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EFFECT OF MARIJUANA ON THE CENTRAL NERVOUS SYSTEM

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SUMMARY
Marijuana is the dried buds and leaves of the Cannabis sativa plant also known as hemp. Marijuana plants contain more than 400 chemicals, 60 of which fit into a category called cannabinoids. Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive component of the plant. There are CB1, CB2 and GPR55 cannabinoid receptors. All are members of the super family of G protein-coupled receptors (GPCRs); both CB1and CB2 are coupled to $G_{i/o}$ proteins but GPR55 couples to $G_{\alpha 11-13}$.CB1 are widely concentrate in specific brain areas that govern pleasure, movement, learning and memory and pain, which includes amygdale, basal ganglia, brain stem, cerebellum, hippocampus, hypothalamus, neocortex, nucleus accumbens, spinal cord. The effect on dopamine release most likely explains why Δ^9-THC can induce signs of reward in animals. As THC enters the brain, it causes the user to feel euphoric or high by acting on the brain's reward system, which is made up of regions that govern the response to pleasurable things. A few users experience dysphoria, anxiety, even frank paranoia symptoms. The cannabinoids have also been shown to impact different stages of memory including encoding, consolidation and retrieval. Cannabis use has been implicated as a potential cause, aggravator, or masker of major psychiatric symptoms, including psychotic, depressive, mood and anxiety disorders. Chronic exposure to Δ9-THC and other cannabinoid receptor agonists generally leads to biological adaptive mechanisms that may be related to the phenomenon of tolerance and also withdrawal symptoms which include restlessness, irritability, mild agitation, insomnia, nausea, sleep disturbance, sweats and intense dreams. From a medical point of view, marijuana is a valuable drug. It lowers certain types of pain; has anti-anxiety, anti-inflammatory and anti-spastic effects; and enhances appetite. It also blocks vomiting.

KEYWORDS: Marijuana; Cannabinoids; Cannabinoid receptors (CB); Delta-9-tetrahydrocannabinol (THC); Dopamine; Reward System.

1. INTRODUCTION

1.1. marijuana

Marijuana is the dried buds and leaves of the Cannabis sativa plant also known as hemp plant (David, 2011). For 5 millennia, Cannabis sativa has been used throughout the world medically, recreationally and spiritually (Pertwee RG 2006). The earliest record of man's use of cannabis comes from the island of Taiwan located off the coast of mainland China (Ernest 1980). In this densely populated part of the world, archaeologists have unearthed an ancient village site dating back over 10,000 years to the Stone Age. Scattered among the trash and debris from this prehistoric community were some broken pieces of pottery the sides of which had been decorated by pressing strips of cord into the wet clay before it hardened. Also dispersed among the pottery fragments were some elongated rod-shaped tools, very similar in appearance to those later used to loosen cannabis fibers from their stems (David, 2011). These simple pots, with their patterns of twisted fiber embedded in their sides, suggest that men have been using the marijuana plant in some manner since the dawn of history. Cannabis sativa appears to have originated in Central Asia and was probably first cultivated for its fiber. It has been grown in China for at least 4500 years. It is thought to have reached Europe by 1500 BC (Ernest, 1980). Even though people have been using the marijuana (or hemp) plant, Cannabis sativa, in medicine and manufacturing for at least 5,000 years, it is better known for its recreational drug uses (Jim, 2011).

Marijuana is a mixture of dried, shredded flowers and leaves of the hemp plant (Cannabis Sativa) There are more than 200 slang terms for marijuana. Among other names, cannabis, pot, dope, weed, grass, ganja, chronic, reefer, herb, Mary Jane(MJ), 420, Acapulco gold, BC bud, buddha, cheeba, green goddess, home grown, hydro, indo, K GB (killer green bud), kind bud, locoweed, bhang, pipes and hashish are the most common (David 2011, National Institute on Drug Abuse 2010). Most

users smoke marijuana in hand-rolled cigarettes called joints, among other names; some use pipes or water pipes called bongs. Marijuana cigars, or blunts, are also popular. To make blunts, users slice open cigars, remove some of the tobacco and mix the remainder with marijuana (Timberlake, 2009). Marijuana also is used to brew tea and sometimes is mixed into foods (National Institute on Drug Abuse, 2010).

Marijuana plants contain more than 400 chemicals, 60 of which fit into a category called cannabinoids. Among the 60 different types of cannabinoids found in marijuana, Delta-9-tetrahydrocannabinol (THC) is the primary psychoactive component of the plant (Felder &Glass 1998). The active product, THC, in marijuana is derived primarily from the leaves and flowering parts of the marijuana plant, although all parts of both the male and female plant contain psychoactive compounds (Jim, 2011). After harvest, THC concentration varies with different preparations like bhang (1%), ganja (1–2%), sinsemilla (up to 6%) and hashish (8–14%). The concentration of THC in hashish can range from about 15–50% (Raka and Yatan, 2008). Hashish is a substance taken from the tops of female marijuana plants and made from the concentrated resin, or sap, of the hemp plant. It contains the highest amount of THC (Jim, 2011).

Table.1. The Most Common Methods of Use of Marijuana (source: Bonsor K. 2007)

Cigarette - Also called joint, dried marijuana leaves are rolled into a cigarette. Approximately 10 percent to 20 percent of the THC is transferred into the body when smoking a joint.
Cigar - Some users slice open a cigar, remove the tobacco and refill it with marijuana. The marijuana-filled cigar is often called a blunt.
Pipe - You've probably seen people smoke pipes of tobacco, but these pipes are also used to smoke marijuana. About 40 percent to 50 percent of the THC is transferred into the body when using a pipe.
Bong - These are water pipes that typically have a long tube rising out of a bowl-shaped base. Water pipes trap the smoke until it's inhaled, raising the amount of THC taken in.
Food - Marijuana is sometimes baked into foods, such as brownies, or brewed as tea

Among these, the most common way of using marijuana is smoking. Smoking is also the most expedient way to get the THC and other chemicals into the bloodstream. Every time a user smokes a marijuana cigarette or ingests marijuana in some other form, THC and other chemicals enter the user's body. The chemicals make their way through the bloodstream to the brain and then to the rest of the body (Bonsor K. 2007). How fast the user feels the effects of marijuana depend on how he/she use it: if the user breathe in marijuana smoke (such as from a joint or pipe), he/she may feel the effects within seconds to several minutes. If he/she eats foods containing the drug, he/she may feel the effects within 30 -60 minutes. When marijuana is eaten, the levels of THC in the body are lower, but the effects last longer (Bonsor K. 2007). Marijuana with a higher THC concentration is preferred to marijuana with a lower THC concentration, additionally indicating that THC is the primary component to the reinforcing effectiveness of marijuana (Haney et al., 1997).

1.2. Epidemiology of marijuana use

In the 21st century, cannabis is the most widely used illicit drug in the world, with the United Nations estimating that up to 190 million people consumed cannabis in 2007 and smoke inhalation is the preferred method of ingestion (Robson, 2011).

According to World Drug Report of 2010, Cannabis remains the most widely used illicit substance in the world. Globally, the number of people who had used cannabis at least once in 2008 is estimated between 129 and 191 million, or 2.9% to 4.3% of the world population aged 15 to 64. Compared to last year, the lower bound of the estimate decreased and the range widened due to the increased uncertainty of having dropped some countries' estimates which were more than ten years old. In North America, there are an estimated 29.5 million people who had used cannabis at least once in 2008, a decrease from the 31.2 million estimated in 2007. This decrease reflects the availability of new data for Canada, which in 2008 showed a considerably lower number of cannabis users compared to their previous 2004 survey estimates. Cannabis use in the United States and Canada has been declining or stabilizing over the past years, although a slight increase was observed in the United States in 2008 (from 12.3% of the population aged 15-64 in 2007 to 12.5% in 2008) (World Drug Report, 2010).

With millions of users, marijuana use is not limited to one demographic group. It cuts across all racial and economic boundaries. However, marijuana use is highest among younger people. (Johnston, O'Malley & Bachman, 2001). The prevalence of marijuana use in teenagers doubled from 1992 to 1999: One out of every 13 kids aged 12 to 17 were current users of marijuana in 1999 (Bonsor K., 2007).

2. CANNABINOID RECEPTORS

Not until 1990 was the cannabinoid receptor (CB or CBR) with which THC interacts, CB1, cloned, (Marx, 2006) and it was 1992 before anandamide, the endogenous ligand corresponding to THC and binding to CB1 receptors, was discovered. Since then, an additional cannabinoid receptor, CB2, has been identified. These are members of the superfamily of G protein-coupled receptors (GPCRs); both CB1R and CB2R are coupled to $G_{i/o}$ proteins (Howlett et al., 2002). Another recent addition to the cannabinoid receptor family is the G protein-coupled receptor, GPR55 (G protein-coupled

receptors 55), which couples to $G_{\alpha 11-13}$ (Begg et al., 2005).

The two CB1 and CB2 receptors have been found to have different distributions and functions in an endocannabinoid system that extends far and wide within the body as a physiologic modulator not only of the central nervous system but also of the autonomic nervous system, immune system, gastrointestinal tract, reproductive system, cardiovascular system and endocrine network. (Gerra et al., 2010).

2.1. The distribution of CB1 receptors

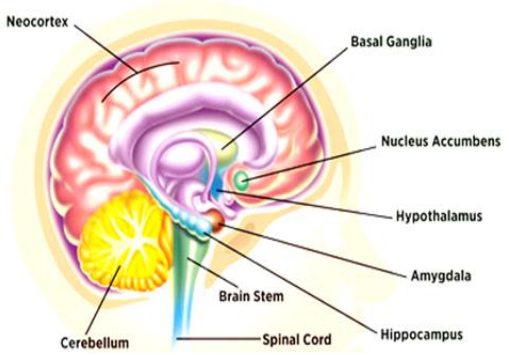
It was only after extensive screening of an expressed rat brain cDNA clone that it was identified as the CB1cannabinoid receptor (Matsuda et al., 1990). CB1receptors are the most common G protein–coupled receptors in the central nervous system and concentrate in specific brain areas that govern pleasure, movement, learning and memory and pain, including the frontal cortex, basal ganglia, hippocampus and cerebellum (Luzi et al., 2008). Specifically, CB1 receptors present in the outflow nuclei of the basal ganglia, substantia nigra, parsreticulata and the internal and external segments of the globus pallidus (Katona et al., 2001). In addition, very high levels of binding are present in the amygdala, hippocampus, particularly within the dentate gyrus, as well as in the molecular layer of the cerebellum. The highest densities are found in association and limbic cortices, with much lower levels within primary sensory and motor regions, suggesting an important role in motivational (limbic)and cognitive (association) information processing (Allyn et al., 2004). In contrast, there are few CB1 receptors in the brainstem which may account for the lack of toxicity associated with very high doses of D9-THC or other cannabinoid ligands (Biegon and Kerman, 2001). Central CB1Rs are also localized in regions involved in pain transmission and modulation, specifically in the spinal dorsal horn and periaqueductal gray (Tsou et al., 1998).

In some of the earliest studies, it was established that the administration of D9-THC and other cannabinoid ligands produced widespread dose dependent alterations in brain function in basal ganglia, hippocampus, cerebellum, amygdala and striatum (Pontieri et al., 1999).

In terms of neurons, Combined with electron microscopy and electro-physiology studies, CB1receptors have been shown to be localized presynaptically on GABAergic inter-neurons (Katona et al., 2001). In the basal ganglia, CB1Rs are produced in and transported to the terminals of GABAergic medium-sized spiny neurons of the dorsal and ventral striatum (Julian et al., 2003). Later studies revealed that presynaptic terminals of glutamatergic fibers in the hippocampus and cerebellum also express CB_1Rs, albeit at much lower levels than in GABAergic neurons (Kawamura et al., 2006). CB1Rs were also localized to the glutamatergic terminals of corticostriatal neurons and functional studies demonstrated that their activation leads to decreased glutamate release from corticostriatal inputs. In the brainstem, CB1Rs are expressed at relatively low levels within medullary respiratory control centers (Rodriguez et al., 2001).

In peripheral nervous system, axoplasmic flow of CB1Rs has been demonstrated in peripheral sensory axons, showing transport to terminals where cannabinoids are presumed to produce their antinociceptive effects. Examination of the excitatory (glutamatergic) terminals of Aδ- and C-fibers primary afferents in the spinal cord did reveal the presence of CB1Rs on these terminals (Nyilas et al., 2009). These presynaptic CB1Rs likely account for the ability of cannabinoid agonists to decrease the frequency of excitatory postsynaptic firing in spinal cord neurons, thus contributing to the modulation of spinal nociceptive neurotransmission. Different studies also revealed localized CB1Rs to presynaptic terminals of postganglionic sympathetic neurons, where they are thought to mediate inhibiting effects on sympathetic outflow by inhibiting noradrenaline release (Schultheiss et al., 2005). CB1Rs have also been localized to various neurons of the gastrointestinal tract in different species, including humans (Izzo and Coutts, 2005).

Out of nervous system, the presence of CB1Rs was detected in endothelial cells of various vascular beds (Golech et al., 2004a); so contribute to the vasodilatory actions of CB1R agonists. In addition CB1Rs are expressed in various structures of the human eye (Porcella et al., 2000) and CB1R transcripts are also detected in human spleen, tonsils and peripheral blood leukocytes, although at levels much lower than those found in the brain. In relation to reproductive system, CB1receptors are also found in moderate levels in the testis (Wenger et al., 2001) their function there is unknown.



(a) **(b)**

Fig.1. Distribution of CB1 in Different Areas of the Brain. (Source: Scholastic and the Scientists of the National Institute on Drug Abuse, 2011).

2.2. The distribution of CB2 receptors

By contrast, CB2Rs were initially localized and are most highly expressed by immune competent cells of the spleen, thymus and various circulating immune cell populations (Galiegue et al., 1995). Specially, CB2

mRNA has been localized to B and T lymphocytes, natural killer cells, monocytes, macrophages and microglial cells, mast cells, as well as cultured cell models of these immune cells (Cabral and Dovepettit, 1998).

Additional studies have also confirmed, localization of CB2R in both peripheral and CNS neurons (Duncan et al., 2008). But In contrast to the predominant presynaptic axon terminal location of CB1Rs, CB2Rs appear to localize to the cell bodies and dendrites of central and peripheral (Duncan et al., 2008) neurons. The physiological role of CB2Rs in central neurons is presently unclear; however, administration of CB2R-selective ligands or direct intra-cerebroventricular administration of CB2R does modify behavior (Onaivi et al., 2006). CB2Rs were also localized with CB1Rs to the endothelial cells of human brain capillaries where they were proposed to play a role in regulation of cerebrovascular blood flow and blood-brain barrier permeability (Golech et al., 2004a).

2.3. Non CB1/CB2 receptors

Studies on knockout mice played a significant role to reveal new receptor types. Studies with CB1receptor knockout mice have revealed non-CB1receptor-mediated responses to cannabinoid agonists in the CNS (Howlett et al., 2002). R-(+)-WIN55212-mediated reduction in excitatory postsynaptic currents occurred in both wild-type and CB1 receptor null mice, suggesting that the γ-amino butyric acid (GABA)ergic currents are modulated by an unknown cannabinoid receptor (Hajos et al., 2001). Anandamide, methanandamide and cannabidiol also relax pre-contracted mesenteric arteries obtained from CB1 receptor knockout (CB1-/-) mice or from CB1-/-/CB2-/-double-knockout mice, showing a lack of involvement of either CB1or CB2 receptors in this effect (Jarai et al., 1999).

In another study, anandamide showed analgesic and hypolocomotor effects of similar magn- itude in both wild-type and CB1 receptor knockout mice, again indicating the expression of an anandamide-sensitive non-CB1, non-CB2 receptor in brain tissue (Di Marzo et al., 2000b). This non CB1, non CB receptor, also known as GPR55, is a novel cannabinoid receptor which is present both in brain and the periphery, may account for some of the actions of cannabinoids by activating signaling pathways quite distinct from those used by CBl/CB2Rs (Ross, 2009).

3. CANNABINOID RECEPTOR AGONISTS AND ANTAGONISTS

Classical cannabinoids are tricyclicdibenzopyran derivatives that are either compounds occurring naturally in the plant C. *sativa*, or synthetic analogues of these compounds. The most representative forms are Δ^9-THC and with 11-hydroxy-Δ^8-THC-dimethylheptyl (HU-210), a synthetic compound that displays the highest potency at the CB_1 receptor (Howlett et al., 2002). Non-classical cannabinoids are synthetic THC analogues and the most representative form is the Pfizer compound CP-55 940, a potent and complete agonist at both the CB_1 and CB_2 receptors (Herkenham et al., 1991). Aminoalkylindoles were the first non-cannabinoid molecules that displayed cannabimimetic activity and *R*-(+)-WIN-55,212–2 is the most representative form. (Pacheco et al., 1991). Eicosanoids are the prototypic endocannabinoids, of which anandamide and 2-arachidonoylglycerol /2-AG/ are the most representative compounds (Hillard et al., 1999).

Cannabinoid receptor antagonists*:* Several series of compounds have been developed as CB_1 receptor antagonists. The most representative are diarylpyrazoles. Diarylpyrazoles include both the CB_1 receptor antagonist Rimonabant and the CB_2 receptor antagonist SR 144528. Aminoalkylindoles include a CB_2 receptor antagonist AM 630 and Triazole derivatives include LH-21 (Jagerovic et al., 2004).

4. CELLULAR SIGNAL TRANSDUCTION BY CANNABINOIDS

Both CB1 and CB2 cannabinoid receptors are members of the superfamily of G protein-coupled receptors (GPCRs), especially to $G_{i/o}$ (Gi1, 2 and 3 and Go1and 2) proteins. Another recent addition to the cannabinoid receptor family is the G protein-coupled receptor, GPR55, which couples go $G_{\alpha 11-13}$ (Begg et al., 2005).

Generally, CB1R activation leads to inhibition of adenylyl cyclase blockade of several voltage-gated Ca^{2+}-channels, and activation of several K^+-channels. There is also some evidence that CB1R activation can block the K^+ M-current in central neurons and stimulate mitogenic kinases (Schweitzer, 2000).

Although CB2Rs couple to $G_{i/o}$ proteins and inhibit adenylyl cyclase, they do not couple to inhibition of voltage-gated Ca^{2+}-channels or activation of K^+-channels; this may account for the lack of significant psychotropic effects upon administration of CB2R-selective agonists (Hanus et al., 1999). This multiple consequences of cannabinoid receptor activation, i.e., a reduction in adenylyl cyclase, modulation of ion channels and reduction in intracellular Ca2+, is important for control of multiple cellular signaling processes within the brain.

4.1. Regulation of adenylyl cyclase

4.1.1. Cannabinoid receptor-mediated inhibition of cyclic AMP

Production inhibition of adenylyl cyclase has been characterized in brain tissue and neuronal cells expressing CB1and in human lymphocytes and mouse spleen cells expressingCB2 receptors. For the CB1 receptor, inhibition of cyclic AMP production is the characteristic response to cannabinoid agonists in brain tissue. CB1receptor stimulation resulted in a decrease in intracellular cyclic AMP, net dephosphorylation of the

channels, activation of the A-type potassium currents and hyperpolarization of the membrane. The significance of cannabinoid mediated hyperpolarization of the axon terminals is that it can cause a depression in the response to depolarizing stimuli and failure in neurotransmitter release at the synapse (Childers and Deadwyler, 1996).

4.1.2. Cannabinoid receptor-mediated stimulation of cyclic AMP Production

A second mechanism for cannabinoid receptor-mediated stimulation of cyclic AMP production could depend upon which isoform of adenylyl cyclase is expressed in target cells and the way that the particular isoform responds to Gi/o-mediated regulation. Inhibition of adenylyl cyclase by recombinant CB1or CB2 receptors was observed in cells that co-express either the isoform 5/6 family or the 1/3/8 family as a result of inhibition by Gi (α subunit). On the other hand, stimulation of adenylyl cyclase was observed in cells co-expressing cannabinoid receptors and the adenylyl cyclase isoform 2/4/7 family, as a result of augmentation of a Gs response by the Gβγ dimers released from Gi due to cannabinoid receptor stimulation (Rhee et al., 1998). Stimulation of adenylyl cyclase has been also reported in pertussis toxin-treated cells, suggesting that in the absence of functional Gi/o coupling, the CB1 receptor can activate Gs (Glass and Felder, 1997).

4.1.3. Cannabinoid receptor-mediated $Ca2^+$ fluxes and phospholipases C and A

Cannabinoid and endocannabinoid compounds increased intracellular free Ca2+. Further evidence suggested that a second component of Ca2+ influx was due to CB1 receptor coupling to Gi/o, leading to receptor Tyr kinase transactivation, PKC phosphorylation and regulation of MAPK /Mitogen Activated Protein Kinase (Rubovitch et al., 2004).

4.1.4. Regulation of ion channels

4.1.4.1. Ion Channel Modulation by Protein Kinase A

CB1cannabinoid receptors activate A-type potassium cur-rents in rat hippocampal cells (Childers and Deadwyler, 1996). This response is due to the modulation of the intra cellular cyclic AMP concentrations, thereby regulating the net phosphorylation of ion channel proteins by protein kinase A.

4.1.4.2. K^+ Channel Activation

Exogenously expressed CB1 receptors couple to the inwardly rectifying K^+ channels in pituit- ary tumor cells, that Gi/o proteins serve as transducers of the response (Mackie et al., 1995).

4.1.4.3. Inhibition of Voltage-Gated L, N, P, and Q Ca2+ Channels

L-type Ca2+ channels were inhibited by anandamide and R-(+)-WIN55212 in cat brain arterial smooth muscle cells, which express mRNA for the CB1 receptor The CB1receptor also inhibits N-type voltage-gated Ca2+ channels in neuronal cells through Gi/o protein (Gebremedhin et al., 1999).

4.2. Cannabinoid receptor-mediated signal transduction to the nucleus

Firstly, this is through signal transduction via Mitogen-Activated Protein Kinase /MAPK/ and Phosphatidylinositol-3-Kinase/PI3K/. MAPK (p38) was activated in CHO cells expressing recombinant CB1receptors and in human umbilical vein endothelial cells possessing endogenous CB1 receptors. Secondly, cannabinoid receptor agonists activated c-Jun N-terminal kinase (JNK1 and JNK2) in Chinese hamster ovary (CHO) cells expressing recombinant CB1 receptors. This pathway for JNK activation involves Gi/o proteins, PI3K and Ras is a signaling pathway to regulate nuclear transcription factors (Rueda et al., 2000).

Thirdly, Nitric oxide (NO) production was stimulated by anandamide in rat median eminence fragments. Anandamide also stimulated NO production in cultured human arterial endothelial cells and cultured human umbilical vein endothelial cells (Maccarrone et al., 2000).

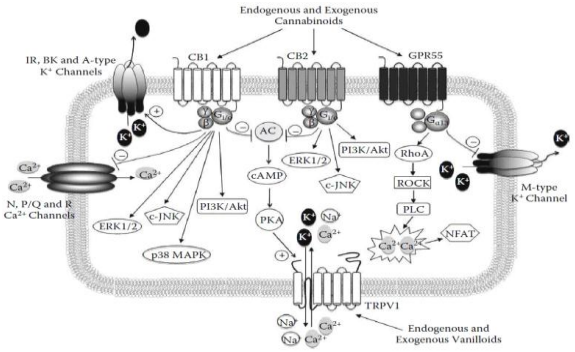


Fig.2. Schematic Representation for G-protein Signaling by Cannabinoids (Source: Spigelman, 2010)

5. THE ENDOCANNABINOID SYSTEM

The endocannabinoid system is a finely tuned physiologic modulator, an "integral part of the body's central homeostatic modulatory system" acting to regulate neurotransmitter release at the level of the synapse. In the mesolimbic reward center, they reinforce pleasurable activities via anandamide, the endogenous cannabinoid that subtly regulates dopamine release (Aggarwal et al., 2009).

Scientists then discovered the body's own natural chemicals, anandamide and 2-AG (2-arac- hidonoyl glycerol), which also act on CB receptors. These chemicals (called endocannabinoids), along with their receptors, make up the endocannabinoid (EC) system. The EC system is found in many areas of the brain, which explains why it affects so many different body functions. Cannabinoids exert their influence by regulating how cells communicate—how they send, receive, or process messages. Cannabinoids act like a

type of "dimmer switch," slowing down communication between cells (Sugiura et al., 1988).

When endocannabinoids are released, they act in a retrograde manner to decrease release of either inhibitory or excitatory transmitters. An influx of calcium ions at the post-synaptic neuron causes a depolarization of the neuron and the generation of endocann- abinoids, dopamine or other neurotransmitters. These neurotransmitters are released into the synapse and bind to the CB1 or CB2, receptors on the pre-synaptic neuron. This action causes a reduction in the amount of GABA released. The pre-synaptic receptor on GABA interneurons most likely controls the release of dopamine. This process is known as depolarization-induced suppression of inhibition (DSI). The process of DSI entails suppression of GABA-mediated inhibition of hippocampal pyramidal cells as a function of the level and duration of pyramidal cell depolarization (Alger et al., 2002).

In the hippocampus, DSI is initiated by depolarization-induced opening of N-type voltage-controlled $Ca2^{+}$ channels (VCCs), which in turn effects release of endocannabinoids via a $Ca2^{+}$ dependent process (Piomelli, 2003). Endocannabinoid compounds diffuse from the post-synaptic membrane and bind to CB1receptors on pre-synaptic terminals of a subclass of interneurons, where they inhibit release of GABA. The process by which diminished release of GABA occurs has not been thoroughly characterized, but may involve K+ channels (Daniel et al., 2004). This retrograde, post-to-pre-synaptic linkage can serve as an elegant mechanism by which endocannabinoids regulate the excitability of hippocampal neurons. Endocannabinoid regulation of synaptic transmission in hippocampus occurs only when there is elevated Ca2+ in the same cell that exhibits DSI. By examining hippocampal cell firing in vivo we have determined that such occurrences for a single neuron are relatively rare, but the probability of endocannabinoid release could be increased by the convergence of other synchronous synaptic events (Piomelli, 2003).

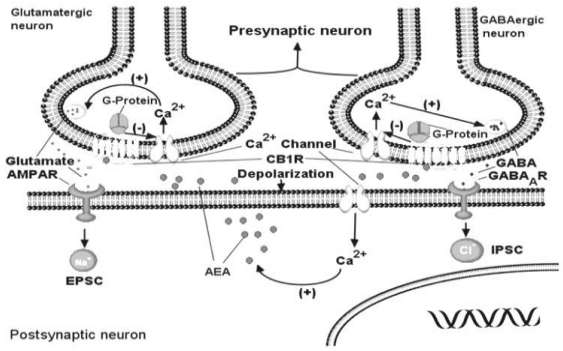


Fig.3. The Endocannabinoid Signaling System. AEA: anandamide, EPSC: excitatory postsyn- aptic current, IPSC: inhibitory postsynaptic current, AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazo lepropionic acid receptor (source: Balapal, 2007).

In the cerebellum, glutamate released onto Purkinje cells appears to be capable of triggering endocannabinoid production and release both by transiently increasing calcium levels within these cells. Once released from the Purkinje cells, the endocannabinoid molecules are thought to act through cannabinoid receptors that are present on the terminals of climbing fibers and of parallel fibers of cerebellar granule cells to inhibit the ongoing glutamate release (depolarization-induced suppression of excitation) (Maejima et al., 2001).

6. THE EFFECT OF CANNABINOIDS ON EC SYSTEM AND NEUROTRANSMISSION

When a person smokes marijuana, THC overwhelms the EC system, quickly attaching to cannabinoid receptors throughout the brain and body. This interferes with the ability of natural cannabinoids to do their job of fine-tuning communication between neurons, which can throw the entire system off balance. But over time THC can change how the EC system works in these brain areas, which can lead to problems with memory, addiction and mental health. In general, cannabinoids function like a "dimmer switch" for presynaptic neurons, limiting the amount of neurotransmitter (e.g., dopamine) that gets released, which in turn affects how messages are sent, received and processed by the cell (Scholastic and the Scientists of the National Institute on Drug Abuse, 2011).

Although CB_1 receptors generally mediate an inhibitory effect on any ongoing transmitter release from the neurons on which they are expressed, activation of these receptors in vivo sometimes leads to increased transmitter release from other neurons. More specifically, there is evidence that in vivo administration of Δ^9-THC produces CB_1-mediated increases in the release of acetylcholine in rat hippocampus, of acetylcholine, glutamate and dopamine in rat prefrontal cortex and of dopamine in mouse and rat nucleus accumbens (Pertwee and Ross, 2002; Gardner, 2005). At least some of these increases most probably occur because this cannabinoid is directly or indirectly inhibiting the release of an inhibitory transmitter onto acetylcholine, glutamate or dopamine releasing neurons. Thus, for example, Δ^9-THC may augment dopamine release in the nucleus accumbens by acting on CB_1 receptors to inhibit the release of glutamate onto GABAergic neurons that project from the nucleus accumbens to the ventral tegmental area where they exert an inhibitory effect on the firing of dopaminergic neurons projecting back to the nucleus accumbens (Pertwee and Ross, 2002). Similarly, since there is evidence that acetylcholine release in the prefrontal cortex is regulated by inhibitory GABAergic neurons that project from the nucleus accumbens, it is possible that Δ^9-THC enhances cortical acetylcholine release through a 'disinhibitory' process that involves a CB_1-mediated suppression of GABA release onto cortical acetylcholine-releasing neurons (Pertwee and Ross, 2002). It has also been proposed that it is the stimulatory

effect of Δ^9-THC on dopamine release in the nucleus accumbens that accounts for its ability to increase acetylcholine release in rat prefrontal cortex and hippocampus (Pisanu et al., 2006). This effect on dopamine release most likely explains why Δ^9-THC can induce signs of reward in animals. The mixed stimulatory–inhibitory effect that Δ^9-THC has on central neurotransmitter release when it is administered in vivo is one possible reason why this cannabinoid has been reported to exhibit both excitant and depressant effects in behavioural bioassays. Thus, for example, it has been found to display anticonvulsant activity in some in vivo models of epilepsy but proconvulsant activity in others and to induce signs of anxiolytic activity in some investigations with rats or mice but signs of anxiogenic activity in others (Patel and Hillard, 2006).

7. THE EFFECT OF MARIJUANA ON THE BRAIN

Delta-9-tetrahydrocannabinol (THC) is the main active ingredient in marijuana, responsible for many of its known effects. When marijuana is smoked, its effects begin almost immediately. THC rapidly passes from the lungs into the bloodstream, which carries the chemical to organs throughout the body, including the brain. The effects of smoked marijuana can last from 1 to hours. If marijuana is consumed in foods or beverages, the effects appear later—usually in 30 minutes to 1 hour—but can last up to 4 hours. Smoking marijuana delivers significantly more THC into the bloodstream than eating or drinking the drug (National Institute on Drug Abuse, 2010).

As THC enters the brain, it causes the user to feel euphoric or high by acting on the brain's reward system, which is made up of regions that govern the response to pleasurable things like sex and chocolate, as well as to most drugs of abuse. THC activates the reward system in the same way that nearly all drugs of abuse do: by stimulating brain cells to release the chemical dopamine (National Institute on Drug Abuse, 2010).

Under the influence of the inhaled drug, most users experience mild euphoria, relaxation and perceptual alterations, including time distortion and intensification of ordinary experiences such as eating, watching films, listening to music and engaging in sex. A few experience dysphoria, anxiety, even frank paranoia symptoms. As cannabis strains are bred that amplify THC content and diminish counteracting cannabidiol, highs become more intense but so do degrees of anxiety that can rise to the level of panic and psychosis, particularly in native users and unfamiliar stressful situations. Cannabinoids have also been shown to impact different stages of memory including encoding, consolidation and retrieval. Several mechanisms, including effects on long-term potentiation and long-term depression and the inhibition of neurotransmitter release, have been postulated as the underlying causes for these effects of cannabinoids (Maldonado et al., 2002).

Cannabis use has been implicated as a potential cause, aggravator, or masker of major psychiatric symptoms, including psychotic, depressive and anxiety disorders, particularly in young people (Moore et al., 2007). During a 27-year follow-up period on 50,000 Swedish conscripts, the more cannabis individuals had used in adolescence, the more likely they were to develop schizophrenia, with those who had used cannabis on more than 50 occasions nearly 7 times more likely to manifest the disease than those who had never used cannabis (Zammit et al., 2002).

During puberty, a period characterized by significant cerebral reorganization, particularly of the frontal lobes implicated in behavior, the brain is especially vulnerable to adverse effects from exogenous cannabinoids (Malone et al., 2010). Short of full-blown schizophrenia, many other persistent effects have been observed in heavy (defined as weekly or more often) pubertal users, including working memory deficits, reduced attention, reduced processing speed, abnormal social behavior, susceptibility to mood and anxiety disorders and greater likelihood of dependence (Schneider, 2008).

Adolescent cannabis use is also associated with depressive and anxiety disorders that emerge later in life (Hall and Degenhardt, 2007). In a cohort of Australian girls followed up for 7 years from the ages of 14 to 15 years, 60% had used cannabis by the end of the study and 7% were daily users. The study showed weekly use was associated with nearly double the risk of subjects later reporting anxiety or depression (Patton et al., 2002).

Through their actions in the hippocampus, CB1 receptors also modulate mood and through activity in both the hippocampus and prefrontal cortex, they influence many elements of cognition, including concentration, short-term memory processing and attention (Hall and Degenhardt, 2009). Most of the evidence supporting this assertion comes from animal studies. For example, rats exposed to THC in utero, soon after birth, or during adolescence, show notable problems with specific learning/memory tasks later in life. Moreover, cognitive impairment in adult rats is associated with structural and functional changes in the hippocampus from THC exposure during adolescence (National Institute on Drug Abuse, 2010).

THC also disrupts coordination and balance by binding to receptors in the cerebellum and basal ganglia, parts of the brain that regulate balance, posture, coordination and reaction time. Therefore, learning, doing complicated tasks, participating in athletics and driving are also affected (Carter and Ugalde, 2004).

On the other hand CB1 receptors also influence vegetative functions at the hypothalamic level; "the munchies," to which recreational marijuana smokers are prone and for which medical marijuana is prescribed,

result from THC stimulation of CB1 receptors that govern food intake (Izzo and Sharkey, 2010).\

In contrast, most marijuana users will presumably state that their senses appear enhanced, concomitant with an increase in relaxation and euphoria; while forgetfulness is enhanced, their focus on their surroundings is augmented (Earleywine, 2002). These surprisingly contrasting experiences are due to the ingestion or smoking of products of the same plant and neither is inaccurate if one considers the difference in doses presumably taken, the presence in cannabis of at least 2 compounds with opposite effects—δ-9-tetrahydrocannabinol (THC), the psychoactive component and cannabidiol (CBD), a nonpsychoactive constituent and the different users' susceptibilities to the effects of the drug. It is also well known that the activity of THC is biphasic in many assays—low and high doses may cause opposite effects (Iversen, 2008). Cannabidiol modifies the effects of THC. Thus, CBD blocks anxiety provoked by THC; cannabis with high CBD content is associated with fewer psychotic experiences than cannabis with low CBD content, (Schubart et al., 2011) and CBD attenuates the memory-impairing effects produced by THC (Morgan et al., 2010).

Table 2. The Effect of THC on Different areas of the Brain (source: Scholastic and the Scientists of the National Institute on Drug Abuse, 2011).

Brain structure	Regulates	THC Effect on User
Amygdala	Emotions, fear, anxiety	Panic/paranoia
Basal Ganglia	Planning/starting movement	Slowed reaction time
Brain Stem	Information between brain and spinal cord	Antinausea effects
Cerebellum	Motor coordination, balance	Impaired coordination
Hippocampus	Learning new information	Impaired memory
Hypothalamus	Eating, sexual behavior	Increased appetite
Neocortex	Complex thinking, feeling and movement	Altered thinking, judgment and sensation
Nucleus Accumbens	Motivation and reward	Euphoria (feeling good)
Spinal Cord	Transmission of information	Altered pain sensitivity

Table.3. Summary for Consequences of Marijuana Use (source: National Institute on Drug Abuse 2010).

Acute (present during intoxication)
• Impairs short-term memory • Impairs attention, judgment, and other cognitive functions • Impairs coordination and balance • Increases heart rate • Psychotic episodes
Persistent (lasting longer than intoxication, but may not be permanent)
• Impairs memory and learning skills • Sleep impairment
Long-term (cumulative effects of chronic abuse)
• Can lead to addiction • Increases risk of chronic cough, bronchitis • Increases risk of schizophrenia in vulnerable individuals • May increase risk of anxiety, depression and a motivational syndrome

8. MARIJUANA ADDICTION, TOLERANCE AND WITHDRAWAL SYMPTOMS

8.1. Marijuana addiction and tolerance

A large body of evidence now demonstrates that cannabis dependence, both behavioral and physical, does occur in about 7-10% of regular users and that early onset of use and especially of weekly or daily use, is a strong predictor of future dependence (Kalant, 2004). With a lifetime dependence risk of 9% in marijuana users verses 32% for nicotine, 23% for heroin, 17% for cocaine and 15% for alcohol, the addiction risk with marijuana is not as high as that for other drugs of abuse (Robson, 2011).

CB1 receptors modulate the activity of dopaminergic neurons that project to the prefrontal cortex from the brainstem reward center, thereby factoring in susceptible individuals into cannabis abuse and dependence (Breivogel and Sim-selly, 2009). Chronic exposure to Δ9-THC and other cannabinoid receptor agonists generally leads to biological adaptive mechanisms that may be related to the phenomenon of tolerance (A.C. Howlett, 2005). Many researches showed that chronic administration of cannabinoid drugs to animals results in tolerance to many of the acute effects of D9-THC, including memory disruption (Deadwyler et al., 1995), decreased locomotion and hypothermia (Pertwee et al.,

1993), neuroendocrine effects and analgesia (Adams and Martin, 1996).

Cellular modifications in response to chronic agonist stimulation have included cannabinoid receptor down-regulation, as well as desensitization of signal transduction pathways which is showed in rat brain (Sim-Selley, 2003). Research on animal revealed that Brain cannabinoid receptor levels decreased after prolonged exposure to agonists (Oviedo et al., 1993).

Furthermore, a time course study revealed differences in the rates and magnitudes of receptor down-regulation across brain regions (Breivogel et al., 1999). These findings suggest that tolerance may develop at different rates to different effects of Cannabinoids (Allyn et al., 2004).

Chronic exposure of rodents to Δ9-THC increased the MAPK pathway that signals to phosphorylated cyclic AMP response element binding protein and transcription factors in the nucleus (Rubino et al., 2004). These researchers reported evidence that sustained stimulation of the MAPK path-way could be coupled to the development of tolerance to the antinociception and hypomobility responses (Rubino et al., 2004; A.C. Howlett, 2005).

8.2. Marijuana withdrawal

Cannabinoid withdrawal is associated with compensatory changes in the cAMP pathway. Initially, acute activation of CB1Rs inhibits adenylyl cyclase activity. The cerebellum plays a crucial role in the somatic expression of THC withdrawal. Cannabinoid abstinence is markedly reduced when cAMP-dependent protein kinase is activated in the cerebellum (Kuster et al., 2003). Studies regarding the development of abstinence symptoms following use of cannabis in form of smoking have demonstrated presence of withdrawal symptoms which include restlessness, irritability, mild agitation, insomnia, nausea, sleep disturbance, sweats and intense dreams. These are mild and last for a short period only (Johns, 2001).

9. MEDICAL MARIJUANA

From a medical point of view, marijuana is a valuable drug. It lowers certain types of pain; has anti-anxiety, anti-inflammatory and anti-spastic effects; and enhances appetite (Iversen 2008). It also blocks vomiting (Abrahamov, 1995).

Recent research has shown that many of the therapeutic effects of cannabinoids are not due solely to the cannabinoid CB1 receptors, whose stimulation causes the cannabis psychoactivity, but also to CB2 receptor activation, which causes no psychoactivity but attenuates inflammation, decreases injury and accelerates regeneration in many disease states (Pacher and Mechoulam, 2011). As a drug, Synthetic D9-THC (dronabinol) is approved for use in the USA to curtail nausea and vomiting in cancer chemotherapy, and to stimulate appetite in AIDS wasting syndromes (Pertwee, 2006).

In the manner of patient-controlled analgesia (the bedside narcotics pumps used in medical settings), smokers can dose themselves repeatedly throughout the day, inhaling enough THC to get analgesic benefit but not enough to sustain motor or psychoactive adverse effects that will dissipate rapidly, if they occur at all (Van Dam and Earleywine, 2010). Medical users may actually consume less than recreational users, inhaling doses sufficient only to produce desired clinical effects for only as long as needed (Cohen, 2009).

10. CONCLUSION AND FUTURE DIRECTIONS

Marijuana has been used for thousands of years as medical and spiritual use. The most active component marijuana is THC which is responsible for psychoactive effect of marijuana (cannabinoids) on human brain and CB1mediates most of these effects in the brain.

Generally, cannabinoids disturb normal neural function by inhibiting or exciting neurotransmitter release in the brain, especially in reward and memory centers and cause short and long term psychotic symptoms and also impaired memory in users.

Interestingly, in dose dependent manner, cannabinoids also have medical use for many acute and chronic diseases.

Even though many researches done to reveal the effect of marijuana on CNS, further studies need to be conducted on the following areas:

1. The role of the new receptor GPR55 in CNS
2. The role of endocannabinoids in regulating brain function
3. The bimodal excitant and depressant psychotic effect of cannabinoids needs further explanation
4. The importance of cannabinoids as medicine also one of key areas in need of further advanced research regarding cannabinoids.

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