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# A CRITICAL REVIEW ON HISTORY, USE, PHARMACOLOGY AND ABUSING OF COCAINE

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**ABSTRACT**

Cocaine is a naturally occurring substance found in the coca plant which is mostly grown in South America. Cocaine has had a significant impact on many societies, cultures, and religions in the past 1200 year. Mental effects may include loss of contact with reality, an intense feeling of happiness, or agitation. Physical symptoms may include a fast heart rate, sweating, and large pupils. Cocaine hydrochloride, which is the powdered form of cocaine, is produced by converting coca paste obtained from the leaves. Cocaine is addictive due to its effect on the reward pathway in the brain. After a short period of use, there is a high risk that dependence will occur. Cocaine binds to dopamine reuptake transporters on the pre-synaptic membranes of dopaminergic neurons. This increased activation of the dopaminergic reward pathway leads to the feelings of euphoria and the 'high' associated with cocaine use. An attempt has been in this article to include all the information regarding the importance of cocaine as medicine, its abusing effects, and its consequences.

**KEYWORDS:** Cocaine; dopamine; coca plant; dependence; euphoria.

## INTRODUCTION

Cocaine is a powerfully addictive stimulant that directly affects the brain. Cocaine has been labeled the drug of the 1980s and '90s, because of its extensive popularity and uses during this period. However, cocaine is not a new drug. In fact, it is one of the oldest known drugs. The pure chemical, cocaine hydrochloride, has been an abused substance for more than 100 years, and coca leaves, the source of cocaine, have been ingested for thousands of years. Pure cocaine was first extracted from the leaf of the Erythroxylon coca bush, which grows primarily in Peru and Bolivia, in the mid-19th century. In the early 1900s, it became the main stimulant drug used in most of the tonics/elixirs that were developed to treat a wide variety of illnesses. Today, cocaine is a Schedule II drug, meaning that it has a high potential for abuse, but can be administered by a doctor for legitimate medical uses, such as a local anesthetic for some eye, ear, and throat surgeries. There are basically two chemical forms of cocaine: the hydrochloride salt and the "freebase." The hydrochloride salt, or powdered form of cocaine, dissolves in water and, when abused, can be taken intravenously (by vein) or intranasally (in the nose). Freebase refers to a compound that has not been neutralized by an acid to make the hydrochloride salt.[1]

Cocaine, also known as coke, is a strong stimulant mostly used as a recreational drug. It is commonly snorted, inhaled as a smoke, or dissolved and injected into a vein.[2] Mental effects may include loss of contact with reality, an intense feeling of happiness, or agitation. Physical symptoms may include a fast heart rate, sweating, and large pupils.[3] High doses can result in very high blood pressure or body temperature. Effects begin within seconds to minutes of use and last between five and ninety minutes.[4] Cocaine has a small number of accepted medical uses such as numbing and decreasing bleeding during nasal surgery. Cocaine is addictive due to its effect on the reward pathway in the brain. After a short period of use, there is a high risk that dependence will occur.[5] Its use also increases the risk of stroke, myocardial infarction, lung problems in those who smoke it, blood infections, and sudden cardiac death.[6] Cocaine sold on the street is commonly mixed with local anesthetics, cornstarch, quinine, or sugar, which can result in additional toxicity. Following repeated doses, a person may have decreased the ability to feel pleasure and be very physically tired. Cocaine acts by inhibiting the reuptake of serotonin, norepinephrine, and dopamine.[7] This results in greater concentrations of these three neurotransmitters in the brain. It can easily cross the blood-brain barrier and may lead to the breakdown of the barrier.[8] Cocaine is a naturally occurring substance found in the *coca* plant which is mostly grown in South America.[9] In 2013, 419 kilograms were produced legally. It is estimated that the illegal market for cocaine is 100 to US$500 billion each year. With further processing crack, cocaine can be produced from cocaine.[10]

**Fig. no. 1: Coca leaves and fruits**

**Fig. no. 2: Coca leaves**

## COCAINE

### Historical Perspective

Cocaine has had a significant impact on many societies, cultures, and religions in the past 1200 year. Shortly after its introduction to the United States in 1854, the nonmedicinal use of cocaine became predominant, eventually leading to abuse and dependence.[11] Cocaine (benzoylmethylecgonine) is extracted from the leaves of the South American plant Erythroxylum coca.[12] It exists in two major forms: Cocaine hydrochloride and alkaloidal freebase (crack) cocaine. Cocaine is well absorbed through mucous membranes, resulting in a slower onset of action, a later peak effect, and a longer duration of action when used orally or nasally compared with intravenous injection.[13]

### Epidemiology of Abuse

Today, cocaine abuse and dependence is epidemic in theUnited States. A total of 34.3 million Americans (14.6%of surveyed population) have used cocaine at some time, and2.1 million Americans (0.9% of the surveyed population) used cocaine the month before the survey.[14] In New YorkCity between 1990 and 1992, cocaine metabolites were found in the blood and urine in 26.7% of people who sustained fatal injuries. More than 30% of deaths after cocaine use were attributed to drug intoxication; 65% involved traumatic injuries. A total 143,000 emergency department visits mentioned cocaine in 1994, and nearly 199,000 in 2002.[15]

### Cocaine use in humans

### Overview

Cocaine hydrochloride, which is the powdered form of cocaine, is produced by converting coca paste obtained from the leaves, into the water-soluble salt form that is either snorted or injected into a vein. Cocaine base, or "crack" cocaine, is the base form of a salt, which is usually made using sodium bicarbonate and can be smoked. Cocaine can also be taken orally, which is not common in developed countries but remains widespread in the Andes. Injection, snorting, and the smoking of cocaine increases the rapidity with which cocaine enters the brain over the oral form, contributing to the euphoria and its reinforcing effects. Once ingested, cocaine is metabolized in two major inactive metabolites, benzoylecgonine (detected by most drug testing) and ecgonine methyl ester. In the United States, approximately 2–3% of the population reports recent cocaine use, but the majority of cocaine users do not develop dependence. The current estimate of the lifetime cumulative probability of developing cocaine dependence among cocaine users is 20.9%. compared to 67.5% of nicotine users, 22.7% of alcohol users, and 8.9% of cannabis users.[16] Among the risk factors for developing cocaine dependence are being young at first use, male, with injected or smoked cocaine use.[17] Only a small percentage of cocaine abusers are in treatment at a given time, and at present, no pharmacologic treatment is effective for cocaine dependence. Behavioral treatments for cocaine dependence are available, but most are of limited effect.[18] Numerous previous clinical trials have investigated many medications for the treatment of cocaine dependence, yet none have shown a true success.[19] One reason for this is that many of these medications that have been tested were originally developed for other disorders, and there is a need to develop pharmacologic treatments that target the alterations in neurochemistry occur in the human brain specifically following exposure to cocaine.

### Complications of cocaine abuse

There are enormous medical complications associated with cocaine use. Some of the most frequent complications are cardiovascular effects, including disturbances in heart rhythm and heart attacks; such respiratory effects as chest pain and respiratory failure; neurological effects, including strokes, seizure, and headaches; and gastrointestinal complications, including abdominal pain and nausea. Cocaine use has been linked to many types of heart disease. Cocaine has been found to trigger chaotic heart rhythms, called ventricular fibrillation; accelerate heartbeat and breathing, and increase blood pressure and body temperature. Physical symptoms may include chest pain, nausea, blurred vision, fever, muscle spasms, convulsions, and coma. Different routes of cocaine administration can produce different adverse effects. Regularly snorting cocaine, for example, can lead to loss of sense of smell, nosebleeds, problems with swallowing, hoarseness, and an overall irritation of the nasal septum, which can lead to a

chronically inflamed, runny nose. Ingested cocaine can cause severe bowel gangrene, due to reduced blood flow. And, persons who inject cocaine have puncture marks and "tracks," most commonly in their forearms. Intravenous cocaine users may also experience an allergic reaction, either to the drug or to some additive in street cocaine, which can result, in severe cases, in death. Because cocaine has a tendency to todecrease food intake, many chronic cocaine users lose their appetites and can experience significant weight loss and malnourishment.[20]

**The mechanism of action of cocaine**

Cocaine modifies the action of dopamine in the brain. The dopamine-rich areas of the brain are the ventral tegmental area, the nucleus accumbens, and the caudate nucleus – these areas are collectively known as the brain's reward pathway. Cocaine binds to dopamine reuptake transporters on the pre-synaptic membranes of dopaminergic neurons. This binding inhibits the removal of dopamine from the synaptic cleft and its subsequent degradation by monoamine oxidase in the nerve terminal. Dopamine remains in the synaptic cleft and is free to bind to its receptors on the postsynaptic membrane, producing further nerve impulses. This increased activation of the dopaminergic reward pathway leads to the feelings of euphoria and the 'high' associated with cocaine use.[21]

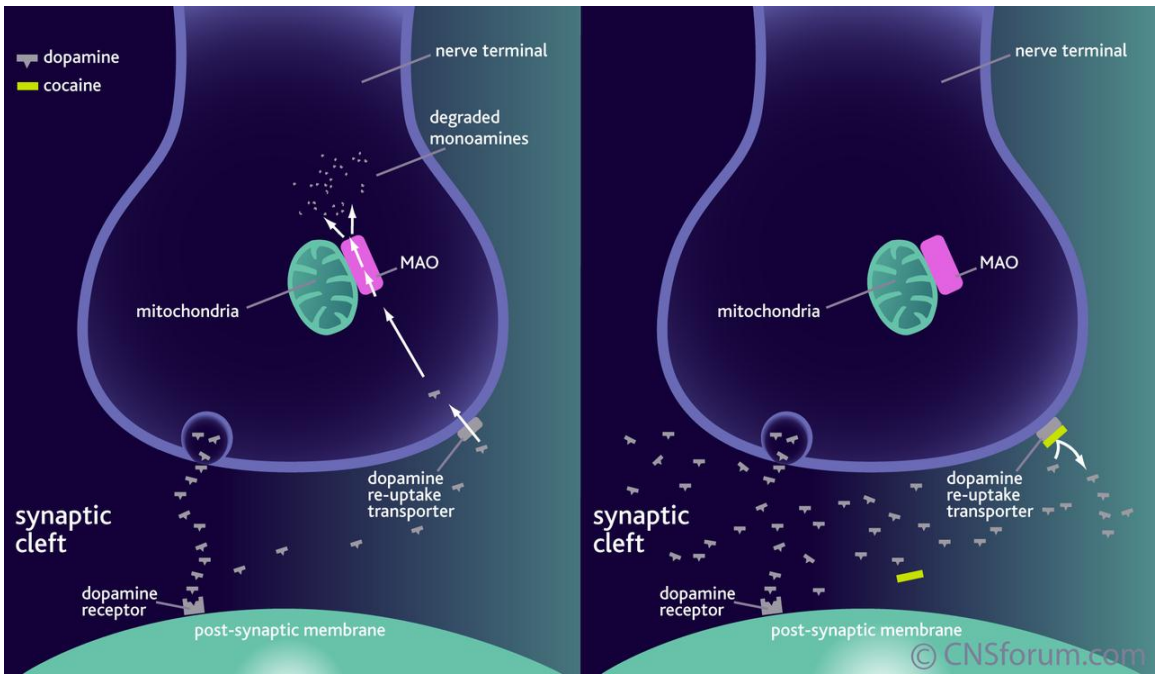


**Fig. no 3: Diagrammatic representation of the mechanism of action of cocaine.**

**Cocaine, Dopamine, and the Brain**

Like most other drugs of abuse, cocaine acts on the brain by changing the signaling of the endogenous neurotransmitters. The major neurotransmitter systems of the brain, gamma-aminobutyric acid (GABA) and glutamate, are responsible for signaling perception, cognition, and motor output that control behavior. But the GABA and glutamate systems are modulated by other neurotransmitters, including the opioid, serotonin, and dopamine systems. Among these, the dopamine system is the most closely associated with modulating motivated, reward-driven behavior and it is also the most directly associated with addiction. The dopamine system of the brain originates in the midbrain, and the cell bodies of the dopamine neurons are located in the substantia nigra and ventral tegmental area. The dopamine projections consist of four pathways: (1) mesolimbic, which projects from the ventral tegmental area to the nucleus accumbens of the striatum, plays a crucial role reward-driven behavior and addiction; (2) mesostriatal, consisting of projections from the substantia nigra to the dorsal striatum which largely plays a role in modulating cognitive processes and motor output; (3) mesocortical, which projects from the ventral tegmental area to the prefrontal cortex, directs behavior toward abstract goals[22] and (4) tuberoinfundibular, which regulates the hypothalamus-pituitary system. While the function of these projection systems can be segregated based on the brain regions they project to, it's important to recognize that there is overlap across these pathways. In addition, although the limbic pathway is crucial for reward-driven behavior, both preclinical and human studies show that the dopamine systems involved in cognitive processes also show involvement in addiction.

**Cocaine at the Synapse**

Cocaine has a very direct effect on dopamine signaling. At the dopamine nerve terminal of the striatum, cocaine binds the dopamine transporter (DAT) and blocks the re-uptake of dopamine by the presynaptic dopaminergic

neurons. Since re-uptake via the DAT is the major mechanism for terminating the dopamine signal in the striatum, cocaine administration results in a significant increase in extracellular dopamine, several orders of magnitude over baseline levels, based on microdialysis studies.[23-25] The excess in extracellular dopamine is dependent on the firing of the neuron since dopamine is released from the presynaptic dopamine neuron as it fires, but then is not reabsorbed by the DAT. Cocaine actually blocks the uptake of the monoamine neurotransmitters, not just dopamine, and also increases the concentrations of serotonin and norepinephrine. In fact, cocaine has a similar affinity for each of these monoamine transporters. However, it is the effect on extracellular dopamine that has been shown to produce most of the behavioral effects that are associated with addiction. For example, it is the increase in dopamine, rather than cocaine's effect on serotonin or norepinephrine, that is most directly associated with the reinforcing effects of cocaine. A crucial study of cocaine analogs in monkeys demonstrated that the potency of DAT inhibition (rather than inhibition of the norepinephrine or serotonin transporters) correlated with their ability to support cocaine self-administration.[26] Similarly, inhibition of the norepinephrine transporter (NET) and serotonin reuptake transporter (SERT) has little effect on the behavioral effects of cocaine in nonhuman primates, while drugs that block the DAT also inhibit cocaine's effects. In addition, cocaine self-administration is dependent on the mesolimbic dopamine pathway being intact, which is not the case for noradrenergic or serotonergic neurons.[27]

**The Role of Dopamine**

The recognition that dopamine plays a crucial role in addiction has been established for decades, but the actual role of dopamine in mediating the reinforcing effects of drugs of abuse has been an evolving concept. Dopamine does not appear to simply signal "reward" in the setting of a drug or food reward, although dopamine neurons fire in response to, or in the expectation of, a reward. Instead, dopamine appears to mediate the reinforcing effects of natural rewards (and drugs of abuse), in that the dopamine signaling makes the behavior required to obtain the reward more likely to be repeated. Dopamine neurons fire in response to a reward, which results in higher levels of dopamine being released in the nucleus accumbens, and increases the likelihood that the organism will repeat the behavior in an attempt to receive more of the reward. The exact mechanism by which dopamine does this has been the subject of a long debate.[28] showed that dopamine transmission in the nucleus accumbens influences effort-related behavior and that dopamine depletion results in an animal are less likely to exert effort to receive a food reward. Thus, dopamine can be understood as mediating the behavioral economics of motivated behavior and regulating the reinforcement value of a reward (i.e. the extent to which a given reward is worth the effort required). Dopamine can also be viewed as mediating the "incentive salience" of a reward, meaning the extent to which the reward is wanted by the animal.[29]

**Toxicological Screening**

Screening for cocaine and its metabolites can be performed on many biological fluids and tissues including urine, serum, saliva, gastric aspirates, breast milk, meconium, and even hair.[30-32] In the acute setting, urine testing is widely used and is least expensive. Two methods are generally employed. The first is an immunoassay *qualitative* method for cocaine'smost common metabolite, benzoylecgonine. Depending on the concentration cutoff set by the lab, this test can be 94% to 100% specific. The lower the concentration cutoff (lowest is 150 ng/mL), the higher the sensitivity and specificity. The immunoassay test can be confirmed if desired by a *quantitative* gas chromatography-mass spectrometry method. This is substantially more expensive and is done only when specifically requested. In general, urine testing will remain positive up to 6–14 days, but the results of both tests, however, depend on the amount of cocaine used, the time it was used last, and the patient's renal function. Test results should, therefore, be interpreted while taking the above into consideration.[33-35]

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