Cocaine Addiction and Prevention of Excess Dopamine: A Review

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The increasing availability of illegal drugs poses a greater risk of individuals being exposed to drug abuse and addiction. Cocaine, in particular, is becoming more prevalent, making individuals more susceptible to addiction. The primary cause of cocaine addiction is the euphoric experience that occurs after the intake. This experience is the result of excess dopamine in the synaptic cleft. When cocaine is ingested, it bonds to the receptors of the transmitting neurons, leaving excess dopamine unable to bond with the receptors. Addiction to not only cocaine but also other abusive drugs pose many risks to the human body and can potentially be fatal. While various addiction treatments such as neurosurgery, Transcranial Magnetic Stimulation (TMS), and ultrasound have been studied and theorized to control addictive behaviors, current treatments can only regulate the excessive dopamine in the synaptic cleft. In other words, they fail to prevent the production of dopamine and the euphoric experience beforehand. This paper reviews these current addiction treatments and suggests a potential treatment using carbidopa to prevent the production of dopamine.

Introduction

Substance abuse is the uncontrolled overindulgence in, or dependence on, a substance regardless of negative consequences. Initially, substance use may provide a euphoric high, but repeated abuse can lead to dependence, characterized by intense cravings and obsessive behaviors for the substance. With continued intake, an individual develops tolerance to the drug, requiring more significant amounts to maintain the desired effect. Likewise, repetitive use of addictive drugs affects the brain's reward center, altering brain activity and impacting the way the brain experiences pleasure by influencing neurotransmitters and hormones. This dependence on drugs can lead to addiction and increase the risk of respiratory and cardiovascular disease, cancer, and mental health conditions.

The prevalence of cocaine addiction has increased worldwide over the years due to easier access to it. In 2021, 22 million cocaine users were reported, and an estimated 0.5% of the global population used cocaine in 2023[1]. The increasing rate of cocaine use and addiction leads to global health concerns. In response, many medical professionals are studying treatments for cocaine addiction.

Previous studies have focused on treatment methods to tackle the dopaminergic pathway that provides cocaine users with their euphoric experience. Dopamine (DA) is a monoaminergic neurotransmitter regulating emotions. DA also functions as a neurohormone and plays a role in the brain's "reward center" as well as in various bodily functions such as controlling motor functions, motivation, and reward-related learning[2]. Dopamine is produced when the enzyme tyrosine 3-monooxygenase converts tyrosine into levodopa, and the enzyme aromatic-L-amino-acid (AADC) metabolizes levodopa into DA, which is then released into the synaptic cleft[3]. When DA is released, it binds to DA receptors and is then removed from the synaptic cleft to be transported back into the transmitting neuron through the DA transporter. While DA is in the synaptic cleft, receptors can sense it. It may be regulated via various mechanisms such as action potential propagation, DA production, vesicular loading (control of the number and efficiency of vesicular release sites), and regulation of DA transporters[4].

It is crucial to understand how cocaine alters dopaminergic pathways due to dopamine's key role in addiction. The following sections will explain specific mechanisms by which cocaine impacts dopamine transmission and evaluate the existing clinical treatments designed to alleviate their effects. This analysis aims to pinpoint the shortcomings of current treatment methods and propose new potential strategies for addressing the root causes of cocaine addiction.

Discussion

Cocaine and Its Effect on the Dopaminergic Pathway

Cocaine intake results in a high level of DA. Cocaine binds to the DA transporters, blocking the pathway for DA to travel back into the transmitting neuron[5]. As a result, DA accumulates in the synaptic cleft, leading to an excess of DA around the receptors. This increase in receptor activation may cause an individual to feel euphoric, energized, and sexually motivated, but it can also lead to sleep deprivation, poor impulse control, and aggressiveness.

Intake of cocaine disrupts the dopaminergic pathway by act-

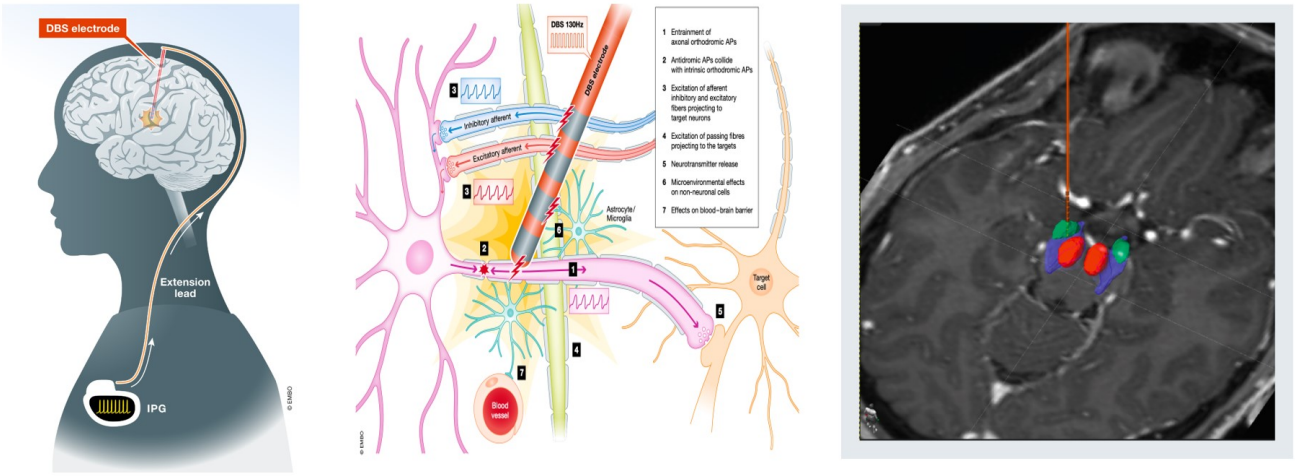

Fig. 1 Deep Brain Stimulation (DBS)
(a): Clinical DBS: a DBS electrode is connected to a neurostimulator (internal pulse generator, IPG) which sends an electrical current to the electrode.
(b): The DBS electrode stimulates the nucleus accumbens to regulate neurotransmitters.
(c): DBS targeting the nucleus accumbent[6]

ing as a DA antagonist, binding and blocking dopamine receptors, which prevents the reception of dopamine by the next nerve cell.

Current Clinical Treatment

While the most prominent addiction treatment is lifestyle management, various clinical treatments targeting the brain's dopaminergic pathway have been studied.

The paper will first review the Neurosurgical approach. Fig 1. shows that the neurosurgical approach uses Deep Brain Stimulation (DBS) placed in the brain's nucleus accumbens[7]. The nucleus accumben is located in the rostral cerebral hemisphere, the front part of the brain (Fig 1. (c) shows a 3D model of the nucleus accumbens in the brain). Neurosurgery has already been accepted as a treatment for various neurological disorders such as Parkinson's disease; thus, its viability in treatment for drug addiction is promising. A study by Lu et al.[8] showed a reduction in addiction after stereotactic neurosurgery but caused various side effects. Another study in 2022 by Polyakav et al.[9] examined 1000 stereotactic operation data and concluded that the efficiency of the surgery was around 70%. Despite its promising results, scientists still have to improve the side effects and risks caused by the surgery.

Another way to treat addiction is transcranial magnetic stimulation (TMS), a non-invasive physical treatment that uses a magnetic field to stimulate the brain. TMS has been used to treat cocaine, methamphetamine, alcohol, and eating disorders. The TMS device uses a coil to deliver a fluctuating magnetic field to the brain, creating an electrical current. When TMS delivers multiple pulses to the brain, it is called repetitive TMS (rTMS). The idea is that rTMS can alter neuronal activity and cortical excitability early in addiction. However, TMS still needs to be approved for treatment by any national regulatory agency due to its success rate of only between 70% and 80% and its limitation in treating deep brain regions because the strength of the magnetic field declines with the distance from the coil[10].

A lab at Carnegie Mellon University has been researching a theoretical non-invasive therapy for drug addiction using ultrasound. This therapy utilizes high or low-frequency energy waves to target deeper regions of the brain that transcranial magnetic stimulation cannot reach. The researchers have found that different neuron regions respond differently to ultrasound, but they have identified a critical parameter for stimulations that can balance excitatory and inhibitory neuronal activities. This research has broad applications and could potentially be used to treat various neurological and psychiatric conditions, such as addiction and depression. The researchers are still working on improving ultrasound's spatial resolution and precision and testing its effectiveness in clinical situations.

Alternate Treatment for Cocaine Addiction

While all of these clinical trials are currently underway to treat cocaine addiction, they are effective only for patients who are already addicted and have excess dopamine in their synaptic cleft. This section of the paper will discuss the potential use of carbidopa in cocaine addiction treatment.

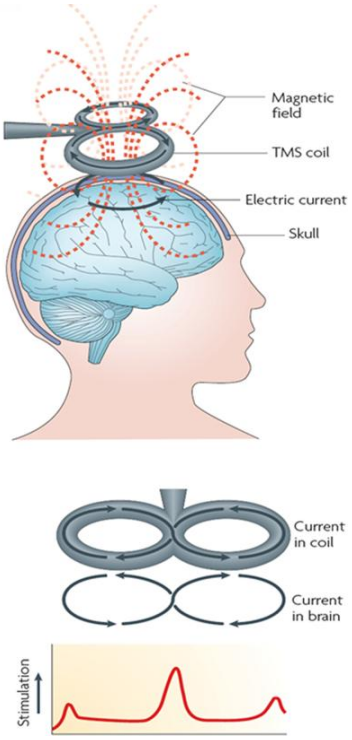

Fig. 2 Transcranial Magnetic Stimulation (TMS)
An electric current runs through the TMS coil, creating a magnetic field around the coil. This magnetic field creates an electric current in the brain, stimulating the transmission of neurotransmitters. [10]

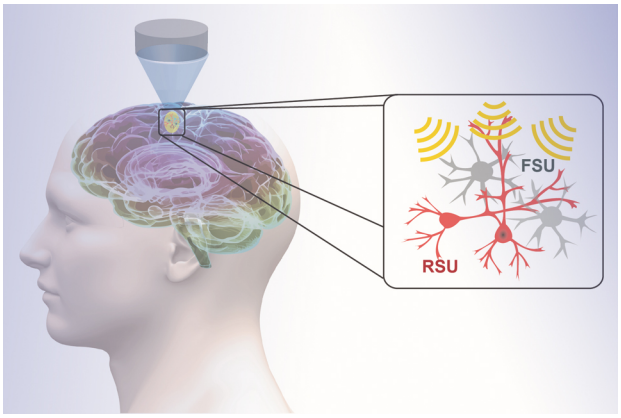

Fig. 3 Ultrasound
Excitatory Neurons (RSU) respond to ultrasound pulse whereas Inhibitory Neurons (FSU) don't respond to ultrasound pulse [10]

Carbidopa is a medication used to hinder the conversion of levodopa to dopamine outside the central nervous system (CNS) [12]. Carbidopa achieves this by inhibiting the activity of aromatic-L-amino-acid decarboxylase (DDC), an enzyme that converts levodopa into dopamine [13] as seen in Figure 4. This prevents the production of dopamine before its release, thus preventing the euphoric feeling from cocaine.

Previous studies have provided valuable insights into the application of carbidopa in drug addiction treatments. In a study conducted by Schmitz et al. [14], 136 cocaine-dependent users were administered carbidopa. The researchers found that the carbidopa-treated patients had submitted cocaine-negative urine samples, indicating that they had successfully refrained from using cocaine. This suggests that inhibiting dopamine production in cocaine use may help prevent addiction, dependence, and tolerance by reducing the "euphoria" effect of cocaine. As an alternative to existing methods that focus on treating the effects of "euphoria" after it occurs, I propose a new drug that could prevent the "euphoria" by inhibiting the activity of Aromatic l-amino acid decarboxylase (AADC) and thus reducing dopamine production.

However, carbidopa's focus on peripheral DDC and its chemical properties prevent it from crossing the blood-brain barrier [15]. As a result, carbidopa is unable to enter the brain, where dopamine is produced after consuming cocaine. Therefore, developing an alternative version of carbidopa is crucial because it can penetrate the blood-brain barrier and reach the brain. Carbidopa can potentially be used with levodopa, a precursor of DA, to cross the blood-brain barrier and control dopamine production.

Carbidopa can deplete dopamine levels by irreversibly binding to AADC. However, a prescription for carbidopa carries potential risks such as facial twitching and head bobbing [13]. Patients receiving carbidopa should be 18 years or older and should be closely monitored. Moreover, due to existing concerns, safety protocols for prescribing carbidopa should be enhanced.

Study Comparison

Comparing the two existing clinical methods, TMS and DBS, the long-term observation of treated patients showed reduced cravings over a long period. TMS-treated patients had a persistent reduction in cocaine use for six months post-treatment, and DBS-treated patients showed reduced cocaine craving for 2.5 years [16]. A comparative study between TMS and Ultrasound has been conducted on their effect on the motor cortex, but no studies comparing their effect on cocaine abstinence have been conducted yet.

While a comparative study between carbidopa and other clinical treatments does not exist, a comparative study between DBS and levodopa-carbidopa on Parkinson's Disease demonstrated that no significant differences in the motor function of the patients were shown when treated with carbidopa or DBS; both showed a positive effect on the patient's motor function [17]. Based on the fact that Parkinson's disease patients with impulsive behaviors show similar behaviors to illicit substance abusers, the effect of DBS and levodopa-carbidopa treatment on

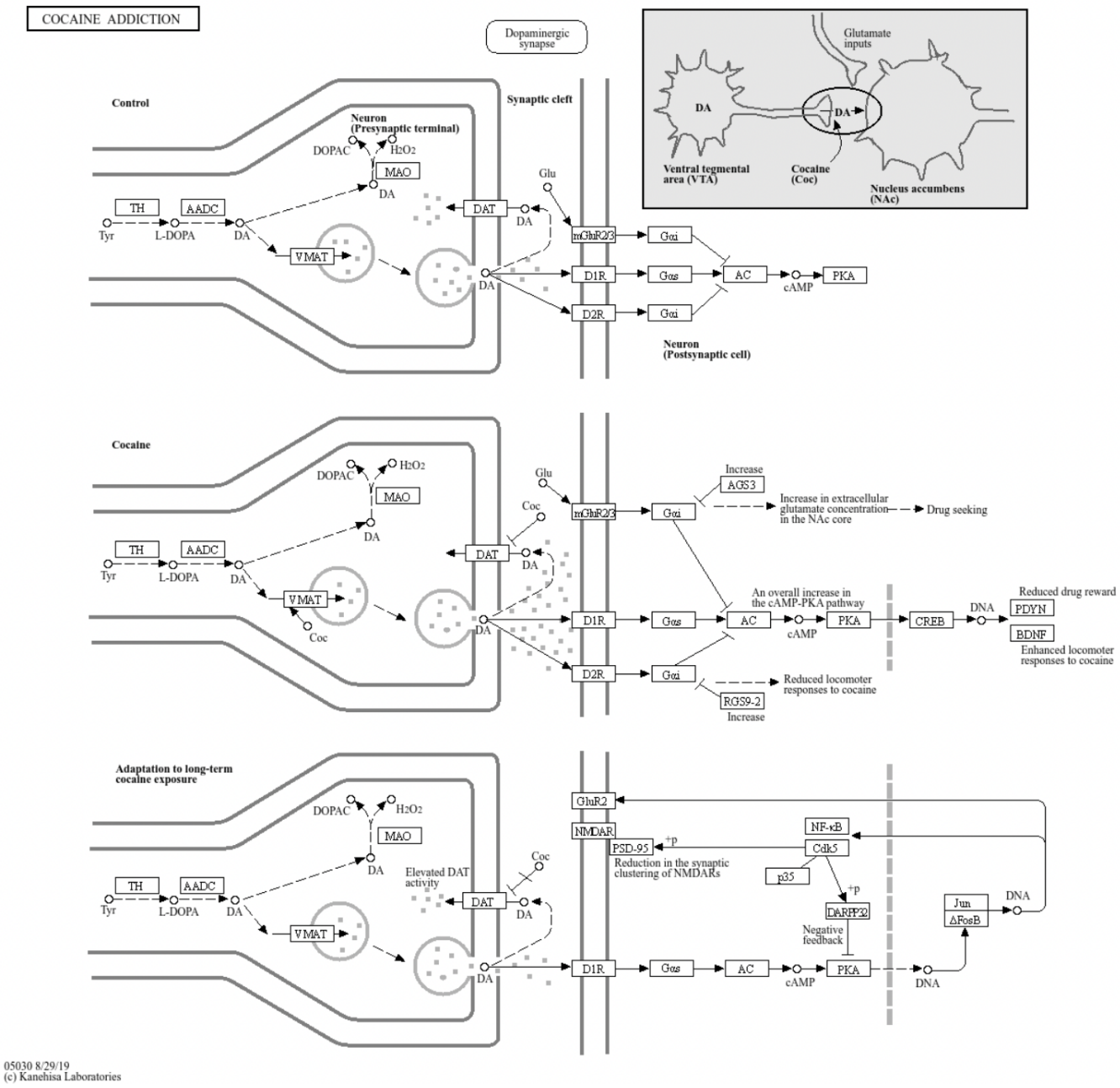

Fig. 4 Cocaine Addiction and the Role of Carbidopa [11]

cocaine users can be inferred as comparable.

Conclusion

Based on a collective review of existing clinical methods for treating addiction, it has been concluded that all current treatments only address patients after they have experienced the euphoric effects of addictive substances, specifically after the release of DA and excessive DA in the synaptic cleft. Neurosurgical approaches are aimed at treating symptoms resulting from cocaine-mediated damage in the frontal cortex. Transcranial magnetic stimulation (TMS) works by modifying neuronal activity and cortical excitability during the early stages of addiction. Ultrasound reduces drug cravings by stimulating the brain

with high or low-frequency energy. Finally, dopamine-depleting drugs minimize dopaminergic transmission and ameliorate hyperkinesis. To address the limitations of current treatments, a potential clinical treatment involving carbidopa to prevent excess DA production is suggested. By preventing the euphoric experience of those who intake the drugs, carbidopa is more effective in addiction prevention. The current insights into carbidopa research show a promising result and potential implication in addiction treatment for the future. Given its promising insights, future studies could focus on developing a form of carbidopa that can effectively cross the blood-brain barrier to enhance its function in addiction treatment.

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