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Behavioral Effects, Cognitive Effects, and the Physiology of Marijuana Use

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Review Article

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Abstract

Marijuana is one of the most abused and misunderstood illicit drugs in many countries including the United States [1]. Since the 1960s, marijuana use has steadily increased over the years particularly among teenagers and young adults [2]. With an estimated 36 to 38 percent of high school seniors reporting ever having used the drug, this type of drug abuse is an issue that cannot be ignored [3]. One possible explanation for the increase in marijuana use is the confusion about the actual impact that the drug has on the user's health. Different and sometimes biased interpretations of the same data can cause confusion among even the top researchers in the field, not to mention the general public and policy makers [4]. Even though research in the area is increasing, little is still known about the underlying physiological basis for some of the most common behavioral and cognitive effects associated with marijuana use. In order to understand exactly what consequences are associated with marijuana use, researchers must first recognize the basic physiological systems that are affected. Many of the affected systems can cause a disruption in the normal cognitive and behavioral functioning of an individual, leading to questions about the individual's ability to perform certain tasks at their job and the operation of automobiles. Therefore, this manuscript will serve as an objective literature review on the behavioral and cognitive consequences of marijuana use. Furthermore, an attempt will be made to relate the underlying physiology to the behavioral and cognitive consequences of marijuana use.

Keywords: Marijuana; THC; Illicit Drug

Introduction

The cannabis plant, generally referred to as marijuana, was first named and classified by a Swedish botanist named Carl Linnaeus in 1753. The best estimates of where the plant originated suggest somewhere in central Asia [5], but the exact origins are difficult to trace. The archeological record regarding the use of cannabis dates back to around 8000 B.C. where the plant was first used to make fiber and rope. Cannabis was also reported to be used medicinally to cure many ailments in China dating back to about 2700 B.C. Some of the medicinal purposes of marijuana included using the drug as an anesthetic for headaches and for women giving birth, and also to control muscle spasms, insomnia, and indigestion [6]. Additionally, the plant was used for religious purposes in India beginning around 2000 B.C [7]. More recently, cannabis was grown in many areas of Western Europe to use its fiber to make rope, just as the first reported users of cannabis did. Western Europeans also used cannabis to

obtain the oil from its seeds [8]. In Europe, the plant was cultivated for centuries without the psychoactive properties of the drug being recognized. The intoxicating effects of cannabis continued to be overlooked by Europeans until 1846. At this time, an author named Theophile Gautier published Le Club des Hachichins, which described the effects of cannabis as a new pleasure. Many historians point to Gautier's publication as the beginning of widespread marijuana experimentation in Europe [5]. Several of the reported effects of marijuana intoxication include euphoria, enhanced senses, distortions of time and space, delusional thoughts, dissociated ideas, illusions, and under larger doses, hallucinations [7,9].

Cannabis was introduced to what would eventually become the United States in 1611. As is the case with most cultures using cannabis, the plant was first used to make fiber and rope. In fact, the American hemp flourished as a staple crop for over 200 years [5]. Most scholars agree that the use of cannabis for its intoxicating effects was probably introduced to the United States sometime in the mid 1800's by Mexican laborers. By the early 1900's, cannabis was thought to promote evil and was associated with increased violent crime rates, even though there was no scientific study to base any assumptions [7]. In 1937, the United States passed the Marijuana Tax Act, which ultimately led to the elimination of recreational and medicinal use of cannabis [5]. Subsequently, in 1942, marijuana was removed from the United States pharmacopoeia. Some researchers believe that the ban on marijuana only served to precipitate the desire, just as the result of prohibition on alcohol. During the 1960's, marijuana use was exciting and popular in most mainstream societies. Most marijuana users in this decade were university students, college students, and counterculture youth who used the drug for its intoxicating effects [8,9].

Currently, marijuana is the most abused illegal drug in the United States and many other countries. According to the United States Office of National Drug Control Policy [3], around 75 percent of the 20 million illegal drug users in the United States regularly use marijuana. In addition, approximately 60 percent of drug users who are dependent on an illegal substance are also reliant upon marijuana [3].

Another interesting detail to point out is that the tetrahydrocannabinal levels in marijuana have been steadily rising since the 1960's. Tetrahydrocannabinal, or THC, the primary psychoactive chemical in marijuana, was reported to have levels average about 1 percent in the 1960's and 1970's. However, more recently, the average THC levels found in marijuana ranged from approximately 6 to 14 percent [3,9].

Plants

There are a variety of cannabis plants that are grown and cultivated all over the world. The plants can range from small shrubs, usually the male plants, to tall bushy plants, usually female. In order for the plants to thrive, the tall females must use pollen from the male plants to produce seeds. This is accomplished with the help of a sticky residue that the female produces to catch airborne pollen and to protect the new seeds from insects. The residue is also used for its intoxicating properties due to its high THC content [5].

Different forms and potency of cannabis have led some researchers to argue that there is more than one species. In 1993, three species of cannabis were controversially identified: *Cannabis sativa, Cannabis indica, and Cannabis ruderalis* [10]. However, the prominent thought by most researchers in this area still believe that the latter two should not be treated as a different species than Cannabis sativa, but merely as two different phenotypes. Regardless, the plant labeled Cannabis indica is cultivated in more tropical, southern regions and has a high content of psychoactive ingredients. Thus, this type of cannabis is most widely used for its intoxicating effects. Cannabis ruderalis is usually grown in northern regions of the world and has a low content of intoxicating chemicals. This subtype, which is commonly called hemp, is used primarily to make fiber [11].

Forms of marijuana

Marijuana, in its many preparations, has been used for its intoxicating properties all over the world. Many slang terms that have been associated with marijuana include grass, pot, reefer, herb, ganja, and Mary Jane. Marijuana is usually prepared from the dried leaves and flowers of the cannabis indica plant. Most often, it is crushed and rolled in a cigarette or smoked in a pipe. Another common use of marijuana includes using the crushed leaves or flowers in a water bong, or hookah, which humidifies the smoke and allows for deeper inhalation [5,9].

Hashish, a more concentrated THC substance, can also be derived from the cannabis indica plant. Hashish can be found on top of the female cannabis plant in the form of sap or resin. It can also be prepared by boiling the cannabis plant and flowers to collect the resin. The resin is then readily available to smoke by itself or to make other preparations. The THC content in hashish ranges from around 10 to 20 percent [5,9].

Hash oil is an even more potent form of THC than hashish. Hash oil is prepared by extracting the THC from the cannabis plant using organic solvents such as alcohol. The THC content of hash oil can range anywhere from 15 to 30 percent. Hash oil can be inconspicuously smoked by placing a drop of oil on a regular cigarette. Hash oil can also be added to the ingredients in brownies or cookies to be easily consumed, rather than smoked [5,9].

Pharmacokinetics

The pharmacokinetic properties of marijuana are very complex. Hundreds of different substances have been identified in marijuana, making it difficult to accurately identify the exact pharmacokinetics. Many different cannabinoids have been found in marijuana, but the primary active ingredient is delta-9-tetrahydrocannabinal [8,9,12]. For the purposes of the rest of this manuscript, the terms THC, cannabis, and marijuana will refer to delta-9-tetrahydrocannabinal, unless where noted.

Like most intoxicating substances, marijuana can be administered several different ways. The most frequent routes of administration for marijuana include inhalation, orally, intravenously, and sometimes even rectally [13]. The route of administration does affect some of the pharmacokinetics of marijuana; therefore, this section will focus mainly on the most common use, which is inhalation. Before proceeding, it is also important to point out that there have been no differences identified in the pharmacokinetics of THC depending on the gender of the user [13].

Absorption

The absorption of THC through inhalation is very rapid and efficient. The lungs have a large surface area where a great deal blood flow passes through and can transport the drug throughout the body extremel y quickly [7]. Normal inhalation of marijuana causes about ten to twenty-five percent of the THC in the marijuana to enter the lungs. The actual amount of THC that is administered from inhalation depends upon several different factors. These factors have been identified by Gold [9] as:

1) The rate of inhalation
2) The duration of inhalation
3) The amount of smoke inhaled
4) The time that the user holds the inhalation in the lungs

The effects of THC are noticed within seconds to minutes of inhalation and can last approximately 2 to 3 hours without repeated exposure. The blood plasma levels of THC peak within about 15 minutes of inhalation [5].

Distribution

Distribution of delta-9-tetrahydrocannabinal is very rapid considering the high lipid solubility of the compound. The drug is distributed by the bloodstream to virtually all cells and tissues in the body, becoming particularly concentrated in the lungs, kidneys, and the liver. Due to this process, blood plasma concentrations of THC rapidly decrease and do not reflect the concentrations at pharmacologically active sites in the brain [14]. In other words, the blood levels of THC have not been shown to correlate with the “high” experienced by the user.

Metabolism

The metabolism of delta-9-tetrahydrocannabinal begins in the lungs almost immediately upon inhalation. However, most THC is metabolized in the liver by hepatic cytochrome P450 enzymes which convert it into approximately twenty other metabolites. The recently generated metabolites can either be active, meaning the metabolite can still have a psychoactive effect, or inactive [15]. The most prominent of the active metabolites, 11-hydroxy-delta-9-tetrahydrocannabinal is further metabolized into several other inactive metabolites including the 11-nor-9-carboxy-delta-9-tetrahydrocannabinal [5]. All of the inactive metabolites are not as lipid soluble as the other active metabolites of THC, and THC itself, and are therefore more easily excreted [16].

Excretion

The inactive metabolites of THC, including 11-nor-9-carboxy-delta-9-THC, are slowly excreted in the urine. The half life of 11-nor-9-carboxy-delta-9-THC is approximately thirty to sixty hours, depending on the fat content of the individual [17]. Eventually, all of the metabolites are excreted through the urine, kidneys, and feces. About one half of the THC in the body is removed in the form of these metabolites in the first twenty-four hours [6]. However, drug traces can still be detected up to a month after the THC was last ingested [7].

Mechanism of Action

Delta-9-tetrahydrocannabinal was first reported as the main pharmacologically active ingredient in marijuana in the early 1960’s. Over twenty years later, researchers discovered that THC acts on a pharmacologically distinct set of receptors termed the cannabinoid receptors [7]. The naming of these receptors has been somewhat of a controversy and many feel that the designation does not accurately describe the receptor. The reason for this is because all of the cannabinoids that act on the receptor

are not natural ligands. There have been two endogenous ligands discovered for the cannabinoid receptor. The first is an arachidonic acid derivative called anandamide, and the other is 2-arachidonyl glycerol. The function of anandamide and 2-arachidonyl glycerol in the brain is unclear [18], however, they may play a role in pain control [19].

The cannabinoid receptors are primarily located throughout the brain and central nervous system Butovsky E, et al. [20]. In the early 1990's, researchers began to study more peripheral effects of marijuana use and discovered that cannabinoid receptors are also found outside of the CNS. The receptors originating outside of the CNS were slightly different from the receptors found in the CNS, and therefore a distinction was made. The receptors originating inside the CNS were termed "cannabinoid-1" and the receptors found outside the CNS were termed "cannabinoid-2" [21]. High densities of CB-1 receptors have been found in the basal ganglia, cerebellum, frontal cortex, and hippocampus [22]. CB-2 receptors are located in the lymphoid system, the heart, testis, spleen, immune system, and other body tissues that involve pain responses [5,21].

The tetrahydrocannabinal receptor is a seven helix receptor, G-protein coupled, inhibitory to adenylate cyclase, and binds many different cannabinoids. The receptors are located on presynaptic nerve terminals and inhibit calcium ion flow and facilitate potassium flow. Specifically, after THC binds to the cannabinoid-1 receptor, G-proteins become activated. The G-proteins then act on adenylate cyclase, calcium, and mitogen activated protein kinase. The inhibition of adenylate cyclase produces a decrease in cyclic adenosine monophosphate (cAMP), which causes a decrease in cAMP dependent protein kinase. Finally, this process concludes by the protein kinase decreasing potassium channel fluxes. Simply, the activation of the cannabinoid receptors inhibits the release of gamma amino butyric acid (GABA) from the presynaptic nerve terminals [7,18,23].

THC or the endogenous anandamide increases dopamine levels in the nucleus accumbens by blocking the dopamine transporter [7,19]. THC has also been shown to decrease the rate of dopamine synthesis in the mesolimbic system by approximately 16 to 37 percent [24,25]. Additionally, the chronic administration of THC has revealed a down regulation of CB-1 receptors in the nucleus accumbens as well as several other areas in the brain [26,27].

Marijuana addiction has long been a source of debate between anti-drug organizations and pro-marijuana groups [28]. However, a great deal of research has shown that the physiology of marijuana ingestion is similar to that of other addictive drugs. The enjoyable and addictive properties of THC are thought to be mediated by the activation of the CB-1 receptors in the forebrain. Experimental research has shown that the axonal projections from the mesolimbic pathway that end in the nucleus accumbens are certainly responsible for the reinforcing effects of many drugs including cocaine, amphetamines, and marijuana [7,29]. In fact, all of these drugs cause the release of dopamine the nucleus accumbens, which is a central feature in drug addiction. One major difference between cocaine, amphetamines, and marijuana, however, is that cocaine and amphetamines are more potent dopamine agonists than marijuana [18,29]. Although not popularized as a major addictive drug, 220,000 people were admitted to a substance abuse treatment center for marijuana dependence in 1999 [30].

Acute Intoxication

The uses of cannabis have greatly fluctuated since its discovery thousands of years ago. In all of the cultures that have used the plant, eventually discovery of the psychoactive properties has lead to widespread abuse. Cannabis has been used for its psychoactive effects a number of ways, but the easiest way to attain the desired effect is through smoking the substance [5]. The psychoactive effects of marijuana can be fully noticed within seconds to minutes of inhaling the drug. Researchers have discovered that as little as 2½ mg of THC in a typical dose of marijuana is enough to produce measurable subjective and objective effects [31].

Marijuana has been shown experimentally to produce a wide variety of effects in both humans and in non-human animals. Several of the physiological effects that accompany THC ingestion appear consistently with reliable dosing [9]. One of the most common physiological effects of marijuana use occurs approximately an hour after the drug is used. The blood vessels in the eye will become dilated, which causes the eyes to become bloodshot. The eyelid muscles appear to become fatigued and begin to droop. It is this hallmark characteristic of marijuana intoxication that is the most universal and recognized [32]. A heart rate increase is another quite common characteristic associated with marijuana intoxication. Paton & Pertwee [33], among several other researchers, have reliably produced the increase in heart rate with human participants [5,8,9]. Some of the participants' heart rates even exceeded an unbelievable

150 to 160 beats per minute [33]. Marijuana intoxication also reliably produces dry mouth and an intense desire to drink water. An extreme craving for a certain type of food, commonly called "the munchies" is produced as well (5). Marijuana users report several other effects of acute exposure including enhanced senses, distortions of time, dissociated ideas, and under larger doses, hallucinations [7,9].

Behavioral Effects

The behavioral effects of marijuana have been researched for decades, using both animals and humans as subjects. In fact, the relative ease of objective observation gave way to the first systematic studies on the effects of marijuana. However, many of the behavioral effects and the underlying physiology associated with marijuana remain an enormous subject for debate [4]. These studies have many difficult confounds to contend with such as unpredictable dosing and the inconsistencies between the subjective high of the user and the blood plasma levels of THC. As a consequence, studies on the behavioral effects of marijuana need to be interpreted carefully due to the many confounds that can manipulate the results [34]. For example, many of the leading marijuana researchers disagree on some of the long term health effects that the drug has on an individual. Different, and in many cases, biased interpretations of the same epidemiological data can cause confusion among even the top researchers in the field, not to mention the general public and policy makers [4]. Regardless, it is still important to obtain an overall objective view of some of the most consistent behavioral effects of marijuana use and the underlying physiological systems that are affected. This section of the paper will review the effects of marijuana use on several different behavioral parameters including sleep, aggression, motor activity, coordination, and reaction time. The underlying physiological basis for these behavioral effects will also be mentioned.

Sleep

Marijuana users have often reported that while under the influence, they will obtain a better night of sleep than without the drug. In fact, researchers have discovered that smoking marijuana has a sedative effect which causes drowsiness and increases sleep time after a low to moderate dose of the drug. Confirmatory research has reported that 10mg to 20mg of marijuana have been shown to cause minor changes in normal sleep patterns, as evidence by electroencephalography. Specifically, there is a slight reduction of rapid eye movements in REM sleep and stage four sleep is prolonged [35]. After a large dose of marijuana (70 mg) however, the drug is reported to interfere with sleep, causing restlessness and anxiety [36]. Experimentally, large doses of marijuana have been shown to cause severe changes in EEG sleep stage patterns. The severe changes include a reduced amount of REM sleep as well as an extreme reduction in stage four sleep [35,36]. Among their many complaints, heavy chronic marijuana users often report significant insomnia. It is interesting to point out that this symptom seems to be alleviated after the drug is discontinued [33].

The sleep cycle is thought to be chemically regulated through wakefulness promoting substances and sleep promoting substances such as adenosine [29]. A study by Murillo-Rodriguez, et al. [37] tested a hypothesis that the endogenous cannabinoid, anandamide interacts with adenosine to promote sleep in rats Hampson RE & Deadwyler SA [38]. The researchers surgically implanted a cannula into the basal forebrain of Sprague Dawley rats in order to accurately collect and measure adenosine levels. The groups of rats were injected with either dimethyl sulfoxide (vehicle), anandamide, SR141716A (CB-1 antagonist), or anandamide and SR141716A. The results revealed that the rats which were exposed to anandamide had significant increases in the levels of adenosine in the basal forebrain. Behaviorally, the rats exposed to THC had a quicker onset of sleep and longer lasting sleep than the controls. The CB-1 agonist blocked the adenosine increases, thus blocking the quick onset and long sleep. Based on this research, it can be implied that anandamide somehow interacts with adenosine to induce and promote sleep. However, the exact mechanism as to how this process occurs has yet to be uncovered.

Aggression

Marijuana use and its association with aggression has generated a great deal of literature, research, and of course, controversy. From the beginning, historians and linguists have linked marijuana users and violence, deriving the word "assassin" from "hashish" [15]. As previously reported, many of the early ideas regarding marijuana use did not undergo any scientific study and were supplied merely by hearsay evidence [7]. Aggression was undeniably one of those ideas. Even much of the empirical research on the topic appears to be contradictory [5].

Most researchers now agree that low to moderate doses of marijuana (< 20 mg) does not cause aggression in normal individuals with no underlying psychological pathologies [5,15]. Marijuana seems to decrease aggressive feelings and may actually increase friendliness and hospitality. In some cases, however, high doses of

marijuana (50 mg to 100 mg) have been shown to produce aggression in individuals who are under intense stress and otherwise prone to hostile behavior [34]. Marijuana has also been shown to precipitate psychoses in individuals with mental disorders. Choptra & Smith [39] reported that the positive symptoms of their patients with schizophrenia were severely intensified under the influence of marijuana. Specifically, the elevated levels of paranoia that occurred in the majority of the patients were among the most intense changes.

Due to the somewhat conflicting nature that most of the research dealing with marijuana and aggression, no definitive physiological mechanisms can be completely associated. It can be implied however, that the disruption of communication between neurons in the amygdala, the hypothalamus, and the periaqueductal grey matter play a role in unpredictable marijuana induced aggression. Even though the amygdala has not yet been reported to have a high expression of cannabinoid-1 receptors, the structure is in very close proximity to area with a great deal of receptors, the hippocampus [22,29].

Motor activity

Low to moderate doses of THC, 7.5 mg to 15 mg in this case, have been shown to precipitate some effect on gross motor activity [40]. The effect that occurs seems to be biphasic in most individuals. That is, there appears to be a general increase in motor activity in the primary stages of intoxication, followed by a longer lasting general decrease in activity [40]. The reduction of activity in the latter stages of impairment resembles the decrease seen with alcohol intoxication and with benzodiazepine use [15]. Low to moderate doses of the drug have also been shown to produce postural instability and a "total body sway". The intoxicated individual seems to have balance problems while standing up, and may rock back and forth while sitting down [41].

Extremely large doses of marijuana (> 250 mg) have been reported to produce ataxia, a loss of motor control, and tremors [42,43]. Large doses of marijuana have also been reported to produce myoclonic movements in the legs, and in some cases, the facial muscles. In most cases of marijuana induced myoclonus, the user is unaware of the inappropriate muscle movements, most likely caused by a disruption with divided attention [44]. The complex motor disturbance findings associated with marijuana exposure can be attributed to the high density of CB-1 receptors located in basal ganglia and cerebellum [45].

Coordination

Marijuana exposure undoubtedly causes a dose dependent decline in coordination. Various studies have shown that even minimal applications of the drug, 5 mg to 10 mg of THC, can cause significant impairment of performance in simple motor tasks (15,33,46). Small doses of THC (5 mg to 15 mg) have also been shown to impair complex tasks, such as fine movements and hand-eye coordination. The accuracy of nearly all of the coordination tasks appears to be dose dependent (Ashton, 1999) [15].

In a study by Reeve, et al. [47], participants were required to smoke a marijuana cigarette until "high" and then perform a standard roadside sobriety test. The test is used by law enforcement to determine the extent that an individual's coordination is impaired, thus approximating the degree of intoxication. Overall, almost all of the participants (94 percent) failed the sobriety test at 90 minutes. Additionally, 60 percent of the participants failed the test at 150 minutes. Although this study shows an overall deficit in marijuana intoxicated participants, a greater control of the methods would undoubtedly serve to improve the quality of the experiment. For example, rather than allowing the participants to smoke the marijuana cigarette until "high", they should be required to take the same amount of puffs, hold the smoke in the lungs for the same amount of time, and wait the same amount of time until the next puff. It would also be ideal to record physical measures such as heart rate and collect blood plasma samples in order to roughly correlate the participants "high" with their degree of failure.

Other studies have also reported coordination deficits associated with marijuana intoxication using tests such as the critical tracking task, stop signal task in humans [48], and using a rotorod treadmill in mice [49]. It is also important to mention that coordination deficits have been shown to persist for twenty four hours, and in some cases, a few days after the participants used marijuana [19,50].

Reaction time

Marijuana intoxication has been reported to cause a decrease in reactivity. This may be associated with its sedative effects that result in mental slowness and fatigue [51]. Individuals intoxicated from marijuana may require additional time to respond to questions and to comprehend new information. However, some studies have shown that this is not always the case. Wadsworth, et al. [52] reported no significant differences on a computer based simple reaction time with participants exposed to marijuana compared to the control group. Their results also revealed that there were no detrimental

effects on the speed and accuracy of comprehending and understanding new information. In another study, it was shown that only accuracy, not speed, is affected by marijuana use when performing complex and choice reaction time tests [5].

An understandably important area where marijuana has been shown to affect reaction time is driving ability. One of the more important factors in safe driving, reaction time impairments have been shown to be dose dependent. In one study using a driving simulator to assess marijuana impaired reaction time, every participant showed some degree of impairment. The deficits were noticeable after both small doses, 5 mg to 10 mg, and larger doses, up to 25 mg of THC. The deficits associated with the smaller doses of THC lasted a few hours, while the larger doses showed impairment lasting anywhere from 4 to 8 hours [53]. However, marijuana's direct link to traffic accidents is another somewhat controversial topic. The controversy results from the research that indicates most drivers in pharmacologically induced automobile accidents who have cannabinoids in their system also have high blood alcohol levels. These two drugs have been shown to have additive effects on driving ability, and therefore it is difficult to determine which drug causes more impairment [46]. A Department of Transport study performed in the United Kingdom showed that 33 out of approximately 1,300 road accident victims had detectable cannabis in their system, 60 percent of which were not intoxicated with alcohol [54] Other countries have had similar reports and similar results including Australia, Norway, Canada, the Europe, New Zealand, and the United States [15]. Although using small percentages, these studies support the claim that marijuana may in fact contribute to automobile accidents.

Coordination and reaction time are both certainly linked to the same gross physiological systems throughout the motor pathways and the cerebellum. It is very important to try and understand deficits that occur with these behaviors, especially with their implication to tasks such as driving automobiles and flying aircraft. The specific motor pathways thought to be involved with coordination and reaction time include the lateral corticospinal tract, tectospinal tract, and the lateral and medial reticulospinal tracts [29]. Due to the extremely complex nature of motor movement, it is difficult to pinpoint an exact location where a disruption would cause a specific disturbance in coordination or reaction time. However, deficits can be simply attributed to a disruption in normal communication of the large number of CB-1 receptors located in these motor pathways and cerebellum.

Additional research in this area is required in order to clear up any inconsistencies between studies. Coordination and reaction time are important issues to understand, especially with their relation to marijuana ingestion. The obvious implications of the reduced ability to react to the environment and coordinate movements are evident when discussing the operation of machinery or automobiles. The most promising studies in many areas of marijuana research have employed the use of brain imaging techniques such as PET, MRI, and FMRI to pinpoint the exact locations and mechanisms involved. Marijuana research using these techniques focusing on the motor pathways provides an exciting opportunity for future research.

Cognitive Effects

The effects of marijuana have been studied using an assortment of cognitive tests. For example, a study performed in the United States revealed that marijuana users perform less efficiently than control subjects in cognitive tests measuring attention and executive functions [55]. The results of many of the other studies in this area indicate that overall, marijuana appears to negatively affect cognitive processing speed and is consequently inhibitory to many functions [9]. Recently, researchers have focused their attention on the neurocognitive deficits associated with drug abuse. In animals, the use of THC has been shown to alter neurotransmission in the frontal cortex, which is thought to mediate attention and other executive cognitive functions [56]. The next section of this manuscript will review the research dealing with the use of marijuana and its association with attention, memory, sensation and perception, and emotion.

Attention

Several animal studies have indicated that acute exposure to THC induces a severe attention impairment that can last up to fourteen days after the final dose of the drug [56,57]. The use of THC has been shown to disrupt tasks that involve sustained attention and alertness in humans as well (McKim, 2003) [5]. Solowij [57], Solowij, et al [58] reported that THC intoxicated subjects have an impaired ability to filter out relevant information and to focus attention. In fact, many researchers have reported that their subjects are not able to complete the tasks that are required for their specific experiment. These reports indicate that the subjects become too distracted, usually by their own thoughts, to continue the research [5].

As noted earlier, CB-1 receptors are found in high concentrations in the frontal and medial temporal lobes of the cerebral cortex [59]. These areas of the cortex are

thought to be critical to sustained attention in humans. It is also believed that attention depends upon the continuous activation of neurons in the frontal lobe, and the repeated interactions between frontal and posterior brain regions [60]. In fact, an FMRI study on the effects of marijuana and attention observed specific areas of the brain that were termed "the attentional network." The network included the bilateral dorsal medial and lateral prefrontal cortices, the parietal cortices, the occipital regions, and the cerebellum. Their results revealed that active marijuana users had a decrease of activity throughout the attentional network compared to controls. However, an increase of activity was reported in the right superior frontal gyrus and the parietal cortex, which are proposed to be compensatory brain regions for attentional processes [61]. Attention has been reliably shown to be altered under the influence of marijuana. An explanation for the decreased attention capacity in marijuana users could be that the compensatory mechanisms for the process may not function as well as the normal network.

Memory

One of the more well known deficits associated with marijuana use is short term memory loss. Marijuana users tend to get distracted easily and therefore lose track of a conversation or a particular topic [29]. This has been identified as a disruption of working memory, which is the ability to control attention, filter out distracting influences, and manage active representations of present events [62]. According to Ilan, et al. [60], working memory is dependent on the sustained activation of neurons in the frontal lobe and the repeated interactions between those neurons and posterior brain regions. There also seems to be a disruption with consolidation, converting working memories to long term memory, which has been shown to depend upon the functioning of the hippocampal formation [29,63]. Hippocampal functioning is believed to require the presence of the neurotransmitter acetylcholine in order to operate correctly [64,65]. Activity of the acetyl cholinergic axons that project from the medial septum to the fornix of the hippocampus produce theta waves. Hippocampal theta waves have been shown to positively influence the process of long term potentiation and long term synaptic changes [29]. Carlson [29] defines long term potentiation as the "long term increase in excitability of a neuron to a particular synaptic input caused by repeated high frequency activity at that input" (pp.416). Gamma amino butyric acid (GABA) and glutamate are also important neurotransmitters that are indirectly involved in hippocampal functions and memory formation. The role of these two neurotransmitters in the forebrain is to modulate the cholinergic pathways and to active NMDA receptors, which are also required for long term potentiation [45,65]. Recent research has in fact shown that THC disrupts the standard functioning of the hippocampus, which has a high density of CB-1 receptors. Specifically, THC reduces glutamate through G-protein mediated inhibition of calcium channels. Also, these channels do not release a sufficient amount of acetylcholine and GABA from the hippocampus, which are believed to contribute to long term potentiation and synaptic strength [66].

While the physiology of working memory and long term potentiation has been shown to be disrupted by marijuana ingestion, few studies have been conducted on the actual effects on long term memory. Long term memory is defined by Carlson [29] as a "relatively stable memory of events that occurred in the more distant past, as opposed to short term memory" (pp. 454). A marijuana induced disruption of the hypothalamus, and subsequently long term potentiation, would imply that long term memory must be impaired. However, in the few studies that are concerned primarily with this issue, the conclusions all report that the presence of impairments are unclear, but that long term memory may remain intact [7].

Long term memory is a very important issue to discuss regarding drugs of abuse, including marijuana. Due to the many potential confounds that can arise from a long term memory study; the process of experimentation will undeniably be difficult. The investigation of animal models may provide better a better avenue of experimentation with a long term design. The benefits of using animal models include simplicity, convenience, and most importantly a better degree of experimental control [67].

Sensation and perception

The perceptual changes that occur as a result of marijuana intoxication are one of the main reason individuals experiment with and abuse marijuana [9,8]. Marijuana intoxication is thought to produce changes that affect every sensory modality. Nearly every use of marijuana generates a reported increase in sensitivity to sensory input at most modalities [5,15]. However, little empirical research has focused on marijuana intoxication and sensation and perception. Most of the few studies that handle the issue were published in the 1970s and 1980s. Unfortunately, this research is now be considered to be poorly designed and improperly controlled [45]. Regardless, it is still important to discuss some of these studies in order to gain a foundational understanding of the marijuana and sensation and perception association in order to point out directions for future research.

A study by Russo, et al. [68] tested the sensitivity hypothesis on visual acuity in Moroccan night fisherman. The researchers used a portable scotopic sensitivity tester to measure the levels of dark adaptomety and scotopic sensitivity between three volunteer fishermen. Before the study commenced, all of the participants were given an ophthalmic evaluation. All of the participants' results were in the normal range for visual acuity, external ocular movement, papillary symmetry and reaction, and funduscopic examination. The participants were tested before and 30 minutes after smoking. The results of the study did in fact show that improvements in night vision occurred after smoking 10 mg to 20 mg of marijuana. In fact, all of the participants were able to perceive the dark adaptomety stimulus at the lowest possible instrumental setting after marijuana ingestion.

Other visual changes have been reported to occur after chronically smoking marijuana, such as visual information processing and depth perception, and have been shown to persist for months after marijuana use is discontinued [15,69]. The visual effects of long term marijuana use have also been studied in Costa Rica. No significant differences were observed on any of the visual measures used or the presence of eye disease between chronic users and non users. However, there were several reported marginal visual effects of chronic marijuana use. Some of the subtle effects included increases intraocular pressure, increased photosensitivity, decreased dark adaptation, and decreased acuity on the Snellen charts [70]. One problem that has occurred in studying the long term effects of marijuana on vision, especially in Costa Rica, has been the occurrence of high tobacco use. This vital confound needs to be addressed in order to differentiate the long term effects of tobacco versus the long term effects of marijuana. Because the same populations that use marijuana also report a high incidence of tobacco use [71], this problems is not likely to be easily solved. A possible solution could be the use of animal models to study the long term visual effects of marijuana use, such as primates. As discussed earlier, animal models provide better experimental control and simplicity, which would be ideal for this type of research.

Marijuana has also been reported to acutely increase sensitivity to hearing as well as vision [15]. In the most comprehensive auditory study on the effects of marijuana to date, Liedgren, et al. [72] performed an enormous battery of auditory tests between a group of marijuana intoxicated individuals and a placebo group. The tests included pure tone threshold, speech reception threshold, speech discrimination, and acoustic impedance measures. The acoustic impedance measures were performed to identify any disruptions in the sensation of sound. The results of this study revealed that all of the auditory test scores of the intoxicated participants did not differ from the test scores of the placebo group.

The implication of the previous study indicates that marijuana does not produce sensitivity to hearing, possibly just the perception that it does so. The auditory system and its pathways through the brain are very complex, and a disruption of auditory perception can occur in many regions along the way. For example, a disruption in the superior olivary complex, which is located in the medulla, is thought to have an inhibitory effect on the locating the source of a particular sound [29]. Furthermore, a disruption of the parabelt region of the anterior temporal lobe would produce a skewed analysis of complex sounds, thus resulting in difficulty understanding normal speech and possible auditory hallucinations [73]. Therefore, a disruption in many different sites in the brain can lead to the disturbance in audition, as reported by marijuana users.

An additional reported sensitivity to a sensory modality has been the sense of smell, or olfaction. Marijuana users often report that their ability to notice changes in odor is enhanced after smoking. However, research has seemed to ignore this sense in favor of the others. Until olfaction gains more popularity in the research field, the evidence for a marijuana induced increase in olfactory sensitivity remains unclear. Perception in the olfactory system depends on the undisturbed process of relaying information from the olfactory bulbs to specific regions of the brain. Research has shown that neurons send information through the olfactory tracts in the brain to the amygdala, the pyriform cortex, and the entorhinal cortex. Indirectly, information is also passed to the hippocampus, hypothalamus, and the orbital frontal cortex. Thus, if any of these regions are disrupted, as they appear to be with marijuana intoxication, perception of the sense of smell can be altered [29]. This alteration, however, will continue to be insufficiently understood until research begins to focus more on the sensation and perception of marijuana intoxication.

The sense of touch in marijuana users has been reported to be altered under periods of intoxication. Unlike taste, the effects of marijuana on the sense of touch can be objectively monitored. For example, marijuana intoxication has been shown to have analgesic properties that would undoubtedly appear as a function of a pain response [5]. In fact, several studies have reported that the presence of THC does increase pain thresholds in humans [5,8,18]. In 2005, researchers reported the discovery of CB-1 and CB-2 receptors on nerve fibers in

the skin [74]. More specifically, the cannabinoid receptors have been found on the terminals of nociceptive neurons. Nociceptors, or noxious stimuli detectors, are a type of pain receptor that can be activated by extreme pressure. These afferent nociceptors project to the dorsal horn of the spinal cord. The sensation of pain is then mediated by the spinothalamic tract, which is the pathway from the spinal cord to the ventral posterolateral thalamus to the somatosensory cortex [7,29]. According to Julien [7], the analgesic effects of marijuana are produced "by modulating both sensory input from peripheral sites of tissue injury as well as reducing the release of nociceptive neurotransmitters in the dorsal horn of the spinal cord" (pp. 567). In other words, marijuana exposure disrupts the normal communication of pain signals from the site of injury to the spinal cord.

There is more to the sense of touch than just extreme pressure and pain. For example, touch also implies the sensation of gentle pressure and light contact. This is a very important issue when discussing the sense of touch because of the two different physiological mechanisms at work. Extreme pressure and pain are transmitted to the brain via the spinothalamic tract, while light touch information is sent by way of the corticospinal tract [29]. Marijuana intoxication and its effects on gentle pressure and light contact have yet to be studied. Therefore, no conclusions can be made about the actual perceptions of light touch until empirical research focuses on the issue.

One of the more well known sensory alterations associated with marijuana exposure is the enhanced appeal of certain foods. Testing the enhanced sensory sensitivity to taste is a very difficult task to undertake due to many possible confounds. However, a study by used increases in salivary flow to determine the extent of enhanced taste. During the study, the researchers used sweet, sour, salt, and bitter food as stimuli. They monitored several baseline levels before and after marijuana intoxication. The results revealed that salivary flow was actually negatively correlated in every condition with blood plasma levels and the subjective high of the individual.

It is difficult to determine whether exposure to marijuana affects the actual sensation of taste or merely the perception. Regardless, the information associated with taste eventually reaches amygdala, hypothalamus, and basal forebrain [75]. As reported earlier, these areas of the brain are also directly and indirectly related to high concentrations of CB-1 receptors. Clearly, a disruption of the receptors in these regions would cause interference with taste perception.

Marijuana users have reported sensory changes that occur on every modality [5,15]. However, the research dealing with these issues suggest there may not be any actual effect on most of the senses, besides possibly vision and touch. suggests that most of the effects of the drug on perception are related to the disturbances in memory and cognition instead of any sensory modality. As discussed, marijuana does in fact appear to affect specific brain regions that are involved with many perceptions.

Emotion

One of the main reasons for the recreational use of marijuana is for its exciting and joyous effects [76]. Marijuana has a wide variety of effects on mood and emotion which is often influenced by the different types of environments. One of the more common responses to acute exposure of marijuana is a strong feeling of excitement characterize by uncontrollable laughter and euphoria. This reaction is typically seen when marijuana is used in a relaxed social setting. When the drug is taken alone or in a quiet environment, users may experience a more dreamy state where sensory perceptions often seem to be more intense and enjoyable. Everyday ordinary thoughts can turn into significant insights and some users claim that their true creativity is only seen when they are under the influence of marijuana [5]. Researchers have studied many different variables that may affect a user's response to marijuana. The two main factors that appear to influence the user's mood and emotion under the influence of marijuana the most are:

1) the environment where marijuana is used
2) the mood of the other participants

A study performed in 1978 showed that self-ratings on mood correlated with the mood of other subjects in the experiment. The amount of marijuana consumed was not a factor. The researchers concluded that after smoking marijuana, an individual can become more prone to having their mood influenced by other people [77].

Even though many people claim that marijuana elevates their mood, both positive and negative effects have been associated with the drug. Severe depressive episodes and acute panic reactions have been observed at high doses, usually around 50 mg to 100 mg. Some of the paranoia symptoms are associated with the feeling of losing mental control. Several studies have shown that 50 to 60 percent of marijuana users have experienced at least one anxiety attack while they were under the influence [7,9,28]. A study performed by Rodriquez de Fonseca, et al. [78] analyzed the effects of HU-210, a substance that mimics the effects of marijuana in the central nervous systems of rats. The results revealed that

one injection of this substance reduced the release of corticotrophin-releasing factor, a neuro chemical found in the amygdala that normally increases during emotional times or periods of stress. This study implicates a chemical disruption in the CNS that results in a cognitive change.

Amotivational Syndrome

Chronic marijuana use has been associated with what is known as "amotivational syndrome." The syndrome is a description of many of the long term behavioral effects associated with extended marijuana use. Symptoms may include apathy, loss of interest in goal-oriented activities, lack of motivation and ambition, inability to concentrate for long periods, and impaired verbal capacity [5]. Users seem to lose focus of their future plans, causing many individuals to either drop out of school or quit their jobs. The only worry for individuals with amotivational syndrome is their present state, which usually consists of regressive and childlike thinking [79]. A reported 40 to 50 percent of young adults who have been admitted to a treatment program for marijuana exhibit a depressed state of mood that has been attributed to the amotivational syndrome [80].

The exact etiology of this condition is not fully understood. Human computed tomography studies have not revealed any evidence of major cerebral atrophy in long term marijuana users [81]. However, structural brain changes have been observed in rhesus monkeys after being exposed to marijuana for 2 to 3 months. The evidence revealed synaptic abnormalities that were found in great concentration in the hippocampus, septal region, and the amygdala [82]. Another study involving rhesus monkeys revealed that the subjects who were exposed to marijuana daily for one year were not as willing as the controls to work for a reward. The monkeys were required to lever press in order to receive a banana flavored pellet. They were on a progressive ratio schedule of reinforcement, in which the number of lever presses increased each time a reinforce was delivered. The marijuana exposed monkeys had a lower breaking point than the controls, revealing a lower motivation. The authors did not relate these findings to a loss in the ability to respond or a lack of appetite, based on other tasks performed in the study [83].

There have been several claims that severe brain damage occurs in humans as a result of long term marijuana exposure, which leads to amotivational syndrome. However, little scientific research has been able to support this idea No major structural brain damage has been found in humans to help support the idea of an amotivational syndrome, but it is clear that marijuana does affect several short term behavioral and cognitive factors. Based on the conclusions of the available recent research, it appears that long term exposure to marijuana does not cause damage to the brain or significantly alter its physiology [7,18,45,84].

Tolerance

Tolerance is defined by Julien [7] as a "Clinical state of reduced responsiveness to a drug. Can be produced by a variety of mechanisms, all of which require increased doses of drug to produce an effect once achieved by lower doses" (pp. 674). For years there has been some disagreement between researchers about the development of tolerance effects of marijuana. Some relatively recent empirical research has shown that marijuana does indeed produce forms of tolerance [5]. In animals, tolerance to THC has been shown to develop rather quickly. Some researchers have reported that behavioral tolerance develops within about a week of daily THC injections on operant behavior. This tolerance seems to last at least a few weeks [85]. Other researchers have reported the presence of metabolic tolerance. For example, a lethal dose of THC given to normal pigeons, 180 mg, did not have a lethal effect when given to tolerant pigeons [26].

In humans, several experiments have shown that pharmacodynamic tolerance develops to the subjective effects of THC with consistent doses. Some studies have shown that this has occurred only with consistent high doses of THC [86,87], and others have shown that tolerance developed even with low consistent doses [88]. Tolerance has not been shown in humans to appear due to changes in absorption, distribution, or metabolism of THC. Rather, the tolerance effects are thought to be associated with a decrease in the number of cannabinoid receptors in certain regions of the brain [26].

Many users report a reverse tolerance, or sensitization to the drug. Reverse tolerance is the idea that the more THC a person consumes, the more it builds up in the body. Over time, the buildup allows for the user to consume less THC to feel the same "high". For example, a naïve user would have to smoke two joints to get high. At the next session, it would only take the user one joint to produce the same "high" as previously smoking two joints. However, reverse tolerance has not been replicated in the laboratory setting. The prominent idea in this area is that with experience, users may learn to inhale more efficiently and allow for more THC to enter their systems more quickly [5].

Withdrawal

Withdrawal symptoms are defined by Carlson [29] as "the appearance of symptoms opposite to those produced by a drug when the drug is administered repeatedly and then suddenly no longer taken" (pp.106). Although there have been no severe withdrawal effects reported by marijuana users or their physicians, some symptoms do seem to occur after consistent drug use in animals and humans. In one animal study, a withdrawal symptom appeared after an extended administration of high doses of THC. However, the only symptom that emerged was an increase in motor behavior. Researchers believe that there are indeed more severe symptoms of withdrawal associated with THC, but do not emerge because of the long half life and the active metabolites of the drug [89] In humans, withdrawal symptoms can occur after prolonged, and in many cases, brief exposure to marijuana. These symptoms may appear as hot flashes, sweating, hiccups, appetite loss, irritability, insomnia, and anxiety [88,87]. Olds ME & Forbes JL [90] the central basis of motivation: Intracranial self-stimulation studies.

Conclusion

The present manuscript has served as a literature review on some of the more well known and reliable behavioral and cognitive consequences of marijuana use. An attempt has been made to relate the observed deficits in the behavioral and cognitive parameters to the underlying physiological systems that are most likely to be affected. This manuscript has provided evidence that multiple physiological systems are affected by marijuana exposure. Some of the more gross physiological systems involved and disrupted by marijuana exposure include 1) the basal ganglia and cerebellum which are responsible for the motor deficits and coordination problems, 2) the hippocampus, which is involved with certain aspects of memory, 3) the limbic forebrain, which is implicated in attention processes, 4) the amygdala which is involved in emotion, and 5) the frontal regions of the cerebral cortex which involve movement planning and abstract thinking. In addition, marijuana has been shown to facilitate adenosine levels, a chemical thought to be involved in the control of sleep.

A great deal research has been conducted on the physiological effects of marijuana, however there is still very much unknown about the neurophysiologic effects of cannabis on the brain .Future directions for marijuana research should include a re-examination of many early studies on basic behavioral and cognitive processes, especially on sensation and perception. Basic marijuana research provides the foundation for more complex studies, but it is currently difficult to build on the early experiments in this area. For example, most of the research on marijuana before the 1990s is now thought to be poorly designed and improperly controlled [45]. Future research should also continue to use the new advances in technology such as PET, MRI, and fMRI. Using these techniques in addition to re-addressing some basic marijuana research will allow future researchers a better picture of the physiology of marijuana and a strong foundation to build upon.

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