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Neuropsychiatric effects of marijuana

Abstract

Background: Cannabis (Marijuana) is one of the most widely used illicit drugs around the world. In the United States, it is the most commonly-used illicit drug. While there have been increasing numbers of arguments about legalizing marijuana primarily for its medicinal and recreational use, there remain concerns about its impact on the brain: neuropsychiatric problems, in particular, from its chronic use.

Purpose & Method: To highlight recent knowledge, understanding and research of marijuana, its potency, mechanism of action, effects on psychomotor and cognitive performance and other neuropsychiatric function are explored; paying particular attention to the long term effects of Marijuana usage. Marijuana interacts with endogenous cannabinoid (CB) systems in the body. Actions on specific brain receptors are reflected in CB dose-related impairments of psychomotor performance. Further effects relating to psychosis, memory problems, and depression, are also experienced; primarily as a result of cortex degeneration.

Conclusion: Marijuana significantly impacts the brain, specifically, the brain's structure, function and connectivity. Although marijuana use is linked to many neurological and psychiatric effects from long term use, it is often perceived in society as harmless

Keywords: marijuana, cannabinoid, psychomotor, neurophysiological, psychoactive agent, inflammation

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Abbreviations: CB, cannabinoid; THC, delta-9-tetrahydro cannabinol; ECS, endogenous cannabinoid system; HPA, hypothalamic pituitary adrenal

Introduction

Marijuana (Cannabis) is one of the most widely used illicit drugs around the world, particularly in the United States. Its use is widespread among young people. According to a yearly survey of middle and high school students, rates of marijuana use have steadied in the past few years after several years of increase. Specifically, amongst 8th graders (9.4%), 10th graders (23.9%) and 12th graders (35.6%), marijuana use in 2015 was a concerning trend.[1] Furthermore, the number of young people who believe marijuana use is risky is decreasing. The growing common usage of marijuana among young people is an important trend to highlight given that marijuana is proven to cause substantial and life altering changes to one's neurophysiological structure and function.

Marijuana refers to the leaves, flowers, stems, and seeds from the hemp plant, *Cannabis sativa*. Cannabis can be used through smoking, vaporization, food intake or as an extract. The plant contains the chemical *delta-9-tetrahydrocannabinol* (THC), a psychoactive compound as well as other related compounds which have brain-altering capabilities. It is estimated that herbal cannabis contains over 400 compounds in addition to over 60 cannabinoids, which are aryl-substituted meroterpenes unique to the plant genus *Cannabis*. Furthermore, it is also found in the resin of the female plant.[2] Much of the cannabinoids' pharmacology is largely unknown, but the most potent psychoactive agent, THC, has been isolated, synthesized and studied significantly. Other plant cannabinoids include delta-8 THC, cannabinol and cannabidiol. Of notable importance, 11-OH THC is the most potent THC metabolite acting on the CB system.[2]

These and other cannabinoids have additive, synergistic or antagonistic effects with THC and may enhance its actions, particularly when herbal cannabis is smoked. Further, THC has also been shown to cause the release of Dopamine through the nucleus accumbens in the frontal cortex[2,3] a known and proven critical reward pathway in the addiction of opiates.[4,5] There also exists, synthetic cannabinoids such as nabilone, which are typically used for therapeutic and research purposes. Oddly, with the exception of nicotine, non-cannabinoid constituents of the plant are similar to those found in tobacco. It is the purpose of this paper to explore the neuropsychiatric effects of marijuana as a result of both short and long-term usage, inclusive of its pharmacology, interaction with the endogenous cannabinoid system and the underlying physiology that manifests such effects.

Pharmacology

A literature review reveals that about 50% of the THC in herbal cannabis, when inhaled, is almost exclusively absorbed through the lungs. THC then rapidly enters the bloodstream and within minutes it reaches the brain. Its physiological effects are perceived in seconds and are observable within minutes. Oral ingestion of THC has a much lower blood concentration compared to the inhalation route, primarily because of the first pass effect induced by the liver. Hence, its bioavailability ranges from 25%-30% of that obtained by smoking the same dose.[2]

Regardless of the route used, all effects eventually act on the brain through the cannabinoid systems. In simple terms, a joint made out of skunkweed, nether weed and other potent subspecies of *Cannabis sativa*, may contain around 150 mg of THC, or 300 mg if laced with hashish oil. Thus, the modern cannabis smoker may be exposed to doses of THC many times greater than its counterpart of the 1960s and 1970s;[2,6] yet another argument as to why its use among young people and their developing brains is worrisome (Figure 1).

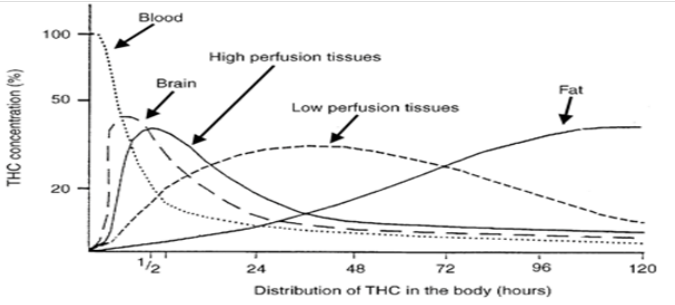

Figure 1 Concentration and distribution of THC in the body over time

The endogenous cannabinoid systems

The endogenous cannabinoid system (ECS) consists of cannabinoid receptors, endogenous receptor ligands and their synthesizing and degrading enzymes. The main function of the endocannabinoid system is to regulate neuronal excitability and inflammation in pain circuits and cascades. ECS also helps regulate movement, appetite, aversive memory extinction, hypothalamic-pituitary-adrenal (HPA) axis modulation, immunomodulation, mood, sleep/wake cycles, blood pressure and neuro-protection;[7] all critical functions for living and survival.

The involvement of CB receptors is important to understand. To date, only two have been identified, CB1 and CB2. CB1 receptors are the most abundant G-protein-coupled receptors in the brain and are expressed at lower densities in many peripheral tissues. These CB1 receptors solely mediate the psychotropic and behavioral effects of cannabinoids and regulate several peripheral processes, such as energy homeostasis, cardiovascular function, and reproduction. CB1 distribution in the brain matches the known pharmacodynamic effects of cannabinoids; in addition, CB1 activation prominently modulates cognition and memory, perception, control of motor function, and analgesia. CB1 receptors are present in very high levels in several brain regions and in lower amounts in a more widespread fashion. These are primarily located on nerve cells in the brain, spinal cord, but they are also found in some peripheral organs and tissues such as the spleen, white blood cells, endocrine gland and parts of the reproductive, gastrointestinal and urinary tracts.[8] These receptors mediate many of the psychoactive effects of cannabinoids. In the brain, in particular, CB1 receptors are found in the cerebellum, basal ganglia, hippocampus and dorsal primary afferent spinal cord regions, which are why cannabinoids influence functions such as memory processing, pain regulation and motor control.[8] A second CB receptor, CB2, also exerts an effect, but perhaps in a more restricted manner.

CB2 receptors have a more restricted distribution. They are found in a number of immune cells and in only a few neurons.[9] The CB2 receptors are mainly found on white blood cells, in the tonsils and in the spleen. Their most important function is in the regulation of cytokine release, hence playing a role in anti-inflammatory and anti-cancer effects.[8]

Neuoropsychiatric effects

There is looming societal concern about the neurological impact of cannabis. As many young people are still developing from a neurological standpoint, the impact of cannabis on such growth and development is particularly concerning. For both short and long term use, the effects of THC from cannabis have been well proven and substantiated. According to recent research, "the effects of *Delta 9-tetrahydrocannabinol* (THC), the main psychoactive ingredient in cannabis, are a pressing concern for global health".[10] Research suggests that those who used cannabis had noticeable and multiple brain regions with low cerebral perfusion on SPECT.[11] When cerebral perfusion is compromised, potential cerebral damage can ensue, hence fueling the controversy of whether long-term marijuana use can cause irreversible deficit or permanent damage in higher cortical brains centers.[2]

The duration of marijuana usage is another mitigating factor. It ranges from acute intoxication to chronic use. Some of the acute effects are characterized as "cannabinoid induced psychosis" which is usually difficult to differentiate from schizophrenic symptoms (paranoia, delusions, grandiosity, auditory hallucinations, and thought insertions, change in perceptions and also blunting affects). Other symptoms of acute intoxication include impaired coordination, decreased muscle strength, decreased hand steadiness, postural hypotension, lethargy, decreased concentration, slowed reaction time, slurred speech, and conjunctival injection,[12,13] and can often lead to hospital admission.[14,15]

Cognition

In spite of some research to the contrary,[16] cannabis has been well proven to precipitate cognition decline. First, it targets and parallels neurological changes similar to that found in schizophrenia. Usage of cannabis results in a significant disruption of hippocampus and prefrontal cortex brains waves, which are vital for memory and decision-making, both areas of which are also involved in schizophrenia.[17] Bartholomew et al.[18] caution however, that young people may often not even notice the memory losses. Further, it also impacts visual motor skills,[18,19] general cognition and thinking processes[20] and can induce psychotic symptoms such as hallucinations and delusions, again, much like what is found in individuals with schizophrenia.[17] Paradoxically, cannabis is the most commonly used drug in individuals who suffer with schizophrenia. [15,21]

The effects of cannabis, have been described in some studies, as those similar to alcohol and benzodiazepine. One can expect that relatively small doses (5-10 mg in smoked marijuana), even in an experienced cannabis user, produces difficulty concentrating, and an inability to execute complex task which requires one's undivided attention.[14] These effects are additive with those of other central nervous system depressants.[2] Further, both clinical and preclinical research shows that marijuana use, particularly prior to age 16, could have long-term effects on cognition, anxiety and stress-related behaviors, mood disorders and substance abuse.

Motor/psychomotor control

The impact of cannabis on motor and/or psychomotor control has been widely studied. For example, one study shows that CB1 receptors are expressed in high concentrations in the some brain areas such as the basal ganglia and the cerebellum, cortex and/or neocortex; areas of the brain responsible for balance, movement and motor control. In fact, areas of the brain impacted the most were the white matter underlying the cortex; where most of the CB1 receptors are found.[14,22] Iverson[14] adds that motor in coordination and delayed reaction time also become impaired. These areas are widely known for motor control of the body, therefore the degeneration of the supporting white matter underling the cortex will ultimately affect neuron conduction and hence, motor control and balance. But the impact of cannabis

doesn't stop there, it also perpetuates into one's mood and perceptual processes.

Mood and perception

Acute cannabis intoxication is known to cause both mood and perceptual changes. Emotions are saddened, perception of time is impaired, and a distorted spatial perception occurs as a result of acute cannabis intoxication.[2] The primary feature of the recreational use of cannabis or marijuana is the production of a euphoria effect, known as the 'high'. The high can be achieved with doses of THC as low as 2.5 mg in an herbal cigarette and includes a feeling of intoxication, with decreased anxiety, alertness, depression and tension and increased sociability. The "high" ensues within minutes of smoking and then reaches a plateau lasting two hours or more, depending on the dose. It is not surprising that the majority of people using marijuana or cannabis do so simply for pleasure, as opposed to its medicinal benefit.[2] These pleasurable effects of euphoria are mediated through dopamine from the nucleus accumbens of the frontal cortex.[10] However, one's mood does not remain high or euphoric. On the contrary, cannabis also produces dysphoric reactions, including severe anxiety and panic, depression, paranoia and psychosis.[2] While these reactions are dose-related and more common in naïve users, anxious subjects and psychologically vulnerable individuals; they are, nonetheless, significant neurological alterations that can impact one's mental health and hence, one's lifelong functioning.[2,15] Further, in spite of skepticism, long term use of Cannabis has also been linked to a motivational syndrome.[6] A motivational syndrome presents like a depression and is symptomatic of apathy, dullness, lethargy, and impairment of judgment.[23]

Long-term effects of chronic cannabis use

The increasing prevalence of recreational cannabis use among the young population has stimulated debate on the possible effects of acute and long-term use. According to Feeney and Kapman[24] "while marijuana use is present among the adolescent population, research has shown that there can be devastating effects on health and well-being". There is considerable evidence that performance in heavy, chronic cannabis users remains impaired even when they are not actually intoxicated. These impairments, especially of attention, memory and ability to process complex information, can last for many weeks, months or even years after the cessation of cannabis use. Whether or not there is permanent cognitive impairment in heavy long-term users is unclear,[2,15,25] but as pointed out earlier, long term use can produce significant neurological changes in structure and physiology.

Although many studies argue about tolerance, dependence and withdrawal in Cannabis use,[6] these effects are substantial. Moreover, tolerance, dependence, withdrawal effects can develop over time from chronic cannabis use. To clarify, drug dependence is characterized as "a condition resulting from the prolonged and usually intense consumption of a drug or drugs which has resulted in psychological and/or physiological dependence on drug consumption. This dependence causes significant problems in one or more areas of the person's life".[26] Tolerance, on the other hand, occurs when an individual requires higher amounts and more frequent dosing of a drug to achieve the same initial effect.[27] It is the development of tolerance that leads some cannabis users to escalate the dosage of drug used, and also where the presence of withdrawal syndrome encourages continued drug use. Thus, chronic cannabis use can lead to cannabis dependence. Cannabis withdrawal syndrome has been demonstrated in both animal and human studies and shows many similarities to that of alcohol, benzodiazepine and opiates. These include restlessness, increased aggression, insomnia, anorexia and muscle tremors.[2] Like many drugs, these undesirable withdrawal symptoms cause the users to increase dosage intake and prompt a more chronic use of Cannabis. In one study, a daily dose of 180 mg of THC (equivalent to 1-2 smoke marijuana) for a period of 11-21 days is significant enough to cause or illicit withdrawal syndrome. As stated by Iverson "a portion of regular users of cannabis develop tolerance and dependence on the drug and have an increased risk of psychiatric illness" (2003).

Conclusion

In conclusion, marijuana (Cannabis) use has a significant impact on the brain. Many studies show that cannabis use has adverse effects on the brain structure, function and connectivity. Although some studies and articles stress its medicinal benefits, the detrimental impact of cannabis on the human brain far outweighs the medicinal advantages. Whether it is from an acute intoxication or chronic, long-term use of cannabis, the neurological damage involving cognition, memory, motor function and perception remains significant and troublesome. While many adolescents increasingly believe that cannabis is a harmless drug and continue to have a high prevalence of its use, more awareness and attention is needed so as to prevent any adverse outcomes in this young and growing population, who are still developing physiologically.

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Conflict of interest

The author declares no conflict of interest.

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