Chasing The High: Genetic Predisposition and Reaction to Cocaine Addiction

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How far would you go to chase a high? Run one more mile, pour one more coffee, snort one more line? Addiction is a stigmatized word, often ranging from healthy addictions to life-altering ones that can take many shapes and forms. Your neighbour might run 10 miles every morning and be claim to be addicted to running, while the newborn baby down the street is battling a cocaine addiction or your friend cannot function for the day without hitting a line. Cocaine can drastically alter the user's life, as it is highly addictive and provokes many further illnesses and problems, not to mention cause major financial burdens. An average of five million Americans are regular cocaine users (Addiction Statistics, 2021). This essay will introduce a background on cocaine, discuss the predispositions of having an addiction to cocaine, discuss the response to cocaine addiction, and provide research ideas to further understand cocaine addiction, all from a biochemical point of view.

Cocaine is a drug classified as a stimulant, like caffeine. Made from the leaves of the coca plant and originally used as a sedative, it mostly now circulates as an illegal street drug. It can be mixed with synthetic opioids, such as fentanyl, which makes cocaine more dangerous and increases instances of overdoses and death. Cocaine can be snorted through the nose, rubbed on the gums, or dissolved and injected directly into the bloodstream. It can also be converted to crack cocaine and inhaled. Cocaine is often taken by users in binges, to maintain the high. (NIDA, 2021). No matter the way of consumption, cocaine always penetrates the brain through the bloodstream. The high is achieved by the buildup of dopamine, a neurotransmitter that sends messages to the body and is commonly associated with pleasure. Usually, dopamine is recycled back into the cell, but cocaine prevents and blocks the reuptake, which can often stop nerve cell communication due to dopamine build-up. This build-up in the brains' reward system encourages drug taking, and with prolonged drug use, the reward system can adapt and promote drug insensitivities (NIDA, 2021).

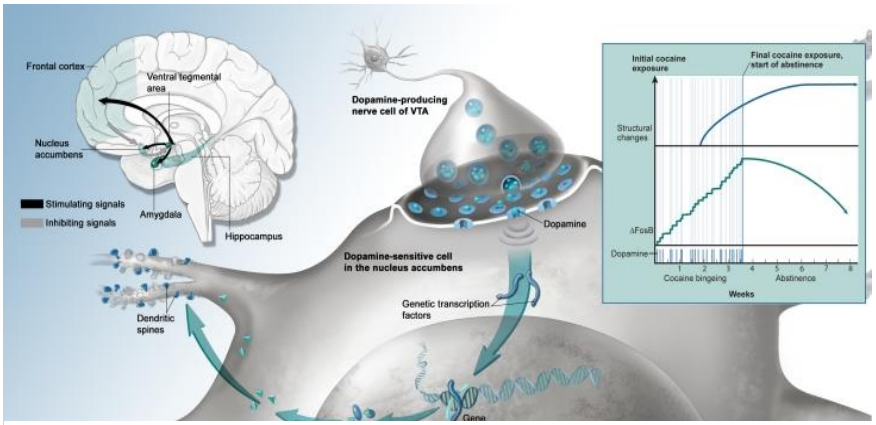

Figure 1. Cocaine's rapid effects in the brain (Nestler)

Dopamine originates in dopaminergic cells, cells

that make dopamine, and according to Nestler, "manufacture dopamine molecules and launch them into their surroundings. Some of the free-floating dopamine molecules latch onto receptor proteins on neighboring (receiving) cells. Once attached, the dopamine stimulates the receptors to alter electrical impulses in the receiving cells and thereby alter the cells' function" (2005). Cocaine works by tying up the dopamine transporter, a protein within the dopaminergic cells that collects dopamine from the cell, thus causing a build-up and overstimulating the cells (Nestler, 2005). This process works hand in hand with another type of dopamine receptor, which can predispose users to addiction.

Just like how it can be determined that a person will have blue eyes, people can be born either already addicted to cocaine, or predisposed to have a cocaine addiction. According to the National Institute on Drug Abuse, there are an estimated 750,000 cocaine-exposed pregnancies each year (2021). They also state that babies that are exposed to maternal cocaine use are often premature, with low birth weights and smaller than average children; children may also experience problems later in life, such as behavioural and brain ability (NIDA, 2021). In another study conducted by Nader et al., on the effects of cocaine on D2 receptors in monkeys, certain markers can indicate a predisposition. D2 receptors are a secondary type of dopamine receptor and are "linked to inhibitory G-proteins and initiate their action by inhibiting the enzyme adenylate cyclase" (Daly et al., 1994). Nader et al., after performing studies with methylphenidate, a type of dopamine transport inhibitor, found that subjects who enjoyed the dose of methylphenidate had lower levels of D2 receptor binding, based on receptor availability. This suggests a sensitivity between these receptors and stimulants (p. 3). They also state that "studies have shown lower D2 receptor availability in cocaine abusers" (Nader et al., 2005; p. 4). While there are no known genes associated with predisposition to cocaine addiction, there are certain studies that isolate genes that may contribute (Huggett et al., 2020). Currently, there are four significant genes associated with a predisposition to cocaine addiction; however, their relevance is not currently known. Of those genes, NADH:ubiquinone oxidoreductase subunit B9 gene (NDUFB9) (plays a role in oxidative phosphorylation in the inner mitochondrial membrane), and complement C1q like 2 (C1qL2) (aids in regulating the glutamate receptor), were main parts associated with the cocaine addiction co-expression network (Huggett et al., 2020; p.10). The D2 receptors could be associated with predisposition to addiction, but there is

not enough information if D2 receptor levels are a consequence of predisposition or prolonged cocaine use (Nader et al., 2005; p. 4). "Research suggests that compromised hippocampal neurogenesis/memory formation is a biological mechanism contributing to chronic cocaine use" (Hugget et al., 2020) In general, stress can also be a risk factor in developing an addiction, as well as early childhood stress and child mistreatment. They can lead to affected levels of corticotropin releasing factor and hypothalamic-pituitary-adrenal axis, which have recently been linked to risks in developing addiction (Sinha, 2008). As stated by Jordan et al., "early adolescent substance use dramatically increases the risk of lifelong substance use disorder" (2017). Therefore, there are a lot of factors that can lead to a predisposition to addiction, but addiction can also develop over time.

Addiction is an inability to control the need for a substance and can be formally defined as "recurrent failure to control the behaviour (powerlessness) and continuation of the behaviour despite significant negative consequences (unmanageability)" (Goodman, 1990). What if you are not born with a predisposition to addiction? How do your brain and body get addicted? It boils down to dopamine; the craving for unnatural dopamine levels leads to addiction or dependence. "[Cocaine dependence] is characterized by persistent cellular and molecular adaptations in multiple brain regions" (Hugget et al., 2020), there is also research surrounding the hippocampus' role in cocaine dependence. Another important part of the high/dependence is related to the limbic systems' nucleus accumbens (NAc). The cells in the NAc, due to dopamine, will naturally produce pleasure associated with survival and satisfaction instincts. The cells' response to these feelings makes us want to re-experience them (Nestler, 2005). When dopamine is artificially built up in the NAc by using cocaine, it will cause large amounts of pleasure, more than the natural producing levels (Nestler, 2005). Another study, conducted by Huggett et al., suggests the "PFC is a critical region for the neuropathology of cocaine addiction" (2020; p. 2). A model of rodents suggested that "PFC glutamate neurons allow a type of top-down control of reward circuitry and increase motivation to seek/use cocaine" (Huggett et al., 2020; p. 2). Taking cocaine once can turn into a nasty habit, and perhaps if there was a better understanding of addictions and less of a stigma surrounding them, alternative treatments and preventative measures could be considered.

There are a lot of options when battling addictions; nonetheless, further studies and measures could be presented for alternative ways when traditional methods do not work. Hugget et al., (2020), conducted studies to identify tissues related to the genetics of predisposition to cocaine addiction, which can help researchers develop a further understanding (p. 12). As there is little known about multiple tissue types and their effects, it could in turn lead to more preventative measures before addiction or dependence develops. As cocaine is an inhibitor of dopamine receptors, a beneficial way to counteract the overload of dopamine could be receptor agonists, dopamine releasers, or dopamine uptake inhibitors; however, dopamine releasers, such as amphetamine, show the most promising effects on cocaine abuse (Negus et al., 2015). Negus et al., found that with a chronic dosage of amphetamine to monkeys, there was decreased cocaine use. These research efforts could be put forth for human trials, and aid millions of people suffering from cocaine addiction (2015).

To conclude, consuming cocaine can start innocently, and quickly develop into an addiction, especially if there is no prior knowledge of predisposition to addiction. While cocaine addiction in the body is a complicated process, and outward addictions are highly stigmatized, continual research is being conducted for the development, predisposition, and treatment of cocaine addiction. There is still a long road ahead to discovering and understanding substance use disorders and effectively treating them, but as society moves towards a more conforming and welcoming civilization, hopefully, research will continue to pave the way for those struggling with addictions and they can receive the assistance they deserve.

Works cited:

Addiction Statistics. 23 Nov. 2021, https://www.addictioncenter.com/addiction/addiction-statistics/.

Chloe J. Jordan, Susan L. Andersen, Sensitive periods of substance abuse: Early risk for the transition to dependence, Developmental Cognitive Neuroscience, Volume 25, 2017, Pages 29-44, ISSN 1878-9293, https://doi.org/10.1016/j.dcn.2016.10.004.

Daly, Jeffrey M., and Stephen Salloway. "Dopamine Receptors in the Human Brain." *Psychiatric Times*, Psychiatric Times, Volume 11, Issue 5, 1 May 1994, https://www.psychiatrictimes.com/view/dopamine-receptors-human-brain.

Goodman, A. (1990), Addiction: definition and implications. British Journal of Addiction, 85: 1403-1408. https://doi.org/10.1111/j.1360-0443.1990.tb01620.x

Huggett, SB, Stallings, MC. Cocaine'omics: Genome-wide and transcriptome-wide analyses provide biological insight into cocaine use and dependence. *Addiction Biology*. 2020; 25:e12719. https://doi.org/10.1111/adb.12719.

Nader, Michael A., and Paul W. Czoty. "PET Imaging of Dopamine D2 Receptors in Monkey Models of Cocaine Abuse: Genetic Predisposition Versus Environmental Modulation." *American Journal of Psychiatry*, vol. 162, no. 8, Aug. 2005, pp. 1473–1482., https://doi.org/10.1176/appi.ajp.162.8.1473.

Negus, S., Henningfield, J. Agonist Medications for the Treatment of Cocaine Use Disorder. *Neuropsychopharmacol* **40,** 1815–1825 (2015). https://doi.org/10.1038/npp.2014.322

Nestler, Eric J. "The neurobiology of cocaine addiction." *Science & practice perspectives* vol. 3,1 (2005): 4-10. doi:10.1151/spp05314

NIDA. "Cocaine DrugFacts." *National Institute on Drug Abuse*, 8 Apr. 2021, https://www.drugabuse.gov/publications/drugfacts/cocaine Accessed 19 Nov. 2021.

NIDA. "What are the effects of maternal cocaine use?." *National Institute on Drug Abuse*, 9 Jul. 2021, https://www.drugabuse.gov/publications/research-reports/cocaine/what-are-effects-maternal-cocaine-use Accessed 23 Nov. 2021.

Sinha, Rajita. "Chronic stress, drug use, and vulnerability to addiction." *Annals of the New York Academy of Sciences* vol. 1141 (2008): 105-30. doi:10.1196/annals.1441.030

Figure Citations:

Nestler, Eric J. "The neurobiology of cocaine addiction." [Figure]. *Science & practice perspectives* vol. 3,1 (2005): 4-10. doi:10.1151/spp05314