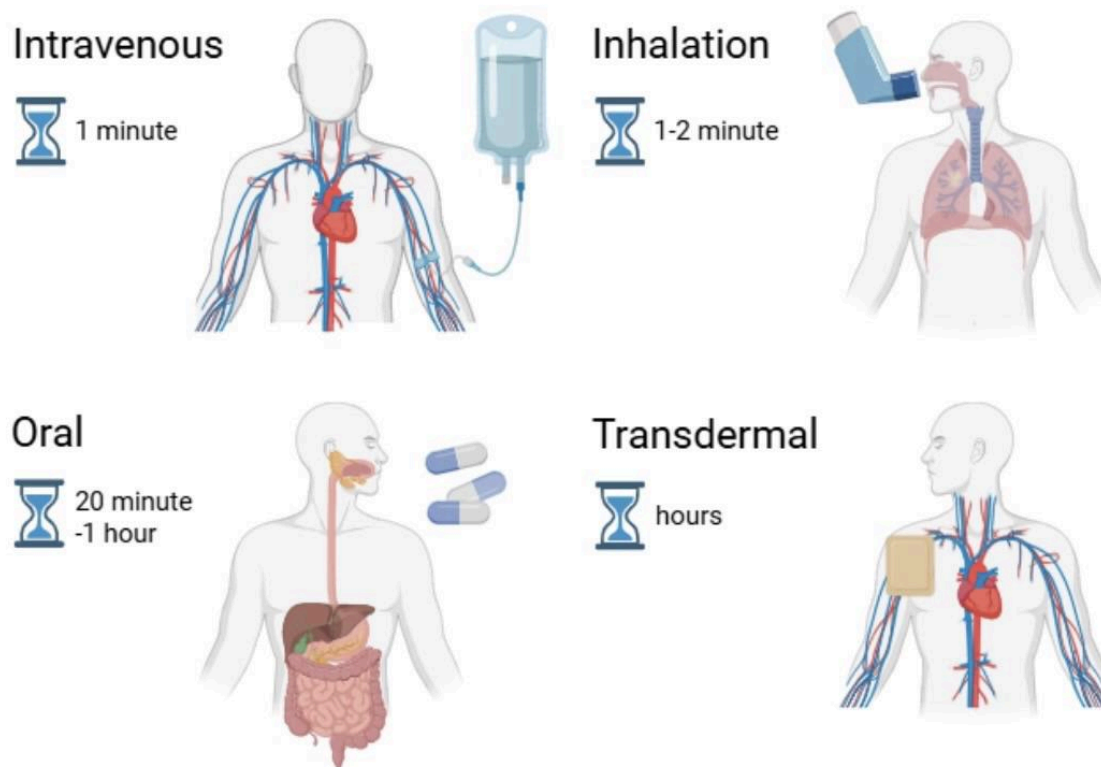


Figure 3. Mechanism of caffeine action on adenosine receptors.

When a drug is administered into the body, various routes exist. Intravenous and inhalation administration, a method that puts the substance right into the bloodstream, takes a few minutes. Oral administration takes more time, around 20 minutes to an hour, since it goes through the liver. Transdermal administration, a method that is designed to provide steady release of drugs, takes hours to be fully absorbed into the body.

Repeated exposure to both sugar and caffeine can produce neurobiological adaptations, but these changes are usually less severe than those produced by highly addictive drugs. Intermittent sugar consumption in animal studies has been associated with changes in dopamine and endogenous opioid signaling, which may contribute to increased motivation to consume sugar (Avena et al.). However, current evidence is insufficient to conclude that sugar produces addiction in humans comparable to nicotine, cocaine, or opioids (Westwater et al.).

The effects of repeated caffeine use are better established in humans. Chronic caffeine consumption causes adaptations in adenosine signaling, reducing its stimulating effects over time and additionally contributing to tolerance. When caffeine intake is suddenly stopped, these adaptations can produce withdrawal symptoms such as headache, fatigue, difficulty concentrating, and irritability (Juliano and Griffiths). These effects demonstrate physical

dependence, but they rarely lead to the severe compulsive drug-seeking behavior and loss of behavioral control associated with SUD.

Behavioral reinforcement also helps explain why people continue consuming sugar and caffeine. According to the incentive-sensitization theory, repeated exposure to rewarding stimuli can strengthen the motivation to seek them even when their pleasurable effects do not increase (Berridge and Robinson). Environmental cues and habits may therefore encourage repeated consumption of sweet foods and caffeinated beverages. However, most people can reduce or stop their intake, and withdrawal symptoms are generally milder than those associated with highly addictive drugs (Juliano and Griffiths; Westwater et al.).

Overall, sugar and caffeine demonstrate that activation of reward-related pathways and the development of dependence are not sufficient by themselves to produce addiction. Both substances can affect reward systems and cause neurobiological adaptations, tolerance, withdrawal, and repeated consumption. However, these changes are generally less likely to develop into the compulsive use and impaired behavioral control characteristic of SUD. Thus, sugar and caffeine provide useful examples of how substances can share some biological and behavioral features of addictive drugs while having much lower addictive potential.

4. Nicotine, Marijuana, and Alcohol: Drugs that Can Result in both Addiction and Substance Use Disorder

Whereas sugar and caffeine have a unique place on the spectrum of addiction, nicotine, marijuana, and alcohol belong to a more clearly defined category of regulated psychoactive substances. Although they affect the brain and body in different ways, all three can lead to physical dependence and SUDs. Studying these substances helps us understand how repeated drug use can cause physiological changes in the brain and reinforce behaviors that encourage continued use. However, using these substances does not necessarily lead to addiction, as the risk varies from person to person.

4.1 Nicotine

Nicotine has a high addictive potential because it rapidly enters the brain and directly activates the brain's reward system. After entering the bloodstream, nicotine binds to nicotinic acetylcholine receptors and stimulates the mesolimbic dopamine pathway, increasing dopamine levels in the nucleus accumbens (Benowitz; Henningfield and Fant). Consequently, this rewarding effect reinforces repeated nicotine use. The pharmacokinetics of nicotine additionally contribute to its addictive potential. When nicotine is absorbed through cigarettes or other tobacco products, it can reach the brain within seconds (Benowitz). This rapid effect creates a strong association between nicotine use and its rewarding effects.

Repeated nicotine exposure also causes neurobiological adaptations. Changes in nicotinic acetylcholine receptors contribute to tolerance, while reducing or stopping nicotine use can lead to withdrawal symptoms and cravings (Benowitz). In addition, nicotine use can become associated with certain environments, emotions, or routines. These cues may eventually trigger cravings even before nicotine enters the body. Nicotine therefore demonstrates how pharmacological effects, neurobiological adaptation, and behavioral reinforcement can work

together to promote addiction. These joint effects help explain why nicotine generally has a greater addictive potential than substances such as caffeine.

4.2 Marijuana

The pharmacological actions of marijuana differ from those of nicotine. Its main psychoactive ingredient, Δ^9 -tetrahydrocannabinol (THC), attaches to cannabinoid CB1 receptors, which are involved in reward, memory, emotion, and decision making (Volkow et al., “Adverse Health Effects of Marijuana Use”; Zehra et al.). It is noteworthy that, unlike nicotine, THC does not directly activate the dopamine system. Instead, activation of cannabinoid receptors indirectly influences dopamine signaling and other reward-related brain regions. Repeated marijuana use can also produce changes in the endocannabinoid system, leading to tolerance and withdrawal symptoms when use is stopped (Budney et al.).

The risk of developing Cannabis Use Disorder (CUD) is evidence that addiction and dependence must not be regarded as synonymous terms. While dependence may involve tolerance and withdrawal, SUD is more strongly associated with continued or compulsive use regardless of negative consequences (Hasin et al.; Budney et al.). The risk of developing CUD depends not only on the drug itself but also on patterns of use, environmental elements, and individual development. This is particularly important during adolescence, when brain systems involved in decision-making are still developing while reward systems remain highly responsive (Volkow et al.; Zehra et al.). Marijuana therefore demonstrates that a substance does not need rapid or intense pharmacological reinforcement to contribute to the development of a SUD.

4.3 Alcohol

Unlike nicotine and marijuana, alcohol affects multiple neurochemical systems. It influences the inhibitory GABA system, the excitatory glutamate system, and reward-related systems utilizing dopamine and endogenous opioids (Deitrich et al.; Koob and Volkow). Because alcohol acts through several neural pathways, continued exposure can produce significant neuroadaptations. With prolonged alcohol use, the brain adapts to preserve a balance between inhibitory and excitatory activity. When alcohol use is suddenly reduced or stopped, these responses are able to disrupt this state, producing withdrawal symptoms and negative emotional conditions (Stephens and Wand). These changes can support continued drinking. While alcohol may initially be consumed for pleasure, chronic use can shift motivation toward avoiding stress, anxiety, or other negative feelings.

In addition, environmental factors influence the risk of Alcohol Use Disorder (AUD). Alcohol is widely available and socially accepted, while stress, family environment, social interactions, and drinking patterns established during adolescence can further change the risk of problematic use (Dani and Harris; Stephens and Wand).

Alcohol therefore illustrates the complex dynamics of addiction. Its pharmacological effects alone do not determine whether a person develops AUD. Rather, addiction results from the interaction of neuroadaptation, reinforcement, environmental effects, and individual vulnerability.

Nicotine, marijuana, and alcohol are psychoactive substances that can lead to Substance Use Disorders (SUDs), although not everyone who uses them becomes addicted. Nicotine is recognized by rapid reinforcement of the reward system, marijuana affects reward more

indirectly through cannabinoid receptors, and alcohol acts on multiple neurochemical systems and can produce strong physical dependence. Although these mechanisms differ, repeated exposure, behavioral reinforcement, environmental elements, and individual vulnerability shape SUD risk.

5. Fentanyl and Cocaine: Drugs with a Strong Addictive Capacity

Fentanyl and cocaine represent the third category of substances reviewed here and have a much greater potential for addiction and severe SUD than the substances discussed above. Despite this shared high addictive potential, they act through very different pharmacological mechanisms: fentanyl primarily activates opioid receptors, whereas cocaine primarily blocks dopamine reuptake. These two drugs therefore demonstrate how very different pharmacological mechanisms can lead to similarly powerful addiction and severe SUD.

5.1 Fentanyl

Fentanyl is a highly potent synthetic opioid that acts primarily on μ -opioid receptors involved in pain, reward, and emotional effects (Han et al.; Blackwood and Cadet). Its high potency and rapid effects result in its strong potential for dependence and addiction. Repeated fentanyl use causes neuroadaptation, leading to tolerance and the need for higher doses to achieve similar effects. When use is reduced or stopped, these responses can produce severe withdrawal symptoms (Blackwood and Cadet). As dependence develops, motivation may shift from seeking the drug's rewarding effects to avoiding withdrawal, representing a transition from positive to negative reinforcement. The rapid delivery of fentanyl to the brain can further strengthen reinforcement by creating a strong association between drug use and its effects. Together, its high potency, rapid action, neuroadaptation, and severe withdrawal contribute to fentanyl's high addictive potential, although the development of Opioid Use Disorder (OUD) is also influenced by individual and environmental elements.

5.2 Cocaine

Unlike fentanyl, cocaine does not act on opioid receptors. Rather, cocaine acts as an inhibitor of the dopamine transporter, consequently reducing dopamine reuptake and increasing dopamine availability in the synaptic space, which leads to potent activation of neural circuits responsible for the process of reward (Hemby; Nestler). The rapid onset of dopamine signaling explains the drug's strong reinforcing effect, as in the case of nicotine. The rapid effect is important because when drug use and reward occur close together, the brain can form a stronger connection between them.

Chronic exposure to cocaine is known to induce neuroplastic changes in the mesolimbic dopamine pathway and other areas of the brain responsible for behavioral control (Thomas et al.; Nestler). In particular, the prefrontal cortex plays an important role as it participates in executive control over behavior. The environment can also have an impact on cocaine dependence. The repeated association with drug-related environments is capable of reinforcing the responses and lead to craving upon another exposure to those environments. Genetics and epigenetics can also have a role in one's vulnerability to cocaine dependence (Pierce et al.).

6. Behavioral Addictions: Online Gaming, Social Media, and Short Form Videos

Behavioral addictions provide an important comparison because they do not involve an external pharmacological substance. Online gaming, social media, and short-form videos can nevertheless engage brain reward circuits and reinforce repeated behaviors (Berridge and Robinson; Volkow et al., “Addiction: Beyond Dopamine Reward Circuitry”).

Digital platforms provide frequent and instant rewards through likes, notifications, new content, achievements, and unpredictable rewards. With repeated use, the motivation to engage may shift from pleasure (“liking”) toward cue-driven desire (“wanting”), consistent with incentive-sensitization theory (Berridge and Robinson). As a result, cues such as notifications, opening an app, or boredom can trigger the desire to engage again.

However, behavioral addictions should not be equated with SUDs. Unlike drugs, which directly alter neurochemical systems through external substances, behavioral addictions develop through repeated experiences, learning, and conditioning. They therefore demonstrate that compulsive behavior can develop through reinforcement and environmental signals even without direct pharmacological action.

Thus, substance and behavioral addictions differ in how they affect the brain, but share important processes of reward, reinforcement, learning, and cue-driven behavior. This comparison suggests that addiction is not defined simply by the presence of a drug, but by repeated reinforcement and learning that can eventually contribute to obsessive behavior.

7. Comparative Analysis: Common Mechanisms and Key Differences

Our study of each category shows a core neurobiological link between chemical substances and rewarding behaviors. First, the key factor is activation of the brain's mesolimbic dopamine pathway, which regulates reward-related learning, reinforcement, and incentive salience. In other words, despite their different mechanisms, these substances and behaviors can influence reward-related pathways involving dopamine signaling.

However, the main differences lie in the extent, the process itself, and the neuroplastic changes produced by activation. Strong pharmacological substances like fentanyl and cocaine overwhelm the physiological homeostatic mechanisms of the body, resulting in extensive receptor down-regulation, neuronal synaptic restructuring, and impairment of executive control functions in the prefrontal cortex that is characteristic of SUD. Nicotine, marijuana, and alcohol can also lead to SUD, but through different combinations of pharmacological effects, neuroadaptation, dependence, learning, and environmental components. Sugar and caffeine generally produce much weaker effects, while behavioral addictions involve no external drug and instead develop mainly through repeated reinforcement, learning, and conditioning.

8. Conclusions

This review shows that addiction cannot be explained simply by the rewarding effects of a substance or behavior. Rather, it develops through a complex interaction among pharmacological effects, neuroadaptation, reinforcement and learning, environmental effects, and individual vulnerability. Comparing substances over a spectrum—from sugar and caffeine to nicotine, marijuana, alcohol, fentanyl, and cocaine—along with behavioral addictions, shows that similar reward-related processes can produce very different levels of dependence and addiction.

This comparative perspective also has important practical consequences. Lower-risk substances and rewarding behaviors may be better addressed through education, healthy habits, and prevention, whereas substances with a high potential for severe SUD require stronger prevention, clinical treatment, and harm-reduction strategies. Adolescence is also an important period for prevention because brain systems involved in reward and decision making are still developing. Understanding the roles of stress, environment, learning, and individual vulnerability may further help develop more comprehensive and personalized addiction treatment. In conclusion, addiction should be viewed as a spectrum rather than as a simple response to reward. The transition from repeated use to dependence and SUD depends not only on the substance or behavior itself, but also on how strongly and repeatedly it affects the brain and how those effects interact with the individual and the environment. Knowing these differences and shared mechanisms provides a more complete framework for preventing and treating addiction.

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