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Review Article

Cannabinoid pharmacology: Research on medicinal cannabins and its therapeutic application

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ABSTRACT

Cannabinoids, the active compounds in Cannabis sativa, have garnered significant attention due to their diverse pharmacological effects, primarily mediated through cannabinoid receptors, CB1 and CB2. CB1 receptors, predominantly found in the central nervous system, are involved in regulating various physiological processes, including pain perception, appetite, and memory, while CB2 receptors, primarily located in immune tissues, play a role in modulating immune responses. The psychoactive component, Δ9-tetrahydrocannabinol (THC), functions as a partial agonist of both CB1 and CB2 receptors, eliciting effects on gastrointestinal, hepatic, and cardiovascular systems. In contrast, cannabidiol (CBD), a non-psychoactive cannabinoid, interacts with various receptors and channels, demonstrating potential therapeutic benefits, particularly in neuroprotection and anti-inflammatory responses. The endocannabinoid system (ECS), comprising endogenous ligands like anandamide (AEA) and 2-arachidonoylglycerol (2-AG), along with their metabolic enzymes, plays a crucial role in maintaining physiological homeostasis. These endocannabinoids are synthesized on demand and act upon CB receptors to influence a wide range of biological functions. Synthetic cannabinoids, such as dronabinol and nabiximols, have been developed for therapeutic use, particularly in managing chemotherapy-induced nausea, pain, and spasticity in multiple sclerosis. Historically, Cannabis sativa has been used for its medicinal properties across various cultures. The recent surge in research has provided insights into the complex interactions between cannabinoids and the ECS, paving the way for novel therapeutic applications. However, the psychoactive nature of some cannabinoids and the potential for adverse effects necessitate further investigation to fully harness their medicinal potential.

1. Introduction

Cannabinoid refers to the specific chemicals found in the Cannabis sativa plant. The primary psychotropic substances are Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD).[1] The chemical is a terphenophenolic. Cannabinoids are signaling chemicals generated from cell membranes.[2] Cannabinoid receptors are G-protein-coupled receptors (GPCRs) that are activated by a variety of natural, synthetic, and plant-derived cannabinoids. These receptors are found on neurons, blood cells, and endothelial cells, and play a role in a wide range of biological processes.[3] Currently, there are two distinct categories of cannabinoid receptors known as CB1 and CB2.[4] The distribution of cannabinoid CB1 receptors is primarily restricted to the central nervous system, however they can also be detected

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in certain peripheral organs. Cannabinoid CB2 receptors are located extracranially, specifically in conjunction with immunological organs. The CB1 cannabinoid receptors are the most plentiful type of cannabinoid receptor. However, some cannabinoids also interact with CB2 cannabinoid receptors, transient receptor potential (TRP) channels, and peroxisome proliferator activated receptors (PPAR's).[5] THC and CBD are the primary psychotropic components of cannabis sativa. Studies have demonstrated that THC functions as a partial agonist for both CB1 and CB2 receptors. During this process of activation, THC has the ability to initiate several physiological processes, such as regulating gastrointestinal, hepatic, and cardiovascular systems, as well as influencing pain perception and the release of neurotransmitters in the nervous system.[6] Anandamide (arachidonoylethanolamide) and 2-arachidonoyl glycerol (2-AG) are the first identified and most extensively studied endocannabinoids. These are lipid mediators that have biological activity and are produced from long-chain polyunsaturated fatty acids. The endocannabinoid system (ECS) mediators, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are broken down by two specific enzymes: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. In contrast to traditional neurotransmitters, these substances are not kept in synaptic vesicles. Instead, they are generated as needed from phospholipids found in the postsynaptic cell membrane.[7] The efficacy of AEA and 2-AG in activating their receptors is contingent upon their concentration in the extracellular region, a parameter regulated by:

a. Calcium-dependent biosynthesis via N-acyl phosphatidylethanolamine specific phospholipase D (NAPE-PLD) b. Cellular absorption via the hypothesized AEA membrane transporter (AMT) c. Intracellular degradation by fatty acid amide hydrolase.[8]Synthetic cannabinoids are a novel category of chemical substances that have the ability to alter human behavior. These products are devoid of cannabis, however elicit comparable effects upon ingestion. Smokeable herbals known as 'K2', 'Spice', 'Yucatan', 'Chill', or 'Black Mamba' have been frequently offered as synthetic cannabinoids. These products were marketed as legal and safe for use.[9] Dronabinol, a synthetic form of 9THC, has been authorized in the United States for the management of chemotherapy-induced nausea and vomiting, as well as for stimulating appetite in individuals with AIDS. Two primary factors that need to be taken into account are the pharmacokinetic properties (such as the method of administration, whether oral or inhaled) and the impact of other components of cannabis (such as cannabinol and cannabidiol) on the effectiveness of treatment. Sativex is a standardized cannabis extract that is relevant to the discussion over medical cannabis. Sativex is a precisely measured cannabis extract that is delivered as a spray under the tongue. It contains almost equal amounts of 9THC and cannabidiol, as well as small levels of other cannabinoids.

2. Overview of Endocannabinoids System (ECS)

2.1. Cannabinoids receptors

The location of CB1 receptors has been identified by the use of quantitative autoradiography. The auto radiography investigations were highly relevant for the discipline due to three key factors. Initially, they provided evidence that CB1 receptors were abundantly present in the specific brain areas associated with the psychoactive properties of D9 -THC. In contrast, the expression of CB1 receptors was minimal in brain regions that were not influenced by cannabis, such as the respiratory centers of the medulla. Furthermore, they enabled accurate measurement of CB1 receptor levels and revealed that CB1 receptors are expressed more profusely compared to the majority of other GPCRs. Ultimately, when used in conjunction with in situ hybridization (as explained later), they proposed that CB1 receptors may be localized in high concentrations on axon terminals. The CB1 receptor is the sole cannabinoid receptor discovered in the brain, whereas the CB2 receptor has been replicated, but its presence is restricted to immune organs. The CB1 receptors, which are most abundant in the basal ganglia, hippocampus, and cerebellum, can be categorized into three groups based on their efficiency in activating G-proteins: high (found in the hypothalamus), intermediate (found in the amygdala, thalamus, sensorimotor cortex, and brainstem), and low (found in the cerebellum, frontal cortex, hippocampus, and striatum.[10] CB2 was discovered and replicated in 1993, three years after the discovery of CB1. It was found in the marginal zones of the spleen and the HL60 promyelocytic leukemic cell line. Recently, comprehensive reviews have provided detailed descriptions of the cloning, structure, and distribution of it in human tissues.CB2 activation can enhance neuronal homeostasis and ensure survival by exerting its effects at many levels:

1. Neurons are affected by the inhibition of excitotoxicity, oxidative stress, and apoptosis.
2. Astrocytes are influenced by this factor, which stimulates the release of substances that promote cell survival (such as transforming growth factor-β) and reduce inflammation (such as interleukin-10 and interleukin-1 receptor antagonist).
3. This factor also affects microglial cells and other immune cells that enter the body, regulating their inflammatory response by controlling their movement and production of cytokines.[11]

3. Endocannabinoids

Soon after anandamide was found, it was shown that it can activate a specific pathway involved in signal transduction through a certain cannabinoid receptor. The documentation of the techniques involved in isolating, cloning, and expressing these enzymatic activity was completed after a few more years.[12] Although molecules such as palmitoylethanolamide (PEA) and oleoylathanolamide (OEA) do not exhibit these characteristics, they do show notable analgesic and anorexigenic effects, respectively. The baseline level of 2-AG in the brain is approximately 1000 times higher than that of AEA. By altering the pharmacology, the metabolism of 2-AG can be modified to have substantial impacts on retrograde signaling facilitated by endocannabinoids, while AEA stays unaltered. These studies indicate that 2-AG functions as the primary endogenous ligand for CBRs in the central nervous system (CNS). However, research has shown that AEA can independently activate TRPV1 and inhibit L-type Ca2+ channels.[13] Using marijuana or other Cannabis sativa products during pregnancy or while breastfeeding affects the neurobehavioral development of children.[14] The hypothesized biosynthetic process for AEA involves the non-reliant energy fusion of ethanolamine with unattached arachidonic acid.[15]

3.1. Function and significance in human body

The hippocampus is a constituent of the medial temporal lobe, a cerebral area that has a crucial function in the acquisition of knowledge and the formation of declarative or episodic memory.[16] Minimal doses of CB1 receptor agonists enhance the consumption of food. Conversely, CB1 receptor antagonists decrease both the consumption of food and the overall weight of the body. Sativex (Nabiximol), an oromucosal spray made from cannabis extract containing constant quantities of Δ9 -THC and cannabidiol (CBD), effectively alleviates symptoms in patients with multiple sclerosis (MS). Individuals diagnosed with Huntington's disease (HD) experience a notable reduction in CB1 receptors.[17] Possible applications of cannabinoid receptor agonists and substances that can alter cannabinoid transport or metabolism encompass their utilization as sleep-inducing medications, pain relievers, anti-nausea drugs, asthma treatments, blood pressure-lowering agents, immune system modulators, anti-inflammatory and brain-protective substances, anti-seizure medications, drugs for managing glaucoma, muscle stiffness, "movement disorders," eating disorders, and alcohol withdrawal. The modulation of CB2 receptors has been associated with several processes including analgesia, hepatic fibrosis, osteogenesis, and atherogenesis.

4. Historical Perspective on Cannabis Use

4.1.

4.1.1. Traditional and medicinal use through history

Cannabis is considered one of the most ancient plants that has been grown for human consumption. Archaeological evidence indicates that hemp was cultivated for the purpose of producing fiber and rope as early as 12,000 BCE in central Asia. Numerous artifacts, like as hemp textiles and depictions of hemp fiber, dating back several millennia BCE, have been found in various regions of China.[18] In India, the herb was utilized for both medicinal and non-medicinal purposes. The primary significance of its social and religious applications was particularly associated with the celebration of Durga Puja. Additionally, throughout the year, it was employed at various family festivities such as weddings and childbirths to promote a calm and convivial atmosphere and a healthy appetite. Only the less potent forms of cannabis were consumed: bhang, which is similar to marijuana, was ingested orally, and the somewhat more potent form, ganja, was smoked. However, the most powerful form, also known as hashish, was not utilized for these specific objectives. The purported advantages of this product included sedative, relaxing, anxiolytic, and anticonvulsant effects.[19]

5. Phytocannabinoids: Chemistry and Pharmacology

5.1. Tetrahydrocannabinol (THC)

5.1.1. Mechanism of action

D9-tetrahydrocannabinol (THC) is the primary psychoactive compound found in Cannabis sativa and is the subject of much research as a cannabinoid (CB). Cannabinoid (CB) medicines bind to and affect the activity of CB1 and CB2 receptors, with CB1 receptors being the more abundant in the brain. Since the 1970s, there has been increasing data indicating that THC and other CB1 agonists have a stimulating effect on the HPA axis in several animals. Cannabinoids (CBs) primarily affect the hypothalamic-pituitary-adrenal (HPA) axis by acting in the brain, as shown by the (i.c.v.) administration of THC and anandamide. The impact of THC is not evident in rats with hypothalamic differentiation, indicating that the main effect is likely to occur outside the hypothalamus. However, the paraventricular nucleus (PVN) and corticotropin-releasing hormone (CRH) seem to play a role in this process.[20] A total of over 100 mature male Sprague-Dawley rats, weighing 225 grams upon arrival, were obtained from Charles River Labs for the study. The training and testing sessions took place in six identical isolated foringer-type operant chambers. These chambers were equipped with two foringer levers, which were situated on both sides of a motor-driven dipper. The reinforcement involved a brief 3-second presentation of 0.2 ml of Carnation Slender, which

was diluted in a 1:1 ratio with water. Electromechanical equipment was utilized to carry out reinforcement contingencies and record data. Testing for generalization. To assess the extent to which different dosages of THC and diverse medicines produce a similar response (stimulus generalization), experimental tests were conducted twice a week (on Wednesdays and Fridays). These tests were conducted between sessions when the participants received either 3.2 mg/kg of THC or a placebo. The experimental treatments were administered using the same emulphor-ethanol-saline vehicle mentioned earlier, at a dosage of 5 ml per kilogram. Unless explicitly stated differently, all treatments were administered intraperitoneally one hour before to a 15-minute session. On experimental treatment days, the reinforcement scheduling process was modified in the following manner: the initial reinforcement was scheduled after 10 responses were produced on either lever. The responses were initially collected to determine the animal's "preference" for that particular test treatment. If the left lever was chosen, it indicated that the animal had selected the drug side, suggesting that the treatment had been generalized with the training drug condition. Conversely, if the right lever was chosen, it indicated that the animal had selected the vehicle side, suggesting that the treatment had not been generalized with the training drug condition. Generalization by the use of THC and similar compounds. Animals that were taught to differentiate between 3.2 mg/kg THC and a control substance showed a tendency to choose the THC lever in a dose-dependent manner when exposed to lower dosages of the drug.[21]

5.2. Psychoactive and therapeutic effects

The augmentation of MTT 410 metabolism and the elevation of intracellular ATP levels indicate that THC also improves the mitochondrial function of STs. Mitochondrial activity plays a vital role in the formation and functioning of the placenta, primarily because it is responsible for ATP production and steroid synthesis. The latter process largely takes place in the syncytio trophoblast.[22]

5.3. Cannabidiol (CBD)

5.3.1. Mechanism of action

CBD has direct interactions with a range of receptors, enzymes, and ion channels. Additionally, it has been demonstrated to interact both directly and indirectly with the endocannabinoid system. CBD exhibits low affinity for cannabinoid receptors when compared to other cannabinoid ligands in the orthosteric location. Remarkably, CBD at far lower concentrations in the nanomolar range effectively counteracted the effects caused by orthosteric agonists of CB1 and CB2 receptors, namely CP55940 and R-(+)-WIN55212. Cannabidiol (CBD) acts as an antagonist for GPR55, a receptor that is associated with G13 alpha protein. This interaction regulates the process of actin cytoskeletal reorganization in cells, namely during movement and migration. The effective concentration at which CBD inhibits GPR55 activity (EC50) is 445 nm. Research has also shown that CBD attaches to additional Gi-coupled receptors, specifically opioid receptors, including the μ-opioid receptor (MOR) and δ-opioid receptor (DOR), with binding affinities of 7000 nm and 10,000 nm, respectively. CBD also exhibits a binding affinity of 11 nm for D2 receptors, which have a strong affinity for dopamine.[23] There is a limited amount of data available from clinical trials that investigate the impact of CBD and CBD-enriched products on seizure frequency, safety, and drug interactions. Much of the information regarding the anti-seizure properties of marijuana and cannabinoids is based on personal accounts rather than scientific evidence. However, it has been demonstrated that CBD can effectively alleviate neuropathic pain associated with multiple sclerosis (MS). Patients with multiple sclerosis (MS) have higher amounts of endocannabinoids in their blood plasma. However, in an animal model of MS called experimental autoimmune encephalomyelitis (EAE), the levels of endocannabinoids in the brain have actually decreased. mice lacking CB1 receptors and subsequently induced with EAE exhibit a faster progression of dementia compared to mice that have CB1 receptors, suggesting that CB1 receptors have a neuroprotective role.[24]

5.4. Non-psychoactive and therapeutic effects

CBD inhibited LiCl-induced nausea by activating somatodendritic autoreceptors in the dorsal raphe nucleus, which decreased the release of forebrain 5-HT.[25] Cannabidiol (CBD) and other cannabinoids have several modes of administration, including consumption, inhalation, or injection. There is a scarcity of studies examining the therapeutic possibilities of topical treatments. CBD functions as an FAAH inhibitor, which means it blocks the activity of the FAAH enzyme. It also acts as a CB2 inverse agonist, meaning it opposes the effects of CB2 agonists. Additionally, CBD acts as a TRPV1 agonist, activating the TRPV1 receptor. There is a possibility that CBD could have a role in regulating the itch response, but currently, there is limited scientific evidence support ing this application.[26]

6. Other Phytocannabinoids

6.1. Cannabinol (CBN)

Cannabinol (CBN) is not naturally produced by the Cannabis plant itself, but rather is generated by the breakdown of tetrahydrocannabinol (THC) due to extended storage or exposure to heat (29). The cannabinoid was originally isolated from the plant in the early 1940s. It was discovered that the substance demonstrated

notable anticonvulsant, sedative, and other pharmacological properties through its interaction with the effects of THC. Research has demonstrated that CBN reduces heart rate, slows down bowel movement, and hinders the clumping of blood platelets.[27]

6.2. Cannabigerol (CBG)

CBD and CBG have shown to possess anti-apoptotic activities in healthy cells when exposed to oxidative and inflammatory conditions. The primary mechanism by which cannabis exert their anti-apoptotic effects is through the control of cytokines and antioxidant activity, achieved by reducing the generation of nitric oxide.[28] CBG easily penetrated the blood-brain barrier (BBB) and, overall, intraperitoneal treatment resulted in increased levels of CBG in both the plasma and the brain. The difference in concentration between the two species, rats and humans, was relatively minimal.[29] CBG had neuroprotective effects in a separate ex vivo paradigm involving rat hypothalamus neurons exposed to hydrogen peroxide, but only at low doses.[30] Cannabidiol (CBD) and Cannabigerol (CBG) have the ability to shield cells from oxidative stress caused by hydrogen peroxide (H2O2).[31]

7. Endocannabinoid System and Its Role in Physiology

7.1. Cannabinoid receptors

7.1.1. CB1 receptors: distribution and function

The spatial localization of CB1 receptors has been delineated in the brains of rats and humans, aligning with the behavioral impacts of cannabinoids. The expression of the CB1 receptor was seen in regions that have an impact on various important functions, such as mood, motor coordination, autonomic function, memory, sensory, and cognition. Electron microscope investigations revealed that CB1 receptors are primarily located on presynaptic terminals, however they were also observed on postsynaptic structures and glial cells.It is generally assumed that there is a decrease in the expression of CB1 receptor genes in the brains of both humans and rodents as they age.[32] A high concentration of CB1 receptor immunoreactivity was discovered in the ganglia located directly next to the stomach epithelium. Furthermore, multiple investigations have demonstrated the presence of CB1 receptor positivity on acetylcholine-containing neurons that innervate the smooth muscle, mucosa, and submucosal blood vessels of the rat stomach, thereby confirming the neuronal morphology. It is in line with this that studies have shown that cannabinoid receptor agonists can slow down the process of gastric emptying and prevent the release of stomach acid when triggered by pentagastrin or stress in rats. The receptors were found in the hippocampal formation, with the greatest concentration in the hippocampus. CB1-IR was observed in the main neurons of the Ammon's horn. The substantia nigra exhibited a significant density of CB1-IR. Periaqueductal gray matter exhibited a low density. A limited number of fibers with high levels of CB1-IR were also detected in the medulla.[33] The cannabinoid CB1 receptor is found in the same locations as the pre-synaptic 5-HT transporter protein, which is responsible for taking back this neurotransmitter from the space between neurons (synaptic cleft).[34]

8. Function of CB1 Receptor

The proposed mechanism of sleep promotion could be attributed to the location of the CB1 receptor in sleep-inducing regions. I have postulated that the CB1 receptor, which is found in neurons in the pons and basal forebrain, as evidenced by previous studies, may be stimulating cholinergic neurons located in the same areas. It increases the secretion of acetylcholine (Ach). If the CB1 receptor is present in cholinergic neurons, namely in brainstem regions like the PPT/LDT complex and the basal forebrain, and these neurons are stimulated by ANA, it is possible that they could enhance the release of acetylcholine (ACh) in order to promote sleep.[35] Endocannabinoid/CB1R signaling largely functions to suppress stress, lowering both the endocrine and neural responses to stress. The signaling of CB1R is involved in the process of habituation to stress exposure, which serves as a protective mechanism aimed at reducing reactions to a stimulus that is not hazardous. Conversely, prolonged exposure to stress reduces the signaling of endocannabinoids and CB1R. Considering the crucial function of CB1R activation in promoting pleasure and lowering anxiety, it is theorized that the decrease in CB1R signaling may play a part in the adverse effects of stress.[36]

9. CB2 receptors: Distribution and Function

The CB2 receptor was first separated from HL60 cells, which are a type of human promyelocytic leukemic cell line. Clones of the CB2 receptor have been obtained from mice, rats, and dogs, in addition to the human CB2 receptor.[37] CB2 receptors have a broad distribution in peripheral organs, with a specific abundance in immunological tissues. The CB2 receptor gene transcripts were detected in the spleen, tonsils, thymus, mast cells, and blood cells. Recently, the presence of CB2 immunoreactivity was observed in the vast dermal myelinated nerve fibers, small subepidermal fascicles of unmyelinated fibers, and individual epidermal nerve fibers of normal human skin. Recent results indicate that the activation of CB2R leads to a prolonged decrease in cell membrane potential through the regulation of sodium bicarbonate co-transporters. The self-inhibitory plasticity, which is regulated by 2-AG, was observed in both the CA2/3 region of the hippocampus

and the somatosensory cortex.[38] CB2 receptors play a role in regulating the pleasurable effects of drugs, such as cocaine. However, there are variations across different species, leading to different findings in rats and mice.[39]

9.1. Function of CB2 receptors

Potential areas of focus for ligands targeting the CB2 receptor encompass pain, inflammation, hepatic fibrosis, gastrointestinal motility and inflammation, atherosclerosis, immunological function, ischemia, bone disease, and reproductive disorders.[40] CB2 cannabinoid receptors are highly concentrated in immunological organs, suggesting their presence in microglia.[41]

9.2. Endocannabinoids

9.3. Anandamide

9.3.1. Synthesis of anandamide

The results of our molecular cloning and subsequent investigation of NAPE-PLD provided confirmation of the existence of an enzyme that selectively breaks down NAPEs by hydrolysis. This discovery provided evidence for the physiological significance of the transacylation-phosphodiesterase pathway in the production of anandamide and other NAEs.[42] They are primarily generated from phospholipids in cell membranes by a two-step method known as the "transacylation-phosphodiesterase pathway". The initial step in this route is the N-acylation of phosphatidylethanolamine (PE), where an acyl group is transferred from the sn-1 position of a glycerophospholipid molecule to the amino group of PE. The Ca2+-dependent N-acyltransferase (NAT) catalyzes this process. The second process involves the hydrolysis of the resulting NAPE by NAPE-PLD, which leads to the production of NAE and phosphatidic acid.[43]

10. Degradation of Anandamide

After being absorbed into the body, anandamide is broken down by an enzyme called fatty acid amide hydrolase (FAAH) into arachidonic acid and ethanolamine. This enzyme, once referred to as "anandamide hydrolase" and "anandamide amidohydrolase", is produced by a single gene located on the short arm of human chromosome one. It is mostly found in high quantities in brain and liver tissues, and to a lesser degree in the spleen, kidney, testis, and lungs. Anandamide is also broken down by cyclo-oxygenase-2 into prostaglandin E2-ethanolamide.While the exact physiological importance of this metabolic route remains uncertain, it does indicate a strong connection between anandamide and eicosanoids. Anandamide is additionally broken down by lipo-oxygenase to produce 12 (S)-hydroxy-arachidonylethanolamide, although the exact physiological importance of this process remains uncertain.[44]

11. Function of Anandamide

Research has demonstrated that the use of cannabinergic agonists, whether administered systemically or locally, hinders the process of acquiring and solidifying fear memories. To determine if the influence of the cannabinergic/light-dark cycle extends to this memory system. AEA injections did not have a statistically significant effect when given throughout either phase of the cycle. AEA activities were solely seen during the light phase of the cycle. Our behavioral findings suggest that the stimulation of the cannabinergic system soon following the acquisition of spatial or emotional information hinders the process of memory consolidation.[45]

12. Therapeutic Applications of Medical Cannabis

12.1. Pain management

12.1.1. Mechanism of action in pain modulation

The use of cannabis for pain relief can be traced back to ancient Chinese literature from 2900 B.C. The Shennong Ben Cao Jing, a Chinese compendium on agriculture and medicine, provides the earliest documented evidence of cannabis being used medicinally. It suggests the use of cannabis to alleviate constipation, rheumatic pain, abnormalities of the female reproductive tract, and malaria. Moreover, the plant was employed in combination with wine to administer anesthesia to patients during surgical operations.[46] The National Academies of Sciences, Engineering, and Medicine has determined that cannabis is a highly effective treatment for chronic pain in adults. Additionally, there is strong evidence that oromucosal cannabinoids, particularly nabiximols, can alleviate short-term sleep disturbances in individuals suffering from chronic pain.Scientific progress in understanding the functioning of cannabis has enabled the extraction of its active constituents and the creation of synthetic THC compounds. It is plausible to hypothesize that pure cannabis extracts or synthetic cannabis extracts, specifically THC or THC combined with CBD, will offer a safe and efficient means of reducing pain.[47] Nabilone, marketed as Cesamet®, is a man-made compound that mimics the effects of THC. It has been authorized for use in the United States and the United Kingdom specifically for the treatment of vomiting caused by chemotherapy or cancer-related discomfort. The three primary pain systems are nociceptive, neuropathic, and central. Nociceptive pain arises from physical injury to tissues and is typically characterized as pulsating, persistent, or acute discomfort. The process often involves immune cells releasing cytokines, such as histamine, serotonin, prostaglandin, and bradykinin, in response to signals of injury and inflammation carried by C and A gamma nerve fibers. These signals travel from the lesion site to the dorsal root ganglia, then to the thalamus, and finally to the cerebral cortex. Nociceptive pain serves

the crucial function of alerting individuals to potential harm. Neuropathic pain arises from nerve injury, which leads to the transmission of incorrect pain signals to the thalamus and cortex. Centralized pain occurs as a result of the amplification of the peripheral system due to ongoing dysfunction in the central nervous system.

13. Discussion

Future Directions and Research Opportunities

13.1. Emerging areas of research

Novel cannabinoids and ECS modulators

Endocannabinoids have been discovered to impede or obstruct the growth of cancer cells, primarily via acting as inhibitors of cancer cell proliferation in both laboratory cultures and living organisms. Additionally, research has discovered that the suppression of cell growth in breast cancer cells caused by cannabinoids is due to the interruption of the cell cycle at the G1-S phase transition. This effect is not related to program cell death (apoptosis). Studies conducted in living organisms have found that both naturally occurring and synthesized cannabinoids have demonstrated antineoplastic properties in mice that were injected with xenografts of lung carcinomas, gliomas, thyroid epitheliomas, lymphomas, and skin carcinomas. It is important to consider the published findings that confirm the ability of cannabis to prevent the growth of pancreatic cancer.Endocannabinoids can also regulate liver cirrhosis by serving as mediators of vascular and cardiac functions. Endocannabinoids have the ability to induce vasorelaxation. However, an increased activity of CB1 receptors, which are involved in the mediation of cannabinoids, can lead to improved vasodilation in the mesenteric region. This can ultimately result in the development of portal hypertension.Enzymes involved in the synthesis of endocannabinoids, such as DAGL and NAPE-PLD, have received limited attention. Studying these enzymes in the field of pharmacogenetics could yield valuable insights to enhance our methods of personalized medicine for treating depression. Moreover, it is crucial to conduct a more comprehensive investigation of CNR2 and COX-2 gene polymorphisms, particularly in relation to the distribution and functionality of CB2 receptors, as well as the involvement of the COX-2 enzyme in the metabolism of endocannabinoids (eCBs). Although it may provide challenges, it is crucial to actively pursue the collection of extensive samples in order to further our comprehension and treatment of the intricate illness known as depression.

14. Technological Advances in Cannabinoid Research

New methods of delivery (e.g., nanoparticles, transdermal patch)

The skin has been extensively investigated for two methods of medication administration, namely topical and transdermal drug delivery. Patches and gels are the most often used transdermal devices. Patches are created in several formats, including matrix type, reservoir type, single-layered drug-in-adhesive, or multi-layer drug-in-adhesive. Transdermal medication administration requires candidates with low molecular weight (M.wt) and moderate lipophilicity. In addition, volatile substances with a lower melting point (MP) are more favorable for transdermal formulation. These tactics encompass both passive and active methods for enhancing drug delivery. Passive strategies involve the use of chemical permeation enhancers, pro-drugs, ion-pairs, vesicles, eutectic systems, and saturated systems. Active strategies, on the other hand, include micro-needling, laser, thermal ablation, ultrasound, electroporation, and iontophoresis.

15. Conclusion

In conclusion, the intricate interactions between cannabinoids and their receptors reveal a complex system with significant implications for human health and disease management. Cannabinoid receptors, primarily CB1 and CB2, play crucial roles in various physiological processes, including pain modulation, immune function, and neuroprotection. The endocannabinoid system (ECS), comprising endogenous cannabinoids like anandamide (AEA) and 2-arachidonoylglycerol (2-AG), acts as a key regulator of these processes, maintaining homeostasis within the body. The discovery of synthetic cannabinoids and their therapeutic potential underscores the evolving landscape of cannabinoid research. However, the diverse effects of cannabinoids, ranging from psychoactive to therapeutic, highlight the need for continued exploration to fully understand their mechanisms of action and potential benefits in treating conditions such as chronic pain, multiple sclerosis, and epilepsy. As cannabinoid research progresses, the development of targeted therapies that harness the specific properties of cannabinoids while minimizing adverse effects will be critical. This growing body of knowledge paves the way for innovative medical applications, contributing to the broader understanding of how cannabinoids can be utilized to improve human health.

16. Conflict of interest

None.

17. Source of funding

None.

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