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Review Article

Endocannabinoid system components: A crucial role in regulation of disease

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ABSTRACT

Endocannabinoids (ECs) are characterized as the endogenous ligands of cannabinoid recep-tors (CRs). The research in the field of the endocannabinoid system (ECS) has forecasted a promising role that ECS could play in developing an understanding and management of nu-merous physiological disorders and several diseases. There is a range of analytical techniques that have proved to be fruitful in diagnosing and learning the metabolic and pathological role of these receptors/mediators through various biological indices. Since drug rehab is much faster and less taxing than introducing a new one into the clinic, we may anticipate that the prevailing pharmacology science and data analysis on the ECS shall provide for its effective translation into medical sciences. CB1 and CB2 (G protein-coupled receptors, GPCR) form protein complexes with other GPCRs and non-GPCRs and play a distinctive role in cell sig-naling. This induced inflection of ECS may be modulated for the better of the health care system. This review aims to explore the potential of ECS and new EC-like molecules in clini-cal physiology, pathology, and overall metabolism. The complex ECS that is involved in al-most all aspects of mammalian physiology, pathology, and the range of these maneuvers is debated in this review, as well as they could also be used as drug candidates in the innovation of cannabinoid-based pharmaceutical drugs for a range of diseases.

Keywords: Cannabinoid receptors, Endocannabinoids, G protein-coupled receptors, Metabolism

Introduction

Endocannabinoids (ECs) refer to every chemical substance **(Table 1)** produced endogenously that resembles cannabinoids and does bind with the cannabinoid receptors (CRs) of the body and central nervous system (CNS). The first discovered endocannabinoid was anandamide (1992) [1]. ECs produce the same effects in our body **(Table 1)** as do the cannabinoids of Cannabis sativa (Marijuana) like delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Marijuana is well-known worldwide for its substantial psychoactive properties. It has a tremendous ability to alleviate pain, upsurge appetite, and relieves nausea and apprehension [1]. As per the report of the National Conference of State Legislatures (2021), Marijuana is medically legal in 36 states of the USA [2]. It is also approved for recreational purposes in Washington DC [2]. There is enough research in support of the role ECs impart in energy regulation throughout the body. The corresponding data steadily supports the assumption that ECs` signaling is deeply connected with an increase in energy intake and its storage [3, 4]. Physical activity mobilizes ECs that add to the replenishment of energy reserves as well as anti-depressant effects. The other conditions where the concentrations of circulating ECs vary very significantly include irregular sleep, pain, and inflammation. ECS signaling is stress-responsive and imparts a vital role in maintaining homeostasis after stress. Some studies have shown that the concentration of circulating ECs change drastically in stress-related disorders. Thus evaluation of circulating ECs can contribute safe data about ECS signaling which may help us to test/define the hypothesis. However, a range of associated physiological variables makes it very complex, the reason why we cannot imply circulating ECs as a biomarker for a specific disorder. Challenges in the

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pharmacology of cannabinoids arise from their pharmacokinetics, off-target effects, and psychoactive effects. The two main types of CRs are CB1 and CB2 (G protein-coupled receptors, GPCR) which form protein complexes with other GPCRs and non-GPCRs and play a distinctive role in cell-signaling as shown in **Figure 1**. Some non–CB1/CB2 receptors have been hypothesized, founded on indirect data, however, these are not characterized so far. Ryberg *et al*., however, characterized GPR55 . CB1 and CB2 trigger cyclic adenosine monophosphate (AMP). CB1 is concentrated highly in the CNS (brain and spinal cord), and the peripheral nerve cells. It is very abundant in both gamma-aminobutyric acid (GABA) and glutaminergic-releasing neurons. The former is excitatory and the latter is inhibitory. Thus, the activation of CB1 triggers reactivation of neurotransmitter discharge, which may be stimulating or inhibiting conditional to its location in the brain [5]. Interestingly, CB1 gene assortment has been established but its functional impact is not well understood. Some of its translatory effects are linked with anxiety and melancholy [6, 7]. CB2 is positioned in peripheral neurons highly concentrated in immune-moderating cells, together with microglia (brain). CB2 is expected to play a modulating role against autoimmunity [6, 7]. Based on some animal studies, it is believed that CB2 is associated with the regulation of depression.

Table 1. Comparison of Endocannabinoid Receptors, CB1, and CB2.

Characteristics	CB_1	CB_2	References
Ligands	Anandamide and 2-Arachidonoylglycerol	2-Arachidonoylglycerol	[8]
Major Location	Central nervous system and peripheral neurons	Immune system	[9]
General Action	Constrains discharge of gamma-aminobutyric acid	Mediates autoimmunity	[3]
Pharmacological **Function**			
Digestive system	Decreases gut motility	Decreases gut swelling	[6]
Liver	Stimulates fibrosis, increases fat-retention	Prevents fibrosis, reduces fat-retention	[10, 11]
Circulatory System	Low blood pressure, slows the pulse	Induces thickening of arteries, hypertension	[11, 12]
Drug addiction	Encourages	Discourages	-

Materials and Methods

Databases like Science Direct, PubMed, Google Scholar, and Scopus were explored for the terms; endocannabinoids, cannabinoid receptors CB_1 and CB_2 and their clinical and pharmacological role in modulating stress, obesity, anxiety, pain, hypo/hypertension, tumorogenesis, hepatic steatosis, gamete formation and osteoclastogenesis; and Pharmacologic potential of endocannabinoids between the years 2010 and October 2021 to prepare the current review.

Physiological and pathological role of CB_1 and CB_2

Stress

The stress response can save one`s life when prompted, however, prolonged stress is taxing and has dangerous health consequences. The contribution of ECS is well-recognized to control the sensitivity and intensity of response to stress [6, 7]. Under critical circumstances of stress, vibrant fluctuations in ECS autocrine and paracrine signals lead to both the initiation and dissolution of the response and malfunctioning of ECS may either fasten or delay the normal stress response. Given this ability to regulate stress response, it is very much expected that the ECS can affect an organism's capacity to demonstrate resilience or to be at risk of chronic stress.

The ECS is a chief stress modulator; it controls the discharge of acetylcholine, and adrenaline and also regulates some hormones like norepinephrine. ECS mediates its role in the transformation of emotional stress, cognition, and function of the hypothalamic-pituitary-adrenal axis **(Figure 1)**. The ECS may also intervene in the effect of glucocorticoids that may induce liver steatosis. Hence, the ECS may be considered a vital junction and therapeutic objective to alleviate the negative impact of chronic stress [13].

Obesity

CB_1 is critical for maintaining energy balance in the body. With fasting/starvation, 2-Arachidonoylglycerol (2-AG) concentration upsurges significantly in the forebrain including the hypothalamus which in turn activates CB_1. This gives rise to an urge to consume more food and thus affects the energy balance of the body [14, 15]. CB_1 also increases food appetite by increasing the odor sensitivity of the olfactory pathway [15]. Some people may be overweight because of the extreme CB_1 activation [15]. FAAH (Fatty acid amide hydrolase) is an enzyme that destroys AEA (anandamide). The mutation in this enzyme may increase the concentration of AEA multiple times and stimulate the hypothalamus to increase appetite. A hyperactive ECS was observed in wild-type mice that had developed food-induced obesity [16, 17]. It also increases levels of circulating ECs and receptor sensitivity. However, in the case of pre-satiated mice, the introduction of AEA injection inside the hypothalamus prompted considerable hyperphagia. CB_1inactivation decreases levels of insulin and leptin which significantly metabolizes energy reserves in the body [16, 17].

Nervous system

ECs are fatty acid derivatives that are involved in cell-cell and paracrine intercellular signaling. The action of ECs and associated receptors along the line in the neuromodulation of synapses and its flexibility throughout the CNS has been demonstrated 9]. ECs seem to work predominantly through

retrograde signaling that involves the release of postsynaptic ECs and stimulation of presynaptic receptors **(Figure 2)** [18]. The ECS shows its significance in maintaining homeostasis of the CNS and peripheral nervous system (PNS). Consequently, many neurological maladies may be initiated by the ubiquitous ECS signaling, or the ECS may itself become modified by diseases. For instance, a hyperactive ECS decreases dopamine levels which contributes to the pathophysiology of Parkinson`s disease [19]. Other maladies associated with ECS comprise sclerosis, Alzheimer's disease, seizure disorders, Huntington's disease, and schizophrenia [5, 20]. The studies on pain analysis that evaluate the incidence of hypersensitivity towards the stimulus of pain after blocking CB_1 through the application of several drugs support the hypothesis of pain suppression by ECs [21]. Undeniably, the ECS is spread throughout the CNS and PNS in a manner that proposes its role as a modulator in pain dispensation. CB_1 and CB_2 are linked to the dorsal root in the spinal cord and specific areas of the brain that are sensitive to pain perception [10]. Dorsal root ganglion cells also modulate CB_1 and CB_1 to peripheral cutaneous neurons [10]. Intravenous administration of CBs may aid in modulating pain through the action of the spinal cord [10]. Pain is recognized as a vital target for ECs. The agonists of CB_1 can relieve pain by modulating its action through interneurons of the spinal cord Moreover, CB_2 agonists also have proved their efficiency in plummeting swelling and reversing the hypersensitivity toward pain, skin ailments, and inflammation [22].

Circulatory system

The ECS is extensively strewn all over the circulatory system. ECs show marginal activity in the normal circulatory system but are implicated in many circulatory malfunctions. The ECs released into the bloodstream activates CB_1 and modulate the corresponding hypotension when prompted by the stimulus of shock [23]. The ECS is cardio-protective and can induce both vasodilation and vasorelaxation. In the cardiovascular system, ECs induce vessel dilation by stimulating multiple target sites, inhibiting Ca^{2+} channels, and activating K^{+}channels [23].

CB_1 activation demonstrates its role in blood pressure regulation by assisting in blood vessel dilation and heart contractions. CB_1 activation could thus be considered a therapeutic strategy for treating low blood pressure and thrombosis [23].

Cancer

ECS has been evaluated at the forefront of the fight against cancer over the past decade [24]. The sheer amount of data published about its dual-action both in tumorogenesis and reticence of tumor proliferation and metastatic growth in *in-vitro* conditions has made it a striking new objective for the handling of various types of cancer. Although searching for cancer biomarkers usually reaps a single target which allows for the manipulation of biochemical or hereditary defects, tagging the large ECS as a pharmaceutical-led business brings many benefits alongside problems.

Cannabis and ECs show many similar characteristics both *in vitro* and *in vivo* like both are anti-depressive, and anti-metastatic in many types of cancer. The ECs are also anti-proliferative and anti-apoptotic in a few cancers, however, they are apoptotic in the majority of cancers and promote tumor inhibition. Currently, cannabinoid therapy is restricted to nausea and pain, however, further research is required to explore its full pharmaceutical prospectives [23, 25, 26].

Liver

The ECS is implicated in liver fibrosis. Nevertheless, these studies are based on animal models or laboratory trials. Moreover, the roles of CB_1 and CB_2 in chronic hepatitis B are not evaluated fully yet. However, Dai *et al.*, 2017 [27] have shown that CB_1 and CB_2 are translated in all patients with chronic hepatitis B and the level of fibrosis was translation dependent. Correspondingly, the higher the expression of CB_1 and CB_2, the more was the level of fibrosis in chronic hepatitis B patients. CB_1 helps in controlling hepatic lipogenesis in the liver. The activation of CB_1 aids in the synthesis of fatty acids, which leads to hepatic steatosis and ultimately obesity. Moreover, CB_1 endorses hepatic fibrosis and adds further complications to liver cirrhosis. However, the CB_2 activation reduces inflammation and limits lipid peroxidation, thus CB_2 activity is defensive against liver cirrhosis. Thus, further understanding of the hepatic-ECS relationship may provide breakthroughs in healing many liver ailments [28].

Reproduction

Both male and female reproductive systems are regulated significantly along many lines through the junction of the hypothalamus-pituitary-gonads. The ECS is deeply involved in reproduction via cell signaling. A list of possible mediators involved in this event is still booming. During the last two decades, the role of lipid coordinators sharing the same functions as delta-9-tetrahydrocannabinol (Δ9-THC) of Marijuana has been established. The role of these lipid modulators— radically altered through the action of biosynthetic machinery and hydrolysis—controls the different events of reproduction which includes the discharge of gonadotropins, biosynthesis of steroid hormones, synthesis and discharge of male/female gametes, and effective pregnancy [29].

The CB_1 is present both in males (Leydig cells) and females (ovary, oviducts, and uterus). Moreover, ECS may also be required for normal gametogenesis in males (spermatogenesis) and females (oogenesis). It has been learned that the CB_1 also found in the placenta is essential for embryo implantation [25]. Marijuana use is linked to implantation failures, miscarriages, fetal growth restraint, and premature delivery of babies. More studies are required to unravel the complex role of the ECS in the reproductive system.

Skeletal system

In recent times, immense interest is growing in understanding the potential of cannabinoid receptors in the skeletal system. In addition to immunomodulatory pathways, CB_1 is involved in maintaining proper bone formation and maintaining skeletal growth [30]. CB_2 is abundant in osteocytes, osteoclasts, and osteoblasts and is often age and sex-dependent. CB_2 agonists enhance endocortical osteoblast reproduction and activation while inhibiting osteoclastogenesis **Figure 1**. Schematic representation of stimulus (on the left side) versus induced endocannabinoids mediated response (on the right side). CB_1 and CB_2 are G protein-coupled receptors (GPCR) that may form protein complexes with other GPCRs or sometimes non-GPCRs and play an active role in the endocannabinoid-mediated cell-signaling response. This concept is supported by many studies discussed in this review.

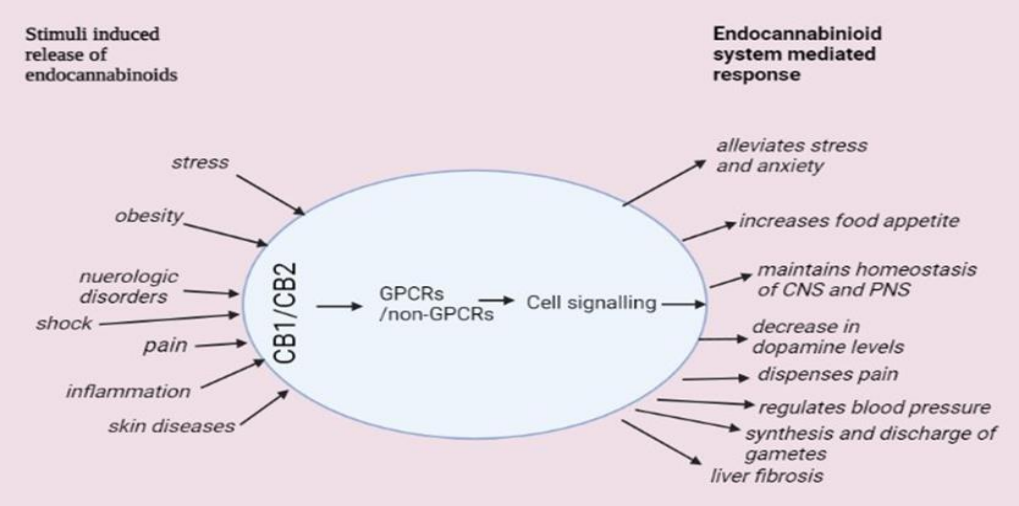

Figure 1. Schematic representation of stimulus (on the left side) versus induced endocannabinoids mediated response (on the right side). CB1 and CB2 are G protein-coupled receptors (GPCR) that may form protein complexes with other GPCRs or sometimes non-GPCRs and play an active role in the endocannabinoid-mediated cell-signaling response. This concept is supported by many studies discussed in this review.

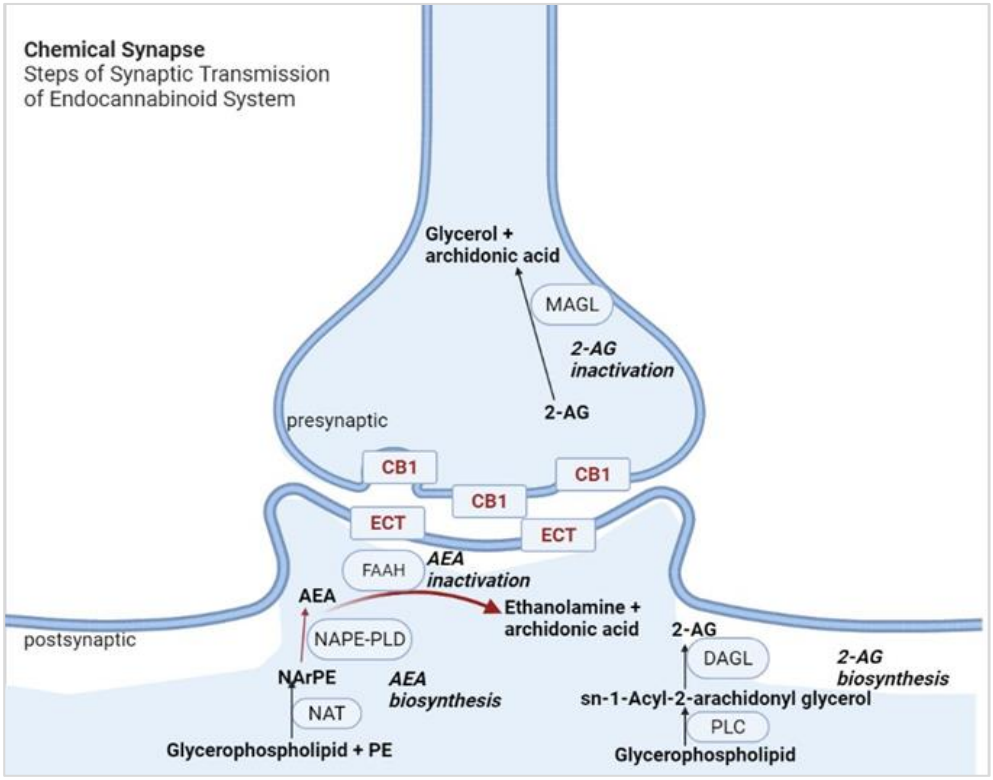

Figure 2. Schematic representation of the ECS chemical synapse at presynaptic and postsynaptic neurons. The former is positioned at the top and the latter at the bottom in the figure.
AEA, anandamide; ECT, endocannabinoid membrane transporter; DAGL, diacylglyceride lipase; MAGL, monoacylglyceride lipase; PE, phosphatidyl ethanolamine; PLC, Phospholipase C; NAT, *N*-acyltransferase; 2-AG, Arachidonoylglycerol; FAAH, Fatty acid amide hydrolase; NAPE-PLD, N-Acylphosphatidylethanolamine phospholipase D; CB1, endocannabinoid receptor 1.

Pharmacologic therapy

Cannabinoid receptor agonists

Epidolex

US Food and Drug Administration (FDA) 2018 approved the use of Epidolex (an oral CBD pharmaceutical syrup) against Lennox-Gastaut`s syndrome and Dravet`s syndrome **(Table 2)**. These syndromes are two rare and serious types of infant-onset epilepsy. Epidolex (cannabidiol) has the potential to cure seizures implicated by these syndromes [31]. After witnessing its encouraging results, FDA stretched the usage of this oral solution in the treatment of seizures related to tuberous sclerosis complex (TSC). TSC is another erratic genetic malady that leads to a benign tumor in the brain and other body parts (heart, lungs, kidneys, eyes, and skin [32].

Sativex

FDA has approved the use of Sativex (an oral spray that contains both THC and CBD) for treating neurological pain endured during multiple sclerosis **(Figure 2)**. Its bioavailability is not determined yet. The drug has been given license in Canada and 25 other countries including many parts of Europe [10, 33-35]. Because of the ongoing COVID-19 pandemic, the phase-3 trial of this drug for confirming its biosafety and efficiency has been delayed for time being [36]. However, its placebo-control trial with about 446 adults suffering from multiple sclerosis/or spasticity is anticipated to be accomplished by late 2022 [36].

Dronabinol

Dronabinol is a synthetic analog of THC that binds with the receptors CB_1 and CB_2. It has low bioavailability (less than10%) [37]. FDA has approved its medical installation as an antiemetic for chemotherapy patients. It is also used to stimulate the appetite of acquired immunodeficiency syndrome (AIDS) patients. However, significant negative effects are associated with its good deeds, the drug is reported to be toxic for CNS particularly [38].

Nabilone (cesamet)

As seen in **Table 2**, Nabilone is a synthetic derivative of THC. It binds with the CB_1 and CB_2 receptors and is FDA approved for its antiemetic properties to take care of those chemotherapy patients where other alternatives have proven unsuccessful. It is not recommended for patients suffering from upper motor neuron syndrome [22, 39].

CB_1 receptor antagonists

CB_1 receptor activates the dopaminergic pathway. The drugs like nicotine, THC, alcohol, opiates and other usually abused analgesics share a common mechanism i.e. the dopaminergic gush in the accumbens nucleus. CB_1 antagonism has shown appreciative results with animal models (human beings and mice). CB_1 antagonists in the case of humans have proved to be beneficial in terms of smoking cessation, reduced alcohol consumption, and decline in cocaine-quest behavior.

Rimonabant (also known as Acomplia or Zimulti)

It is a discerning CB_1 receptor antagonist (SR141716) **(Table 2)**, that binds with centrally acting CB_1. It was marketed in Europe with the trade name Acomplia for treating obesity. However, in the USA, the drug was disapproved and had to be withdrawn due to its serious negative psychiatric effects, particularly depression [40-42].

Nonetheless, ECS is a common controller of cellular activity for both health and sickness. The potential pharmacologic objectives for ECS therapeutic intervention (both agonists and antagonists) are pain, cough, cachexia, antinausea, glaucoma, neurological disorders (for example Parkinson's disease, amyotrophic lateral sclerosis, alcohol-prompted neurological inflammation/degeneration, stroke, Huntington`s disease, multiple sclerosis, trauma, and seizures), autoimmune diseases (inflammatory bowel sickness, autoimmune uveitis, and systemic sclerosis), infection (HIV-1 brain infection), cardiovascular disease (atherosclerosis), psychiatric diseases (anorexia nervosa, anxiety-related sicknesses, substance abuse disorder, impulsivity, attention-scarcity/hyperactivity malady, bipolar disorder, addictive and personality disorders), gastrointestinal diseases (gut motility ailments, liver cirrhosis, bowel inflammation syndrome), cancer (cancer of breast, colon, lymph nodes, skin, and pancreas), osteoporosis and diabetic nephropathy [43].

Table 2. Some important Cannabiniodergic drugs.

Drug names	Composition	Bioavailability	Class of compounds
Epidolex (Epidyolex)	Cannabidiol (CBD)	6% (oral) and 31% (inhaled)	Cannabinoid receptor agonists
Sativex (Nabiimols)	tetrahydrocannabinol (THC) and cannabidiol (CBD)	not determined	Cannabinoid receptor agonists
Dronabinol	THC	10%	Cannabinoid receptor agonists
Nabilone (Cesamet)	THC	20%	Cannabinoid receptor agonists
Rimonabant (SR141716, Acomplia, Zimulti)	Diarylpyrazole	not determined	Cannabinoid receptor antagonists

How to enhance ECS levels?

Endocannabinoids and their receptors are present throughout our body. The ECS has distinct functions in different tissues, but the end aim has always been the same: homeostasis, or maintaining constant internal conditions regardless of external perturbations. Our body creates endocannabinoids on its own. Cannabis in the right doses can also help to regulate and tone your ECS. Nevertheless, the plant isn't the only approach to help your ECS. Endocannabinoid-enhancing foods and outdoor events can spontaneously boost your ECS, which can lead to a variety of health advantages. To strengthen the ECS, a variety of strategies can be utilized in conjunction with or instead of cannabis treatments. Exercises like jogging, yoga, and other forms of physical conditioning, for example, can help to increase endocannabinoid tone. Meditation, massaging, acupuncture, and deep breathing can all help to improve ECS efficiency [44].

Endocannabinoid-fortifying foods

Omega-3/6 fatty acids

Eating foods that promote ECS functioning is yet another strategy to accomplish endocannabinoid harmony. Arachidonic acid, an Omega-6 fatty acid, is used to make endocannabinoids. Endogenous cannabinoid synthesis requires a sufficient amount of fatty arachidonic acid. However, too much can promote inflammation by downregulating cannabinoid receptors. This is why it's critical to consume an Omega-3 to Omega-6 ratio of 1:1. The usual American diet is far too high in Omega-6 fatty acids (1:10) [45]. Hemp seeds, walnuts, chia seeds, flax seeds, and their oil; eggs, yogurt, sardines, and anchovies (seafood) are some worthy sources of omega-3 to encourage balance with omega-6 [45].

Herbs and spices

Some of the ingredients you will need to improve endocannabinoid function are probably already consumed by humans… Many herbs and spices can influence the ECS. Black pepper, clove, oregano, cinnamon, and other plants contain Beta-caryophyllene. It is a CB_2 antagonist and can help reduce inflammation [46].

Aside from Cannabis, other botanical companions also impact the ECS. Curcumin, an active component present in turmeric roots, has been discovered to increase endocannabinoid activity. It has been discovered that maca root (*Lepidium meyenii*) can significantly delay the disintegration of the ECS. Echinacea, which is very popular for its immune-boosting properties, can accomplish this by activating CB_2 receptors [13].

Tea

Catechins are antioxidant chemicals found in tea that possess anti-inflammatory and neuroprotective properties. Tea catechins target and engage with cannabinoid receptors in the CNS, according to Denis *et al*. [13]. The most popular catechin, epigallocatechin gallate (EGCG) is present in green tea. Tea can help to lower cortisol levels, while green tea can help to boost BDNF levels. *Camelia sinensis*, generally known as "tea," has a chemical that keeps endocannabinoids from being broken down, as well as other compounds that activates the CB_1 receptor.

Coffee

Another strategy to stimulate and maintain ECS is to drink coffee. Caffeine's psychoactive characteristics are thought to be mediated through the cannabinoid system [8]. Caffeine ingestion has been demonstrated to boost endocannabinoids' stimulation of CB_1 receptors [8]. Following "social defeat stress," CB_1 receptors are dysregulated, however coffee counterbalances this impact. Conventionally, the coffee bean is collected from the coffee fruit for roasting, and the fruit that surrounds it is thrown away. However, this is a major concern, because the coffee fruit includes several beneficial substances that aren't found in coffee beans. Scientists have discovered that drinking whole coffee fruit concentrate dramatically improves brain function following years of meticulous clinical investigation [8].

Chocolate

Chocolate is a very popular food and with good reason. Cacao (*Theobroma cacao*), a tree from the Malvaceae family from which chocolate is derived, has structurally comparable chemicals to endocannabinoids. These substances can keep your body's natural cannabinoids from being broken down which results in increased aggregate endocannabinoid levels [4, 47]. We get the most from it by purchasing chocolate that contains at least 70% cacao. Cacao nuts are also used in smoothies and other dishes. Chocolate contains a wide range of cannabinoid-like chemicals, with dark chocolate and raw cacao having the highest levels.

Organic foods and probiotics

The ECS is disrupted by pesticides such as chlorpyrifos and piperonyl butoxide. Phthalates are commonly found in plastic and canned food containers, as well as water bottles, and are known to block cannabinoid receptors and disrupt the body's endocrine balance. When possible, use glass or stainless steel food containers and packaging, and avoid eating anything that has been heated in plastic. In general, it's best to consume organic whenever feasible because certain pesticides have been linked to ECS disruption. Endocannabinoid signaling is also harmed by moderate to high amounts of alcohol. Probiotics and fermented foods can help the ECS in the gut work better. Some probiotics have been shown to activate and support the ECS.

Lactobacillus acidophilus was observed to boost the activity of CB_2 receptors in one investigation [48]. Moreover,

probiotics are found to alleviate depression by stimulating the vagus nerve. A well-balanced diet rich in real, whole foods (organic foods), as well as safe drinking water in general, can aid in the maintenance of a good endocannabinoid response.

Endocannabinoid-boosting activities

Every person's ECS is critical to their overall health. Because everyone is unique, discovering techniques to achieve homeostasis is an individual journey. The ECS, as well as the drugs and activities that support it, will keep bringing tremendous therapeutic promise as the relationship between science and health progress [44]. Here are some endocannabinoid-boosting and health-enhancing activities to consider:

Exercise

What do we need to motivate ourselves to exercise? So, here we have it. The importance of physical fitness and other stress-relieving pursuits in the strengthening of the ECS cannot be overstated. Regular exercise in our everyday regimen will maintain our ECS well-tuned, but one should love it. Animal studies educate us that forcing ourselves to exercise can cause our ECS to perceive the action as stress, whereas freely opting for and loving the same engagement will raise endocannabinoid levels. In rat experiments, social interaction and grooming behavior were found to improve ECS function, whereas rats in isolation generated fewer endocannabinoids [4].

Stress reduction

Stress has been demonstrated to downregulate CB_1 receptors [12]. Increased cortisol levels over long periods, like those induced by persistently stressful situations, diminish CB_1 receptors and cannabinoids` binding these receptors considerably.

Furthermore, long-term psychological stress lowers endocannabinoid levels in the brain Overall, experts say there's a lot of proof that the ECS needs to work well to cope with anxiety effectively [12].

Neurofeedback, massage, emotional freedom techniques (EFT), meditation (using the Muse headband), acupuncture, eye movement desensitization and reprocessing (EMDR), and heart-rate variability (HRV) training are some of the stress-reduction approaches. Zinc, ashwagandha, phosphatidylserine, and magnesium are a few supplements that can make you feel better.

Lifestyle

Foods high in fats and sugars have been demonstrated to change levels of AEA, 2-AG, their metabolic enzymes, and CB_1 in numerous animal and human prospective studies. The opposite is also true: many investigations suggest that CB1 agonists increase fat and sugar metabolism. CB1 blockage and CB1/knockout mice reduce the gratifying characteristics of appealing meals. While there is no data to prove CB_1 orthologs in invertebrates besides the chordates, CB1 agonists stimulate eating behavior across the evolutionary ladder, from humans to Hydra.

The ECS is modulated reliably when people lose weight by calorie reduction or fasting. The complexity that arises in adipose tissue vs the CNS has been revealed in several studies. Weight loss by calorie restriction has shown mixed results in human trials. CB_1 and FAAH gene expression, as well as serum AEA and 2-AG, were evaluated in obese postmenopausal women by Engeli *et al*. [12]. They noticed no alterations after losing 5% of their body weight by calorie reduction. Bennetzen *et al*. [3] looked at a younger group of obese men and women and found that losing 10–12 percent of their body weight contributed to increased 2-AG levels in abdominal adipose tissues but no alteration in AEA levels. CB1 mRNA was raised in visceral adipose tissues after weight loss, however, CB_1 mRNA was decreased in abdominal adipose tissue.

Many randomized controlled studies on lifestyle adjustments (e.g., exercise, maintaining an optimal body weight) and complementary and alternative medicine (CAM) therapies were discovered in this comprehensive review (e.g., dietary supplements, stress modification, acupuncture, massage, and manipulation). These are, in our opinion, reasonable ways to improve the ECS [9, 49].

Future research perspective

This review, which is necessary for the continued growth of the number of indicators of the possible use of cannabinoid-related pharmacologic drugs, is a vibrant indication of the evolving prominence of this sector. This is also emphasized by the growing number of articles on scientific databases relating to cannabinoids/endocannabinoids which corresponds with the growing number of cannabinoid drugs in the therapeutic armamentarium. As with any fast-growing research area, not all traces will be useful or effective. However, it is predicted that new pharmaceutical mediators affecting the function of the ECS shall rise and grow into adherents of our pharmacologic industry. Endocannabinoids are essential for bioregulation and play a crucial role in cell signaling. However, since they are hydrophobic by nature, it makes their primary activities are restricted to either paracrine (i.e. cell-to-cell) or autocrine (i.e. same cell); their primary action is not systemic (has very restricted movement in an aqueous environment). Endocannabinoids show some exceptional physiognomies. They demonstrate retrograde transmission in the brain; have a very short half-life and are degraded by the enzyme, FAAH. Scientific studies propose that ECS has an important part in modulating inflammation, pain, tumorogenesis, hepatic steatosis, insulin sensitivity, gamete formation, osteoclastogenesis, and overall metabolism. Therefore, inhibition of ECs may prove vital to reducing the occurrence of metabolic syndromes and amplifying the remunerations of physical workouts. In addition, further introspection of the ECS may lead us to advance diagnosis and treatment for more severe neurological and physiological

maladies. The research based on animal models proposes the anticancer potential of ECs drugs. The ECS is an exceptional and universal cell-signaling scheme that is at the beginning of its exploration. The ECS biochemistry, their mode of synthesis, action, and metabolism has not been an easy illustration to learn, however, new modus operandi like GMOs (genetically modified organisms), therapeutic investigations, and advanced molecular biology techniques are very promising to unravel some of these ambiguities. A much bigger promise is that the understanding of the ECS will develop comprehensions into the mystery of life processes and provide novel pharmacologic options.

Conclusion

The recent identification of cannabinoid receptors and their endogenous lipid ligands has triggered an exponential growth of studies exploring the endocannabinoid system and its regulatory functions in health and disease. Such studies have been greatly facilitated by the introduction of selective cannabinoid receptor antagonists and inhibitors of endocannabinoid metabolism and transport, as well as mice deficient in cannabinoid receptors or the endocannabinoid-degrading enzyme fatty acid amidohydrolase. In the past decade, the endocannabinoid system has been implicated in a growing number of physiological functions, both in the central and peripheral nervous systems and in peripheral organs. More importantly, modulating the activity of the endocannabinoid system turned out to hold therapeutic promise in a wide range of disparate diseases and pathological conditions, ranging from mood and anxiety disorders, movement disorders such as Parkinson's and Huntington's disease, neuropathic pain, multiple sclerosis, and spinal cord injury, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis, to name just a few. An impediment to the development of cannabinoid medications has been the socially unacceptable psychoactive properties of plant-derived or synthetic agonists, mediated by CB_1 receptors. However, this problem does not arise when the therapeutic aim is achieved by treatment with a CB_1 receptor antagonist, such as in obesity, and may also be absent when the action of endocannabinoids is enhanced indirectly through blocking their metabolism or transport. The use of selective CB_2 receptor agonists, which lack psychoactive properties, could represent another promising avenue for certain conditions.

The potential for abuse of plant-derived cannabinoids can also be reduced by using preparations with a carefully controlled composition and carefully selecting the dose and route of administration. The growing number of preclinical studies and clinical trials with compounds that modulate the endocannabinoid system will almost certainly lead to novel therapeutic approaches in many diseases where current treatments are insufficient. We present a comprehensive overview of the current state of knowledge regarding the endocannabinoid system as a pharmacotherapy target in this paper.

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