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The Connection between Dopamine and Marijuana

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ABSTRACT

Known as the most commonly used illegal drug, marijuana has upheld its infamous reputation for decades. This psychoactive drug instills feelings of euphoria and energy when smoked or consumed. As its popularity increases, the perception of the harm induced by marijuana is declining. Uninformed individuals continue to smoke marijuana without considering it risky behavior. Without being aware of the risks that marijuana poses, more individuals are likely to develop addictions. Dopamine is a neurotransmitter in the brain that has many key roles for both the body and the brain. It is responsible for satisfaction, motivation, motor control, and arousal. Through examination of the molecular structure of dopamine, molecular structure of marijuana, and dopaminergic pathways in the brain, it is evident that there is a connection between marijuana use and decreased levels of dopamine. Long-term usage of marijuana has been shown to dysregulate the mesolimbic dopaminergic pathway. The mesolimbic pathway is a branch of neurons projecting from the ventral augmented area to the ventral striatum. Major functions of this pathway include addiction, pleasure, and reward-seeking behavior. Based on these defenses, there is a reasonable conclusion that chronic marijuana use leads to lower levels of dopamine in the brain.

Introduction

Approximately 1 in every 10 people who use marijuana develop an addiction. The main psychoactive component of marijuana is tetrahydrocannabinol, also referred to as THC. In the realm of science, medical uses of marijuana have been explored, however, as any other drug, excessive use of marijuana has a plethora of side effects. THC is a partial agonist at the endocannabinoid receptor (CB1). THC stimulates neuronal firing of mesolimbic dopamine neurons and elevates striatal dopamine levels in animals. Previous studies with cannabis dependent participants suggest that chronic cannabis use is associated with reduced dopamine release.

Dopamine is a neurotransmitter in the brain that is responsible for satisfaction, motivation, motor control, and arousal. It also functions as a chemical messenger between the nerve cells in the brain and the rest of the body. Balanced levels of dopamine are important for both the body and the brain. The reuptake of dopamine plays a role in the fight-or-flight response. High levels of dopamine induce feelings of euphoria, excessive energy, and hallucinations, which is similar to the feeling excessive use of marijuana gives. Scientists have identified the relationship between the two and showcase that excessive use of marijuana leads to lower dopamine levels.

History of Dopamine

George Barger and James Ewens first synthesized dopamine in 1910. 47 years later in 1957, Carlsson identified dopamine as a neurotransmitter in the brain. He later discovered that reserpine effects could potentially be reversed with an intravenous dose of the dopamine precursor L-dopa. This made sense given the dopamine discovery. A year later, Carlsson and his colleagues discovered that the region of the basal ganglia that connects motivation to the motor motions necessary for both simple motor activities and sophisticated cognitive tasks—the striatum—had the highest concentration of dopamine. This finding strengthened the case for dopamine as the neurotransmitter in charge of

regulating motor behavior. Parkinson's disease was eventually identified following further research on the dopamine distribution in post-mortem bodies.

A scientist from Austria named Oleh Hornykeiwicz chose to analyze the amounts of dopamine in the post-mortem brains of Parkinson's disease patients after learning about the regional localization of brain dopamine. He discovered that the striatum had dangerously low amounts of dopamine. Hornykeiwicz collaborated with physician Walter Birkmayer to provide L-dopa injections to 20 patients. This initially worked, but the results were just transient. Evidently, there was a great deal of studies, experiments, and investigations left to do.

Prior to the late 1960s, nothing was known about the discovery of dopamine. George Cotzias made a significant advancement in L-dopa therapy in 1967. He started conducting tests using an oral form of L-dopa to see if it may treat Parkinson's disease while working as a neurologist at the Brookhaven National Laboratory on Long Island, New York. He began by administering small oral dosages of L-dopa and increased them over time. This was the first effective "treatment" for Parkinson's and a significant advance in our understanding of the dopamine neurotransmitter.

Regulation of Dopamine Release

Dopamine is released through exocytosis, a process in which cells rely on energy to transport larger materials from inside cells to the outside. In particular, the materials are released when the plasma membrane and tiny, fluid-filled sacs known as vesicles merge. Only active zones, which hook a small portion of neurotransmitter-filled vesicles adjacent to voltage-gated Ca2+ channels, can release synaptic vesicles. CaV2, CaV3, and CaV1 calcium ion channels are necessary for the release of dopamine. Dopamine activates distant receptors for signaling by using volume transmission, a process in which neurotransmitters disperse in tissue. G-protein coupled receptors are dopamine receptors. Hormones, neurotransmitters (like dopamine), and senses are just a few examples of the intracellular reactions that hormone and G-protein coupled receptors can produce.

Action potential is a major driving force for release of dopamine. Each time an action potential occurs, varying amounts of dopamine are released. The stimulation of B2 receptors, specifically those that contain nAChRs (neuronal nicotinic acetylcholine receptors), also causes the release of dopamine. This is distinct from the action potential of firing. Dopamine production is inhibited, and dopamine absorption is enhanced when D2 auto receptors are activated. Fast-scan cyclic voltammetry (FSCV) has detected that the scan rate of dopamine transmission can occasionally be slower than the rate of exocytosis.

Recently, evidence has shown that there are both fast and slow coding mechanisms for dopamine volume transmission. Dopamine release occurs quickly when dopamine axons fire, and this release stimulates dopamine receptors with a signaling rate of tens of milliseconds. Gamma-aminobutyric acid (GABA), a neurotransmitter that lowers neuronal excitability and has a clamming effect, is released by dopaminergic axons when the vesicular monoamine transporter VMAT2 is active. Because it limits a nerve cell's capacity to produce, transmit, or receive chemical signals from other nerve cells, GABA is also referred to as an inhibitory neurotransmitter. A greater understanding of the spatial distribution of dopamine receptors of dopamine hotspots (short-lived peaks) is necessary to comprehend how the anatomical organization of the striatum supports the time scales of dopamine coding.

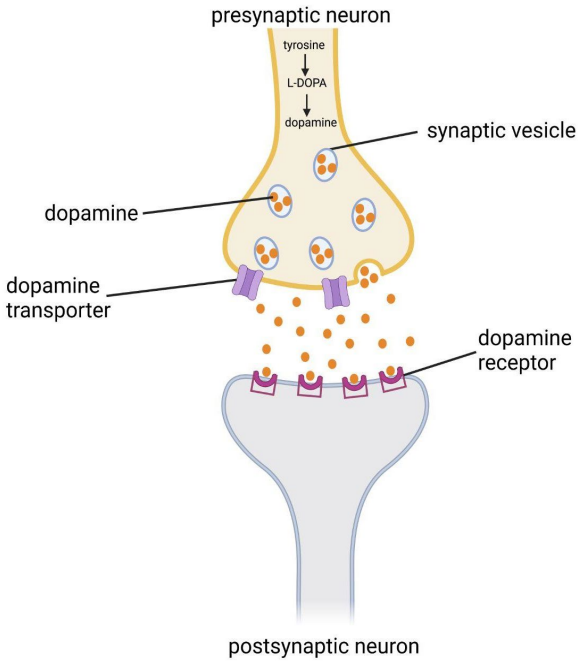

Figure 1. Representation of how dopamine is synthesized in a neuron.

Dopamine is synthesized from amino acid tyrosine via L-DOPA. Dopamine is sorted into synaptic vesicles in the presynaptic neuron. Through the help of a dopamine transporter, dopamine reuptake mediates from the synapse. Dopamine receptors allow for dopamine metabolites to reach the postsynaptic neuron. Created and copyrighted by Aastha Kulkarni.

Molecular Structure of Dopamine & Dopamine Chemical Synthesis

Dopamine is a catechol neurotransmitter, meaning it has a crystal structure with a catalytic core. All catechols have a benzene core with two hydroxyl substituents. It's classified as a catecholamine because it undergoes synthesis in the adrenal medulla and dopamine is released during periods of stress. Dopamine has a molecular weight of 153.18 g/mol. Dopamine synthesis is a two-step process that starts with the amino acid tyrosine. Tyrosine is an amino acid that helps the body produce dopamine. The structure of tyrosine is a phenol side chain with a hydroxyl group. Tyrosine hydroxylase is the key enzyme involved in the production of dopamine. Tyrosine hydroxylase uses a series of events to produce dopamine in the dopamine synthesis pathway. Phenylalanine is an essential amino acid for tyrosine, the rate-limiting step in catecholamine synthesis is the conversion of tyrosine to levodopa. Dopamine, epinephrine and norepinephrine are all classified as catecholamines and products of the tyrosine hydroxylase pathway.

Tyrosine hydroxylase catalyzes the first step of dopamine biosynthesis and is strongly regulated. Tyrosine hydroxylase is made up of four identical subunits, each of which is catalytically active and can oxidize tyrosine to levodopa by using BH4 (tetrahydrobiopterin), ferrous ion, and oxygen. Covalent modifications, protein interactions, and allosteric regulation are used to control this at the transcriptional and posttranscriptional levels. In order to bind the ferric ion at the tyrosine hydroxylase catalytic site, synthesized catecholamines compete with the cofactor BH4 of the enzyme. As a result, high catecholamine levels block tyrosine hydroxylase activity while also using feedback regulation to control its own intracellular concentrations. Depolarized cells use voltage-sensitive calcium channels to enhance their intracellular calcium concentrations in living organisms (in vivo). The process of phosphorylation causes

the regulatory domain of tyrosine hydroxylase to undergo a conformational change and creates dissociation of catecholamine. Tyrosine hydroxylase stability, activity, and intracellular localization are influenced by interactions with other proteins such alpha-synuclein, VMAT-2, AADC, and GTPCH. This in turn has a bearing impact on dopamine synthesis.

All the three catecholamines in the tyrosine hydroxylase pathway bind to the active site with the help of the iron atom. It is essential for iron to be oxidized for the binding to occur. There are two binding sites for dopamine, one which allows competitive inhibition with tetrahydrobiopterin. Tyrosine and dopamine can both bind in the active site but have different effects on the proteolytic pattern of the R domain (Daubner et al., 2011). This is because the amino acid substrate is attached to a different site from these two sites. A study was done on the dissociation constant, sometimes referred to as the K_D value of a variety of catechols, was the subject of a study to determine how strongly a ligand binds to a specific protein. This research contributed to the discovery that the carboxyl group of dopamine is not required for tight binding, whereas the amino group is essential (Ramsey & Fitzpatrick, 2000). It is important to know the sequences Arg37 and Arg38 in order to identify the three-dimensional structure of the R domain. Tyrosine hydroxylase is activated by phosphorylation of the phospho-myosin light chain ser19, but only in the presence of 14-3-3 proteins. Tyrosine hydroxylase's association with the protein -synuclein may contribute to the cellular location of a complex involved in dopamine synthesis and oxidative stress in the neuron.

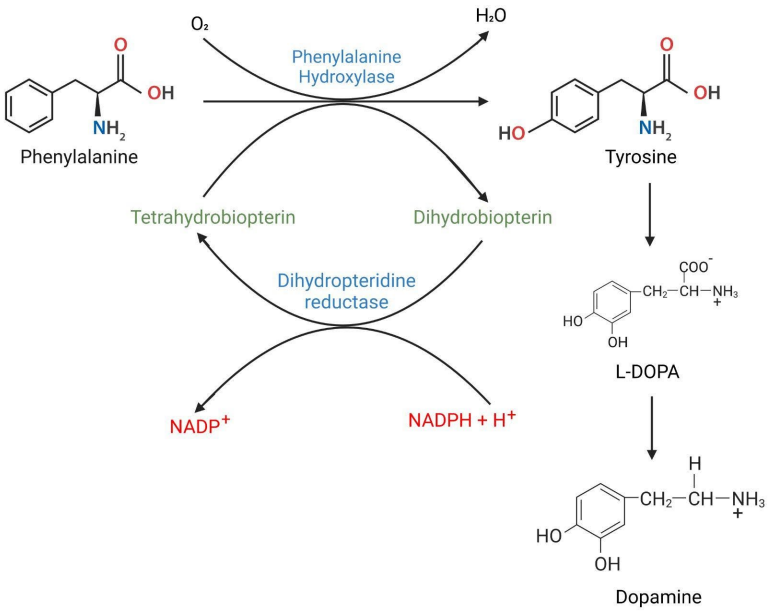

Figure 2. Molecular Pathway of Phenylalanine and Tyrosine.

To convert phenylalanine to tyrosine, one atom of oxygen (O_2) is required. The enzyme phenylalanine hydroxylase is essential for this conversion to occur. During the phenylalanine hydroxylase reaction, the coenzyme biopterin is needed to oxidize tetrahydrobiopterin (also known as H2-biopterin) to dihydrobiopterin. The reaction from phenylalanine to tyrosine is irreversible. Created and copyrighted by Aastha Kulkarni.

Functions of Dopamine and Marijuana

Dopamine plays a major role in movement, pleasure, motivation, and mood. It's commonly referred to as the "feel good" neurotransmitter for your body and is associated with the reward center of the brain. Dopamine influences behavior by causing people to want, desire, seek out, and search. Arousal levels rise, and people are more motivated

to carry out specific tasks. Dopamine essentially establishes a reward-seeking circuit that encourages people to repeat pleasurable behaviors or actions that their brain perceives as desirable. An intense experience is recorded by this circuit or loop, which noticeably alters the brain at the cellular level. Dopamine overproduction in the brain is linked to impulsivity, increased aggression, and more competitive behavior. This can eventually lead to addiction, binge eating, and even disorders such as schizophrenia. Low levels of dopamine makes people feel less motivated and excited about things. This can be linked to depression, psychosis, and even disorders such as Parkinson's disease.

On the other hand, recreational use of marijuana has several effects on the brain. The active ingredient in marijuana is THC, a psychoactive chemical that is generated from cannabis plants. It induces sensations of euphoria and relaxation. A negative effect of marijuana use is the alteration of the hippocampus, resulting in memory impairment. Furthermore, it impairs proper functioning of cerebellum and basal ganglia, which regulate balance, coordination, and motor control. Apart from lower dopamine levels, excessive amounts of THC in the body can have a variety of side effects. People often experience extreme nausea and vomiting, onset of paranoid delusions and hallucinations, and changes in the regular rhythm of the heart. THC can linger in the body of habitual marijuana users for up to 30 days. As a result, marijuana abusers experience prolonged feelings of lethargy and lack of motivation (once again linked to limited levels of dopamine in the brain).

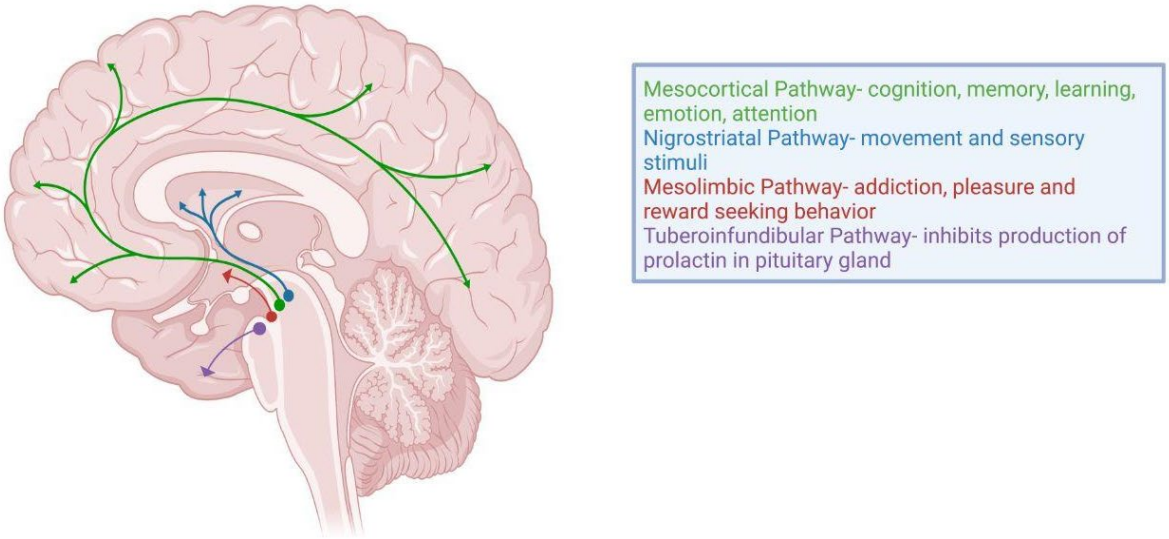

Figure 3. Dopamine Pathways in the Brain

There are four main dopamine pathways: mesocortical, nigrostriatal, mesolimbic, and tuberoinfundibular. Each pathway is responsible for a different function of the neurotransmitter dopamine. Dopaminergic neurons originate from the ventral tegmental area (VTA), where pathways start and lead to different regions of the brain such as the prefrontal cortex, hippocampus, and amygdala. Created and copyrighted by Aastha Kulkarni.

Dopamine Interaction with Marijuana

Anandamide and 2-arachidonoyl-glycerol are endogenous bioactive lipids that stimulate cannabinoid receptor types 1 (CB_1) and 2 (CB_2), which are G-protein-coupled receptors. CB_1 regulates the release of dopamine in the brain. The CB_1 receptor is found in particularly high levels in the neocortex, hippocampus, basal ganglia, cerebellum and brainstem (Marsicano & Kuner, 2008). These receptors are highly enriched at presynaptic and axonal compartments therefore their function is restricted to sites of synaptic activity. The majority of THC's effects on the central nervous system are conciliated by the CB_1 receptor, which binds THC. There is a greater efficacy of G protein-dependent activation of CB_1 receptors in hippocampus glutamatergic neurons than in neighboring GABA interneurons (Steindel et al.,

2013). The CB2 receptor is mainly expressed during periods of active inflammation and is primarily responsible for immunosuppressive and anti-inflammatory actions. This receptor has a more clearly defined pattern of expression in the brain and is mostly present in microglia and resident macrophages of the CNS, which also include immune system cells and tissues. Studies confirm that CB2 receptors play a role in drug misuse, synaptic plasticity, and govern synaptic function. In vivo, CB2 receptors alter gamma oscillations and inhibitory plasticity in the CA2/3 areas of the hippocampus.

Short-term marijuana use is associated with an increase of dopamine release. Long-term marijuana use and exposure are known to compromise the function of dopamine in the brain. The dopamine system undergoes various alterations due to prolonged exposure, particularly throughout adolescence. Dopamine receptor gene expression has been found to vary in response to THC during early development. Later in life, this leads to a reduction in the effectiveness of the dopaminergic response to dopamine stimulation. Heavy cannabis use is linked to poor motivation and reduced cognition. Reduced motivation for goal-directed conduct has been directly linked to lack of motivation. Long-term usage of marijuana has been shown to dysregulate the mesolimbic dopaminergic pathway. This particular dopamine pathway is linked to pleasure, addiction, and reward seeking behavior.

The impairments induced by marijuana use directly correlate with the brain regions controlled by dopamine, as well as the functions that dopamine serves for the body. A study was performed with rats that were repeatedly exposed to THC. In the substantia nigra and ventral tegmental area of the midbrain nuclei, repeated THC administration resulted in decreased dopamine metabolism and less controlled tyrosine hydroxylase mRNA expression (Bloomfield et al., 2016). The results of numerous rat investigations showed that repeated THC administration has effects on dopamine function that are localized. There is evidence that the length of cannabis usage and stress-induced dopamine release in the limbic striatum, a portion of the mesolimbic dopaminergic pathway, are positively correlated in studies of chronic cannabis users in humans. Additionally, there was an indication that chronic cannabis users had lower dopamine transporter density. Dopamine transporters direct the reuptake of extracellular transmitters into presynaptic neurons, which regulates the spatial and temporal dynamics of dopamine neurotransmission. ADHD, bipolar disorder, depression, and Parkinson's disease can all develop as a result of defective dopamine transporters, which can also cause aberrant dopamine levels in the brain.

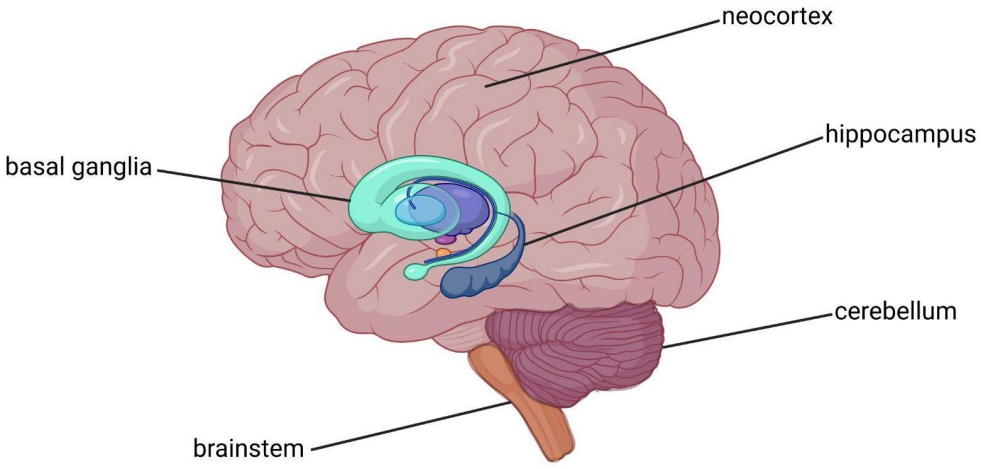

Figure 4. Cannabinoid Receptors in the Brain

The highest concentrations of cannabinoid receptors are in the basal ganglia, hippocampus, and cerebellum. These receptors are activated by anandamide, a neurotransmitter that the human body makes. The active ingredient in

marijuana THC mimics anandamide, therefore binding with cannabinoid receptors. This activates neurons in the brain and creates adverse effects. Created and copyrighted by Aastha Kulkarni.

Molecular Structure of Tetrahydrocannabinol

Tetrahydrocannabinol has a carbocyclic structure with 21 carbon atoms and is usually formed by three rings: cyclohexene, tetrahydropyran and benzene. Surprisingly, nitrogen does not exist in the chemical makeup of THC. Chemically speaking, THC is derived from arachidonic acid and the main representatives are anandamide and 2-arachidonoylglycerol. It is present in cannabis as a combination of mono-carboxylic acids, which gets readily and effectively decarboxylated when heated.

The molecular structure of dopamine and marijuana are very similar. Both have benzene rings, and the molecular formula is similar with one main difference. Dopamine has one nitrogen atom in its molecular formula while marijuana does not have any nitrogen atoms. The number of carbon, hydrogen, and oxygen atoms also differs in each. In 1 mol of dopamine, there are 8 atoms of carbon, 11 atoms of hydrogen, and 2 atoms of oxygen. On the other hand, in 1 mol of marijuana, the number of atoms of oxygen is the same as dopamine, but the number of atoms of carbon and hydrogen is much greater. 1 mol of marijuana has 21 atoms of carbon and 30 atoms of hydrogen.

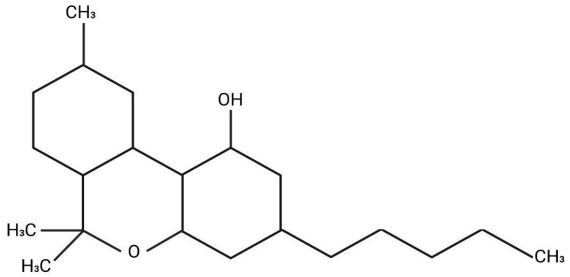

Figure 5. Molecular Structure of Tetrahydrocannabinol

Tetrahydrocannabinol (THC) is the major active component of cannabis products. The molecular formula of THC is $C_{21}H_{30}O_2$. The molecular weight is 314.4 g/mol. Created and copyrighted by Aastha Kulkarni.

Dopamine Concentrations in Brain

The four main dopamine pathways in the brain are mesocortical, nigrostriatal, mesolimbic, and tuberoinfundibular. The mesocortical pathway extends from the ventral tegmental area (VTA) to the prefrontal cortex. This pathway plays a major role in cognition, working memory, and decision making. The dopamine concentration of the mesocortical pathway usually ranges from 10^{-9}-10^{-6} M. The mesolimbic pathway extends from the VTA to the nucleus accumbens. This pathway primarily mediates feelings of pleasure and reward. The dopamine concentration of the mesolimbic pathway usually ranges from 10^{-10}-10^{-4} M. Long-term usage of marijuana has been found to dysregulate the mesolimbic dopaminergic pathway, therefore lowering the concentration of dopamine in the neurons projecting from the VTA to the nucleus accumbens. The nigrostriatal pathway extends from the VTA to the dorsal striatum. This pathway is primarily involved in motor and sensory stimuli and dopaminergic neurons in this pathway stimulate purposeful movement. The dopamine concentration of the nigrostriatal pathway usually ranges from 10^{-9}-10^{-3}. The tuberoinfundibular pathway extends from the arcuate nucleus to the median eminence in the hypothalamus. In this pathway, dopamine inhibits prolactin release in the pituitary gland. The dopamine concentration of the tuberoinfundibular pathway usually ranges from 10^{-8}-10^{-4}.

A study was done on the association between cannabis use and dopaminergic deficiency (Van De Giessen et al., 2016). Using PET scans, she calculated the change in estimation of binding potential ($\triangle BP_{ND}$). BP_{ND} is a commonly used PET scan measure that compares the concentration of radioligand in receptor-rich to receptor-free regions, a kind of brain tissue. The striatum, which has the highest concentration of dopamine in the brain, exhibited a considerably lower BP_{ND} among cannabis dependent individuals. Inattention, a decrease in working memory, and poorer learning performance were all associated with this reduced dopamine release in the striatum. The results are validated and considered to be very significant with a p value of p=.002. According to these results, users of cannabinoids experience impairments in striatal dopamine release. The study also examined cannabinoid receptors and found reduced CB_1 receptor availability in chronic marijuana users. This proves a direct connection between marijuana and dopamine as CB_1 regulates the release of dopamine in the brain.

Another study was performed on the brain reactivity in marijuana abusers. PET scans and [^{11}C] raclopride (radioligand that binds to D2/D3 receptors not occupied by dopamine) were used to measure the ratio of the distribution volume in the striatum. Marijuana abusers displayed decreases in striatal distribution volumes, supporting the idea that long-term marijuana use is associated with lower dopamine levels in the mesolimbic dopamine pathway. As a result, participants experienced lower reward sensitivity and motivation, which is exactly what dopamine controls. A region of interest (ROI) analysis was done to provide the structural substrates for assessing connectivity within individual brains and combining data across populations. According to the ROI analysis, there was a lower baseline BP_{ND} in marijuana abusers. It was also found that early life exposure to THC also reduces the dopaminergic response to stimuli that release dopamine later in life, such as stress and amphetamine. Exposure to THC creates abnormalities in the structure of dopaminergic neurons. Interestingly, effects are region-specific and include reductions across a range of measures of neuronal cell size extending from the ventral tegmental area (VTA) to the nucleus accumbens.

THC Dependence & Mesolimbic Dopamine Pathway

There are major consequences of THC dependency on the mesolimbic dopamine pathway. A study was conducted to examine the effect of chronic cannabinoid exposure in the rat mesolimbic dopamine system. The investigation focused primarily on the anatomical morphology of dopaminergic neurons in the substantia nigra pars compacta, ventral tegmental region, and their primary post-synaptic destination in the nucleus accumbens. With a statistically significant p value of P<.0001, analysis of variance revealed anatomical differences for the mean computed area in the ventral tegmental area (Spiga et al., 2011). The soma of the ventral tegmental region THC-positive neurons significantly shrank after receiving chronic THC treatment. This is remarkable because the main role of soma in the brain is the storage of the nucleus, where the neuron's DNA is housed and where proteins are made to be transported throughout the axon and dendrites. Additionally, it was proven that endocannabinoids modulate synaptic plasticity in the ventral tegmental area and substantia nigra pars reticulata. As previously mentioned, this resulted in the somatic region of the brain shrinking along with decreased dopamine activation. Overall, this study provided evidence that the functional losses may be morphologically correlated with the shrinkage of dopamine neurons and reduction in spine density on their postsynaptic elements caused by prolonged cannabis administration. This may ultimately contribute to negative motivational properties of withdrawal from addictive drugs; however, further studies are needed to corroborate this theory.

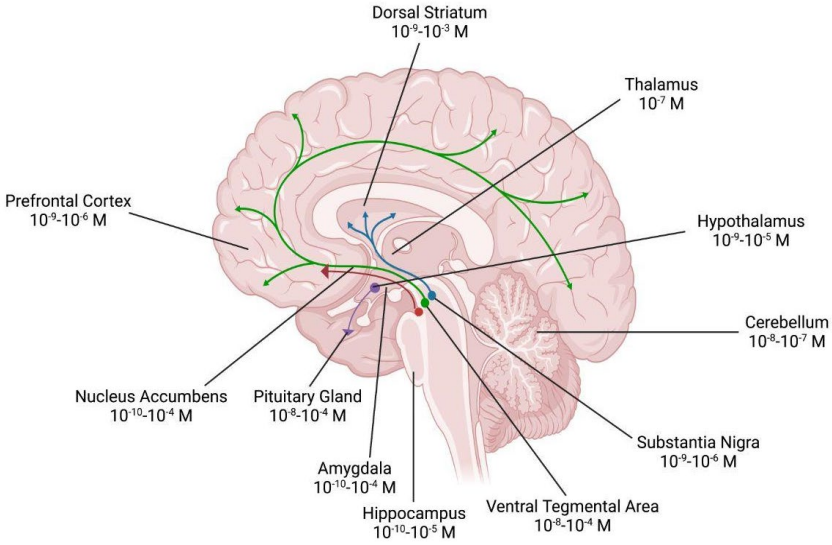

Figure 6. Dopamine Concentration throughout the Central Nervous System

The values above represent the range of molar values for the concentrations of dopamine throughout the brain, from left to right. These values are relative to the four main dopamine pathways: mesocortical, nigrostriatal, mesolimbic, and tuberoinfundibular. The concentrations of dopamine are highest within these four pathways. Created and copyrighted by Aastha Kulkarni.

Conclusion

The neurotransmitter dopamine plays several key roles of satisfaction, motivation, motor control, and arousal. When examining the molecular structure of both dopamine and marijuana and the dopamine concentrations in each part of the brain, it is likely that marijuana usage results in lower levels of dopamine in the brain. The mesolimbic dopaminergic pathway has been shown to be dysregulated by prolonged marijuana use. The neurons of the mesolimbic dopaminergic pathway that extend from the ventral enhanced region to the ventral striatum have decreased dopamine concentrations when this dopamine pathway is dysregulated. As a result, dopamine levels in the brain are diminished. Several studies were able to support the idea that chronic marijuana use reduces striatal distribution volumes and induces shrinkage of the soma of THC neurons extending from the ventral tegmental area to the nucleus accumbens. Extensive use of PET scans and [11C] raclopride analysis was crucial in supporting the decrease of dopamine from extensive marijuana use. Other methods used to corroborate this theory include examination of the molecular structure of dopamine, molecular structure of THC, and dopamine concentrations throughout the brain. A thorough understanding of the chemical synthesis of dopamine was essential in association of chronic marijuana use and lower dopamine levels in the striatum region of the brain. When dopamine levels are lower, brain function is compromised, and this creates negative effects for the entire body. Long-term cannabis use is associated with impaired cognition and lack of motivation, ultimately impacting the main role of dopamine for the body. The reward-seeking circuit is interrupted, and this can lead to dysregulation of the mesolimbic dopamine pathway which compromises the roles of addiction, pleasure, and certain behaviors. Bringing awareness to these effects of marijuana is crucial as many marijuana users are unaware of the harm they are doing to their bodies and brain from long-term marijuana use and THC exposure.

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