

Cannabinoids and Endocannabinoids, and Prospective Modulation of EC Signaling in Neurodegenerative, Cardiovascular and Allied Disorders

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Received: April 22, 2019; Published: November 19, 2019

Abstract

Cannabis Use and Availability: The Cannabis derivatives have been used for recreational and medicinal purposes since ancient times. Because of the additive potential of cannabis products, their sale, possession and use are variously regulated in different countries throughout the world. Still as a psychoactive drug, cannabis continues to find extensive favour among recreational and medical users in the USA and other countries having led to decriminalise cannabis use for recreational and medicinal purposes.

ECS: Receptors, Ligands and Signaling: The endocannabinoid system comprises of the G-protein coupled CB₁ and CB₂ receptors, their endogenous lipid ligands or endocannabinoids, and synthetic and degrading enzymes. The CB₁ is widely expressed within the CNS. The major endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG) exert cannabino-mimetic effects through the CB₁ and CB₂ receptors located on presynaptic membranes in the CNS and in peripheral tissues, respectively.

The CNS Reward Circuitry: The cannabinoid receptors and their endogenous ligands are widely expressed in the brain and particularly influence the neuronal circuits such as the meso-cortico-limbic pathways. The CB₁R signaling influences the motivation for both natural rewards (such as palatable food, sexual activity and social interaction) and modulates the rewarding effects of food and drugs.

Prospects for Therapeutic Modulation of ECS: The ECS is involved in various physiological and homeostatic functions, and its derangement has been implicated in a multitude of pathological alterations and diseases. Modulating the ECS activity holds a therapeutic promise for neurodegenerative, cardiovascular and inflammatory disorders; obesity, T2DM, metabolic syndrome and cachexia; chemotherapy-induced nausea and vomiting; tissue inflammation and pain, cardiovascular, gastrointestinal, intractable epilepsy and various psychiatric disorders.

Conclusion: Current Status of Cannabis Research: The Cannabis research and developmental history has been surrounded with ethical, legal and social issues, and adverse health consequences. The safety issues and addictive property are the main issues complicating the availability and hampering medical use of Cannabis compounds. The Cannabis-based adverse reactions are common and diverse, and dose and duration dependent. Never-the-less, there appear to exist beneficial cannabinoids effective for conditions where no other satisfactory therapies are currently available.

Keywords: Anandamide; 2-arachidonoylglycerol; Cannabis; Cannabinoids; Cannabinoid receptors; Endocannabinoids; Endocannabinoid System; Marijuana; Phytocannabinoids; Synthetic Cannabinoids; Tetrahydrocannabinol

Cannabis Use and Availability

Cannabis use through olden times

The Cannabis derivatives have been used for recreational and medicinal purposes since ancient times [1]. Cannabis extracts known by various names, contain more than 500 compounds, of which about 110 are cannabinoids [2]. Though each cannabinoid has distinct pharmacological properties, tetra-hydro-cannabinol (THC or Δ^9 THC), cannabinol (CBN) and cannabidiol (CBD) have been studied in details and have a broad spectrum of actions, including analgesic and anti-inflammatory effects. THC acts selectively in the central nervous system (CNS) by binding to both CB_1 and CB_2 with high affinity, whereas CBD, a non-psychoactive component, has low affinity for CB_1 and CB_2 receptors [3]. When activated, both these receptors inhibit formation of the second messenger cAMP, and modulate other signal transduction pathways such as extracellular regulated kinases, β -arrestin, and ion channels.

Regulated availability

Because of the additive potential of cannabis products, their sale, possession and use are variously regulated in the past and presently, strictly or slackly, in different countries throughout the world where the legality of cannabis for medical and recreational use varies in each country, in terms of its possession, distribution, cultivation and consumption and use for the medical conditions [4]. The policies in most countries are regulated by the United Nations Single Convention on Narcotic Drugs ratified in 1961, as well as the 1971 Convention on Psychotropic Substances and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances.

The use of cannabis for recreational purposes is prohibited in most countries; however, many have adopted a policy of decriminalization to make the simple possession and use in a low dose a non-criminal act [5]. Uruguay and Canada have fully legalized the consumption and sale of recreational cannabis, whereas in the United States of America ten states and the District of Columbia have legalized the recreational use of cannabis although it remains federally illegal, though the laws varying from state to state when it comes to the commercial sale [6]. The court rulings in Georgia and South Africa have led to the legalization of cannabis consumption. A policy of limited enforcement has also been adopted in many European countries like Spain and the Netherlands where the sale of cannabis is tolerated at licensed establishments. The countries that have legalized the medical use of cannabis include Australia, Canada, Chile, Colombia, Croatia, Cyprus, Finland, Germany, Greece, Israel, Italy, Luxembourg, North Macedonia, Norway, the Netherlands, New Zealand, Peru, Poland, and Thailand. Other countries have restrictive laws allowing the use of certain cannabis-derived pharmaceutical drugs, such as Sativex, Marinol or Epidiolex. Cannabis in India has been used since ancient times and the common cannabis preparations include charas (resin), ganja (flower) and bhang (seeds and leaves), with a milkshake made from bhang. As per the United Nations Office on Drugs and Crime (UNDOC) South Asia, the prevalence of cannabis abuse in India is ~3.2% [7].

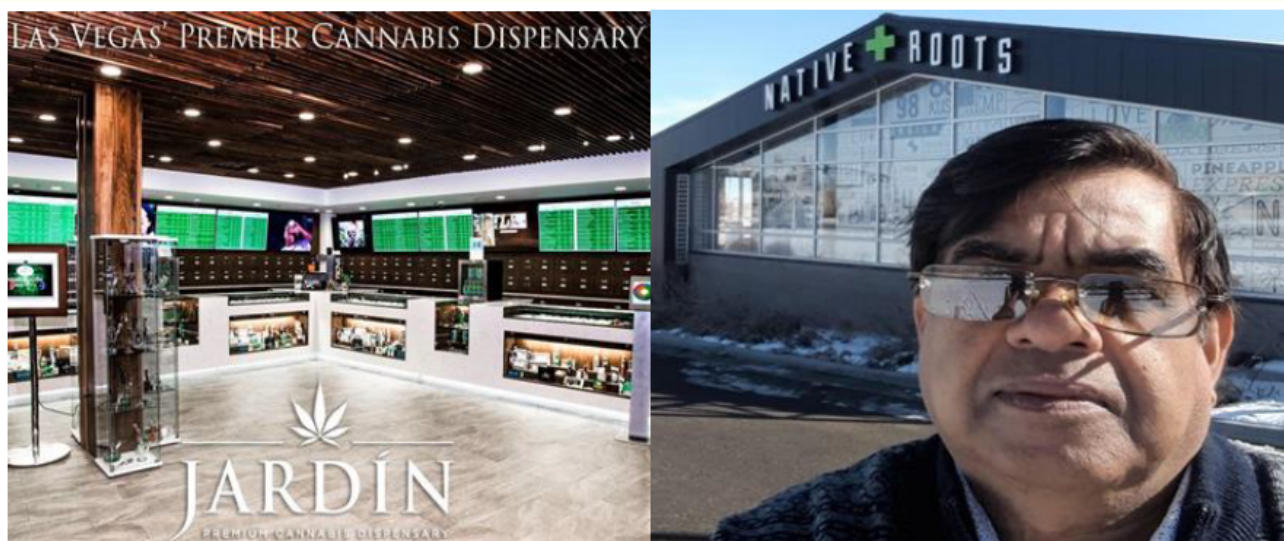


Figure 1: L: A cannabis store in downtown Las Vegas. R: The author outside a cannabis store in Aurora, Denver.

Recreational and medicinal use

As a psychoactive drug, cannabis continues to find extensive favour among recreational and medical users in the USA. A 2013 study asserted that approximately 3.6 million Americans are daily or near daily users and experimenting with marijuana has been a normal part of growing up in the U.S. to the extent that about half of the 1960-post-born population has tried the drug by age 21 [8]. According to a World Health Organization survey, the United States is the world’s leading per capita marijuana consumer [9].

Still the use, sale and possession of cannabis over 0.3% THC in the United States is illegal under federal law. However, individual states have enacted legislation permitting exemptions for various uses, mainly for medical and industrial use but also including recreational use [10]. As of 2019, ten states, two U.S. territories, and the District of Columbia have legalized recreational use of cannabis. Thirty-three states, four U.S. territories, and D.C. have legalized medical use of the drug [11]. As a result, cannabis dispensaries, licensed by each state, sell cannabis products that have not been approved by the U.S. Food and Drug Administration, nor legally registered with the U.S. federal government. Medical use is a common use of marijuana and refers to using the whole unprocessed marijuana plant or its basic extracts to treat a disease or symptom. The U.S. FDA, though, has not officially approved marijuana as a medicine, which has approved only two synthetic cannabis drugs, dronabinol and nabilone, for treating cancer-related and other medical conditions. The recreational use of cannabis now legal in 10 states and the District of Columbia and medical use of marijuana is legal in 23 states [12].

ECS: Receptors, ligands and signaling

Endocannabinoid Receptors

The endocannabinoid system (ECS) comprises of the G-protein coupled cannabinoid 1 and 2 receptors (CB_{1/2}), their endogenous lipid ligands or endocannabinoids, and synthetic and degrading enzymes. The CB₁ is widely expressed within the CNS in cortical neurons and interneurons, astrocytes, oligodendrocytes and oligodendrocyte precursor cells, as well as in leukocytes infiltrating the brain tissue. In the CNS, CB₁ receptors are most abundant in the central nervous system (CNS), distributed densely in motor and limbic regions, in areas involved in pain transmission and modulation as well as in the periphery. CB₁ regulates cognitive, memory and motor functions as well as analgesia and synaptic plasticity [13]. The ECS modulates food intake and energy metabolism, as well [14,15]. Other EC receptors, CB₂ are associated to microglia, brainstem neurons and astrocytes upon cellular activation due to injury or inflammation and are present mostly in peripheral tissues with immune functions including the spleen (Figure 2).

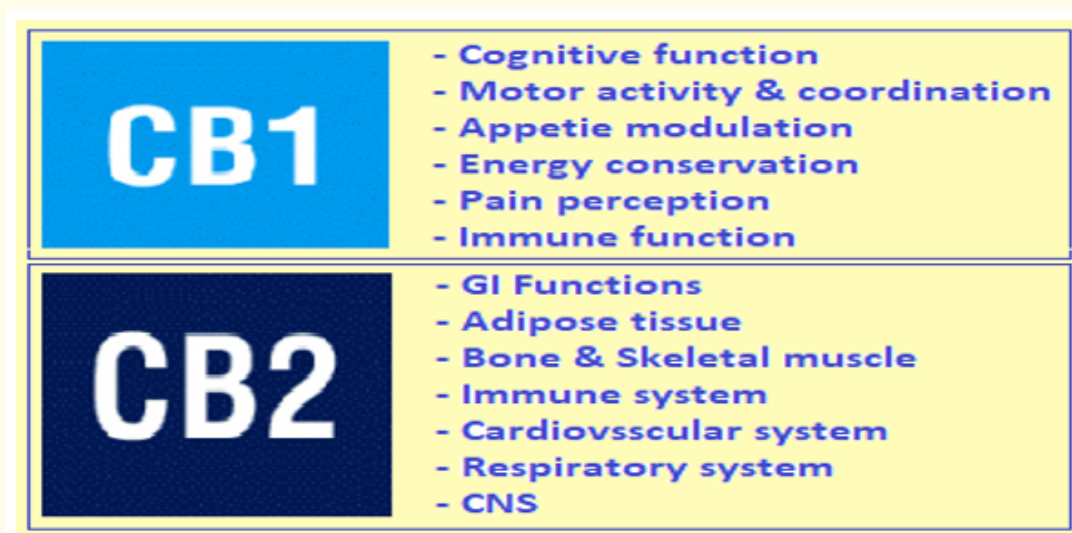


Figure 2: The Endocannabinoid receptors: Distribution and impact of CB₁ and CB₂

Most of the CB₁ receptors are present in cell membrane, but a substantial proportion of CB₁ in the brain is intracellular and found in vesicles, mitochondria and lysosomes. Quantitatively, the human brain has more CB₁ than any other G protein-coupled receptor [16].

The major endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG) exert cannabino-mimetic effects through the CB₁ and CB₂ receptors located on presynaptic membranes in the CNS and in peripheral tissues, respectively. These endocannabinoids are produced from membrane lipids and are lipophilic molecules that are synthesized on demand and are eliminated rapidly by hydrolysing enzymes.

The CB₁ cannabinoid receptor mediates many of the psychoactive effects of THC, the principal active component of cannabis. However, ample evidence suggests that additional non-CB₁/CB₂ receptors may contribute to the behavioral, vascular and immunological actions of THC and endogenous cannabinoids. There has been presence of another cannabinoid G protein-coupled receptor (GPR55), CB₃ receptor. This receptor is highly expressed in large dorsal root ganglion neurons and on being activated by various cannabinoids (Δ^9 THC, the anandamide analog meth-anandamide and JWH015) increases intracellular calcium in the neurons involving G_q, G₁₂, RhoA, actin, phospholipase C, and calcium release from IP₃R-gated stores. The GPR55 activation also inhibits M current. The GPR55 is thus a cannabinoid receptor (CB₃) with signaling distinct from CB₁ and CB₂ [17].

Endocannabinoid ligands

The endogenous ligands of CB receptors, i.e. the endocannabinoids (eCBs), are derivatives of the lipid arachidonic acid (AA). The most important eCBs are *N*-arachidonylethanolamine (anandamide, AEA) and 2-AG. The ever-growing family of eCB ligands of CB₁ includes *N*-acylethanolamines, 2-monoacylglycerols, peptidic eCBs (pepcans), *N*-eicosapentaenylethanolamine (EPEA) and *N*-docosahexaenoyl-ethanolamine (DHEA). EPEA and DHEA, in fact, act as CB₁/CB₂ agonists. There are other compounds that do not bind to CB₁ or CB₂ but are processed by the same synthesizing and degrading enzymes and called eCB-like substances and include *N*-palmitoylethanolamine and *N*-oleoylethanolamine [18].

The endocannabinoids compounds are produced endogenously, plant-derived or chemically synthesised (Figure 3).

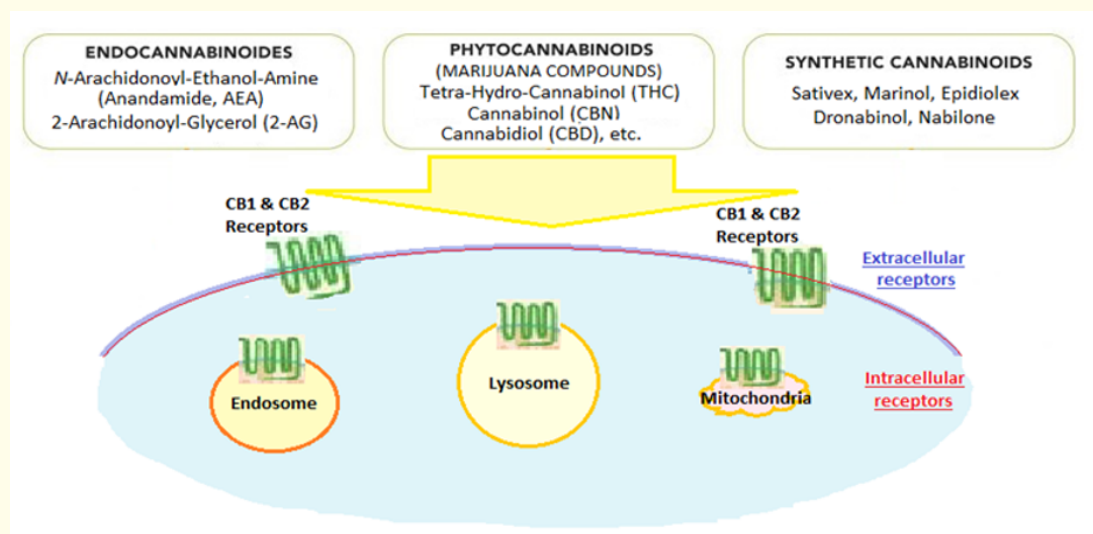


Figure 3: Endo-, Phyto- and synthetic cannabinoids, and extra- and intracellular components of CBR.

Endogenously, they synthesized 'on demand' from membrane phospholipids, and released immediately, without storage in vesicles (Figure 3). Anandamide and 2-AG are produced at post-synaptic neurons. Anandamide is produced in a two-step process involving N-arachidonoylation of the membrane phospholipid, phosphatidylethanolamine, to form N-arachidonoyl phosphatidylethanolamine (NAPE) by a calcium-dependent N-acyltransferase, followed by hydrolysis by a NAPE-selective phospholipase D (NAPE-PLD) to form N-arachidonoyl-ethanol-amine (AEA or anandamide). Anandamide levels are regulated by its breakdown through the action of fatty acid amide hydrolase (FAAH). AEA has a pharmacology similar to THC, though structurally different. It binds to the central CB₁ and, to a lesser extent, peripheral CB₂ receptors. Anandamide is about as potent as THC at the CB₁ receptor [19]. Anandamide is found in various tissues in animals and also in plants, including small amounts in chocolate [20].

AEA has two analogs, 7,10,13,16-docosa-tetraenoyl-ethanolamide and *homo*- γ -linolenoyl-ethanol-amine, having a similar pharmacology. 2-AG binds to the CB₁ receptor and causes sedation, hypothermia, intestinal immobility and mild antinociception in mice. It binds weakly to the CB₂ receptor. N-Arachidonoyl dopamine (NADA) binds to the CB₁ receptor and Like anandamide, NADA is also an agonist for the vanilloid receptor subtype 1 (TRPV1), a member of the vanilloid receptor family. Virodhamine (*O*-arachidonoyl-ethanolamine, OAE) is a full agonist at CB₂ and a partial agonist at CB₁. It is present at lower concentrations than anandamide in the brain, but 2-9 fold higher concentrations peripherally [21]. Lyso-phosphatidyl-inositol (LPI) is another endogenous ligand to novel endocannabinoid receptor CB₃ [22].

The synthetic cannabinoids include nabilone (Cesamet or Canemes, an analog of Marinol), marinol, rimonabant, JWH-018 (a potent synthetic cannabinoid agonist, sold in legal smoke blends collectively known as 'spice'), JWH-073, CP-55940, Dimethylheptylpyran, HU-210 (~100 times as potent as THC), HU-331 (**a potential anti-cancer drug derived from cannabidiol**), SR144528 (a CB₂ receptor antagonist), WIN 55,212-2 (a potent cannabinoid receptor agonist), JWH-133 (a potent selective CB₂ receptor agonist), Levonantradol (Nantrodolum, anti-emetic and analgesic) and AM-2201 (a potent cannabinoid receptor agonist).

ECB synthesis, release, signaling and hydrolysis

Endocannabinoids (eCBs) have been called retrograde transmitters because they travel backward against the usual synaptic transmitter flow. They are released from the postsynaptic cell and act on the presynaptic cell, where the target receptors lie on axonal terminals in the zones from which conventional neurotransmitters are released. The activation of cannabinoid receptors temporarily reduces the amount of conventional neurotransmitters, permitting the postsynaptic cell to control its own incoming synaptic traffic. Though, the ultimate effect on the endocannabinoid-releasing cell depends on the nature of the conventional transmitter being controlled. Thus, when the release of the inhibitory transmitter GABA is reduced, the net effect is an increase in the excitability of the endocannabinoid-releasing cell and when the release of the excitatory neurotransmitter glutamate is reduced, the net effect is a decrease in the excitability of the endocannabinoid-releasing cell.

Once released, endocannabinoids bind to CB₁ receptors located in the presynaptic membrane and the CB₁ receptor activation causes blockage of voltage-dependent N- and P/Q-type calcium channels through the activation of potassium channels and mitogen-activated protein kinase. Following activation of their receptors, endocannabinoids are removed from the synaptic junction/extracellular space by a process of cellular uptake probably mediated by endocannabinoid membrane transporter. Anandamide is then hydrolysed in post-synaptic neurons by fatty acid amide hydrolase (FAAH). 2-AG is synthesized in a two-step process, in which diacylglycerol (DAG) is first produced by the PLC from inositol phospholipids, followed by the hydrolysis of DAG to 2-AG by plasma membrane-associated sn1-DAG lipase (DAGL). Once formed, 2-AG levels are regulated by monoacylglycerol lipase (MAGL), which accounts for ~85% of the hydrolysis and by α/β hydrolase domain which hydrolyses 2-AG to arachidonic acid and glycerol.

Within the CNS and amidst glial and neuronal cells, AEA and 2-AG act as retrograde messengers and on their release act on afferent axon terminals or nearby astroglial processes to inhibit neurotransmitter release. Depending on glutamatergic or γ -aminobutyric acid (GABAergic) neuron type, the CB₁ activation results in inhibition or activation of the neuronal circuit [23,24].

CNS reward circuitry and ECS

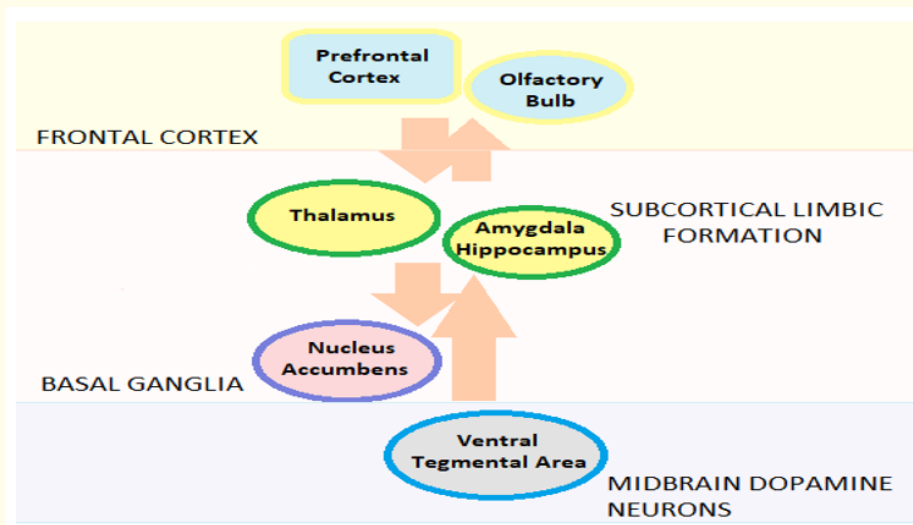


Figure 4: Various components and inter-connexions of the brain Reward Circuitry.

The CNS reward circuitry consists of dopaminergic (DA) neurons in the ventral tegmental area (VTA), nucleus accumbens (NAcb) and the medial forebrain bundle linking the VTA and NAcb [25]. In addition, there are projections from the ventral midbrain to the nucleus accumbens and the olfactory tubercle complex (Figure 3). The posteromedial VTA and central linear raphe cells project to the ventromedial striatum (medial olfactory tubercle and the medial NAC shell) and the lateral VTA projects to the ventrolateral striatum (NAC core, the medial NAC shell and the lateral olfactory tubercle). The medial projection system is important in the regulation of arousal and plays a role in goal-directed behavior; the lateral projection system is activated by rewarding stimuli and the NAC shell and the posterior VTA are the primary areas involved in the reward system [26].

VTA DA neurons play a critical role in motivation, reward-related behavior. The dopamine neurons confer motivational wanting on the reward and associated cues (nucleus accumbens shell region), updates the value placed on different motivational goals (orbital prefrontal cortex), helps consolidate various forms of memory (amygdala and hippocampus), and encode programs facilitating the reward in the future [27]. The VTA has projections to amygdala, cingulate gyrus, hippocampus, NAc, olfactory bulb and prefrontal cortex. The limbic system includes the hypothalamus, the hippocampus, the amygdala, and several other nearby areas. DA in the prefrontal cortex promotes the selection and cognitive control of behavior to facilitate attainment of chosen goals [28].

The cannabinoid receptors and their endogenous ligands are widely expressed in the brain and particularly influence the neuronal circuits such as the meso-cortico-limbic pathways. The drugs enhancing brain reward have common actions on this core DA reward system by enhancing neural firing and DA tone and producing the conditioned place preference (CPP) accompanied by incentive motivation.

Similarly, the cannabinoids activate the brain reward processes and reward-related behaviours [29]. The endogenous cannabinoids, also, through activation of the CB₁ receptor influence the core reward system and activate the reward pathways, though the neural mechanisms involved may be different [30,31].

The CB₁R signaling influences the motivation for both natural rewards (such as palatable food, sexual activity and social interaction) and modulates the rewarding effects of addictive drugs. Also, the endocannabinoid (eCB) levels are increased by the addictive drugs [32]. But, the chronic exposure to these drugs results in impaired eCB signaling contributing to dysregulated synaptic plasticity, increased stress responsivity, negative emotional states and cravings that propel vulnerability to addiction [33]. The eCB system (ECS) has a strong role in modulating relapse-like behaviour induced by conditioned cues and reward priming that can be ameliorated through pharmacologically enhanced eCB tone [34].

ECB physiological activity and overactivity

The eCBs are not stored but are produced on demand initiated upon various stimuli and inactivated through their uptake by an endocannabinoid membrane transporter (EMT). The activity eCBs is finely regulated by the balance between their biosynthetic and degradative pathways. As compared to normally active ECS, an overactive ECS affects food intake, leads to hedonic feeding, energy conservation as fat accumulation, insulin resistance and their various fallouts (Figure 5).

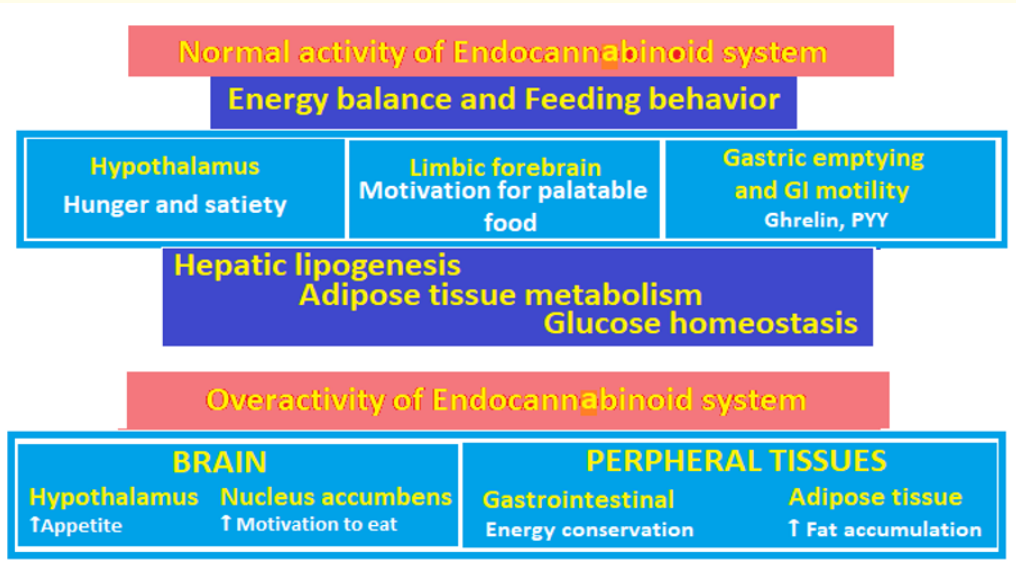


Figure 5: Normal Vs. Overactive endocannabinoid signaling: Components and functional aspects.

Prospects for therapeutic modulation of ECS

The ECS is involved in various physiological and homeostatic functions, and its derangement has been implicated in a multitude of pathological alterations and diseases. Further, the studies have established that modulating the ECS activity holds a therapeutic promise for neurodegenerative, cardiovascular and inflammatory disorders; obesity, T2DM, metabolic syndrome and cachexia; chemotherapy-induced nausea and vomiting; tissue inflammation and pain, cardiovascular, gastrointestinal, intractable epilepsy and psychiatric disorders [35].

Further, the increase or decrease in ECS tone as a result of the altered expression of CB receptors, endocannabinoid synthetic and metabolizing pathways and enzymes in time-dependent manner. The altered ECS activity may be transient and a compensatory response may slow down the progression of the disorder or in other cases the activation of the ECS may be pathogenic as in various forms of shock and diabetic complications or may reflect a deficient homeostasis as in various tumours.

The neuroinflammation

The neuroinflammation is a chronic process resulting from frequent or sustained insult to the brain issue, manifested by endothelial cell activation, tissue oedema and release of inflammatory mediators. It involves activation of resident glial cells (microglia and astroglia) and infiltration by leukocytes and inflammatory mediators. Astrocytes are the most abundant cells in the CNS and regulate physiological processes from forming the blood brain barrier and giving nutritional support to sustaining neurotransmitters turnover, synaptic plasticity and immune functions. Whereas, the microglial cells are the immune sentinels of the CNS, exist in various forms and activation states, can be neuro-protective as well as neuro-destructive and critical for modulating neuroinflammation. The activated microglial cells lead to astrogliosis, which is the hallmark of neuroinflammation. The neuroinflammation may lead to neurodegeneration, axonal loss and synaptic dysfunction.

The ECs or plant-derived cannabinoids exert neuroprotective effects in the CNS by: (a) modulating excitability and calcium homeostasis via effects on various ion channels (Ca^{2+} , Na^+ , K^+), intracellular Ca^{2+} stores and gap junctions and N-methyl-D-aspartate (NMDA) receptors; (b) attenuating excitatory glutamatergic transmissions and modulating synaptic plasticity via presynaptic CB_1 receptors; (c) inducing CB_1 receptor-mediated hypothermia; (d) exerting antioxidant effects; and (e) modulating immune responses and the release of proinflammatory mediators by CB_1 , CB_2 and non- CB_1/CB_2 receptors on microglia, astrocytes, macrophages, neutrophils, lymphocytes and neurones.

The clinical studies show that cannabinoid-based medicines with controlled doses of plant-derived cannabinoids can provide symptomatic relief in a subset of patients suffering from pain and spasticity associated with MS and possibly positively modulate disease progression. Synthetic cannabinoids are also useful in subset of patients with wasting disorders and chemotherapy-induced nausea and vomiting. There, thus, exists possibility of therapeutic exploitation of the endocannabinoid system in neurodegenerative diseases with an inflammatory component. Both preclinical and clinical data suggest that cannabinoids, derived from the *Cannabis sativa* plant and their endogenous counterparts, i.e. the endocannabinoids, may exert neuroprotective effects and slow down the disease progression [36]. Several preclinical and clinical studies outline the therapeutic potential of modulating endocannabinoid signaling in neurodegenerative diseases including multiple sclerosis, Alzheimer's disease and Parkinson's disease [37,38].

Cardiovascular consequences of targeting the ECS in health and disease

ECs exert complex cardiovascular effects that are dominated by a decrease in blood pressure and myocardial contractility, mediated primarily by CB_1 receptors located in the myocardium, vasculature and neurones in the central and autonomic nervous systems. Whereas, activation of cardiovascular CB_2 receptors does not have adverse haemodynamic consequences. CB_1 or CB_2 knockout mice have normal blood pressure, myocardial contractility and baroreflex sensitivity, indicating the minimal role of the ECS in normal cardiovascular regulation. However, in several pathological conditions like shock, heart failure, cardiomyopathies and advanced liver cirrhosis, the ECS may become activated to promote hypotension and cardio-depression through cardiovascular CB_1 receptors. CB_1 receptor signalling may also promote disease progression in preclinical models of heart failure and atherosclerosis and contributes to increased cardiovascular risk by plasma lipid alterations, abdominal obesity, hepatic steatosis, insulin and leptin resistance. By contrast, CB_2 signalling in the heart and vasculature may activate cardioprotective mechanisms and limit inflammation. In rodent myocardial infarction models selective CB_2 agonists exert beneficial effects by limiting inflammatory cell infiltration [39].

Acute or chronic use of cannabis may decrease or increase the heart rate and decrease blood pressure depending on the duration of the use, dose and route of administration. In the human ischaemic hearts, up-regulation of CB₁ and protein kinase A, accompanied by CB₂ down-regulation, increased endothelial NOS and reduced cell survival signaling Increase adverse cardiovascular events especially in obese patients. The elevated endocannabinoid plasma levels are strongly associated with coronary and cardiovascular dysfunction, cell death and dysfunction in human endothelial cells and cardiomyocytes, Heart failure and ischemic cardiomyopathy especially in obese patients. Various case reports associate marijuana smoking with the precipitation of acute coronary syndrome. This occurs in young healthy subjects without any previous cardiovascular disease. A more recent study evaluated the consequences of and the long-term mortality among marijuana users and survivors of acute myocardial infarction and found that habitual marijuana use among patients with acute myocardial infarction has been associated with about 29% higher mortality rate than control group. The activation of CB₁ receptors by synthetic ligands or ECs is similarly associated with adverse cardiovascular consequences [40].

ECS: Role in depression and pain control

In ancient times, the depression-pain comorbidity was frequently treated by cannabis extracts. The main psychoactive ingredient of marijuana, Δ⁹-THC acts through receptors on the cell surface and has wide spectrum of pharmacological effects including euphoria, calmness, appetite stimulation, sensory alterations and analgesia. The first discovered endogenous cannabinoid-like substance, anandamide and another compound, 2-AG are endogenous cannabino-mimetic acting on the cannabinoid receptors and are known as endocannabinoids [41].

Over 80 other phyto-cannabinoids have been identified in the cannabis extracts having a structural similarity to THC. THC is the most studied and activates CB₁ and CB₂ and has various CB₁-mediated undesirable CNS side effects making its the clinical use grossly limited. Another phyto-cannabinoid, cannabidiol, with low affinity to CB₁ and CB₂ receptors, has positive pharmacological effects, such as anti-anxiety, anti-epileptic, anti-bacterial, anti-inflammatory, anticancer and anti-diabetic properties without a psycho-active component [42].

The cannabis extract (nabiximol) containing THC and cannabidiol in 1:1 ratio, has been approved for the treatment of neuropathic pain, spasticity associated with multiple sclerosis and intractable cancer pain. In addition to the synthetic cannabinoids, such as dronabinol and nabilone have robust analgesic effect. Nabilone has been shown to be effective in diabetic neuropathy [43].

The pain has physiological, emotional and cognitive aspects. The nociceptive pathways are triggered by the transduction of noxious stimuli into neuronal action potentials by sensory afferent neurons in the peripheral nervous system and travel through the axons and cell bodies of the primary afferent neurons to synapses in the superficial dorsal horn of the spinal cord. The inputs are integrated and passed onto ascending pathways to the brainstem and thalamus. From the thalamus they are transmitted to the somatosensory cortex and the amygdala and cingulate cortex. The endocannabinoid system distributed throughout the spinal and supraspinal regions and effectively regulates affective and nociceptive processing, and the cross-talk between supra-spinal nociceptive regions may enhance or dampen the incoming nociceptive signals by descending modulatory pathways projecting from the brain to the spinal cord [44]. Depression and chronic pain often co-exist and lead to impaired QOL and contribute to high mortality. The endocannabinoid signaling is altered in patients with chronic pain as well as with affective disorders and elicits potent effects on neurotransmission, neuroendocrine and inflammatory processes, setting of depression and chronic pain. The therapeutic efficacy of nabilone (a Δ⁹-THC analogue) for pain management and quality of life improvement has been demonstrated in cancer patients and patients with fibromyalgia [45].

Conclusion: Current Status of Cannabis Research

The Cannabis research and developmental history has been surrounded with ethical, legal and social issues, and adverse health consequences. The safety issues and addictive property are the main issues complicating the availability and hampering medical use of Cannabis compounds [44]. The modern era for Cannabis research started in 1964, with the identification of chemical structure of

delta-9-tetrahydrocannabinol (D⁹-THC). Later, in the early 1990s, following the first endocannabinoid, anandamide was isolated and identification and cloning of cannabinoid-specific receptors in the CNS were identified and cloned. As of Today, Cannabis is known to have over 100 cannabinoids including major psychoactive ingredients such as D⁹-THC, D⁸-THC, cannabinol and cannabigerol, and various clinical trials are going on for evaluating the therapeutic applications of Cannabis and its derivatives. In 1999, Health Canada and Canadian Institutes of Health Research jointly started a dedicated Cannabis research initiative named Medical Marihuana Research Program. In nutshell, the journey of Cannabis from a substance for addiction to a therapeutic tool has been controversial, but eventful. Thus, when in June 2018, the first cannabinoid-based drug Epidiolex got approval from the USFDA for treating seizures due to Lennox-Gastaut syndrome, Dravet syndrome, it was a major milestone [45].

The Cannabis-based adverse reactions are diverse and dose and duration dependent. Short-term, high-dose use of Cannabis is associated with impairment in memory and motor coordination, distorted judgment and phobic reactions. The long-term use, causes addiction, depression, distorted brain development, chronic bronchitis, myocardial infarction and stroke, and poor educational and social outcomes as well as can precipitate a major psychosis like schizophrenia [46]. In a systematic review by a total of 31 studies evaluating 23 randomized controlled trials and eight observational studies it was shown that there are approximately 4780 reported adverse effects of cannabinoids, of which over 95 percent belonging to a non-serious category [47].

The ECS is intricately involved in the immune consequences following CNS injury, such as the selective modulation of CB₂ receptors holds therapeutic potential in the post-stroke setting. Depending on the initial extent of CNS damage, stroke-induced inflammation can have direct harmful effects, in addition to contributing to the development of secondary CNS pathologies. Due to its anti-inflammatory properties, the CB₂ activation can be protective during the early pro-inflammatory phase of stroke and Inhibiting the CB₂R activity at late phase can reduce post-stroke immunodepression and thus limiting neuro-inflammation. At present, the modulation of the ECS appears to have potential in cardiovascular and neuropsychiatric diseases, apart from autoimmune disorders and cancer by virtue of being able to control of the inflammatory status. There appear to exist beneficial cannabinoids, such as cannabidiol (CBD), present in medicinal cannabis, for effective for conditions where no other satisfactory therapies are currently available. Further, there are synthetic cannabinoids with less addictive properties having considerable therapeutic potential with minimal adverse effects for various diseases including neurodegenerative disorders like Parkinson's disease, Alzheimer's disease and multiple sclerosis, cardiovascular disease, epilepsy and painful conditions like cancer and fibromyalgia.

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