Cannabis and Neuropsychiatric Disorders: An Updated Review

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Abtract

Cannabis plant has the scientific name called Cannabis sativa L. Cannabis plant has many species, but there are three main species including Cannabis sativa, Cannabis indica and Cannabis ruderalis. Over 70 compounds isolated from cannabis species are called cannabinoids (CBN). Cannabinoids produce over 100 naturally occurring chemicals. The most abundant chemicals are delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). THC is psychotropic chemical that makes people feel "high" while CBD is non-psychotropic chemical. However, cannabinoid chemicals are not found only in the cannabis plant, they are also produced by the mammalian body, called endocannabinoids and in the laboratory, called synthesized cannabinoids. Endocannabinoids are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors, and cannabinoid receptor proteins that are expressed throughout the mammalian central nervous system including brain and peripheral nervous system. There are at least two types of endocannabinoid receptors (CB1 and CB2) which are G-protein coupled receptors. CB1 receptors are particularly abundant in the frontal cortex, hippocampus, basal ganglia, hypothalamus and cerebellum, spinal cord and peripheral nervous system. They are present in inhibitory GABA-ergic neurons and excitatory glutamatergic neurons. CB2 receptor is most abundantly found on cells of the immune system, hematopoietic cells and glia cells. CB2 is mainly expressed in the periphery under normal healthy condition, but in conditions of disease or injury, this upregulation occurs within the brain, and CB2 is therefore expressed in the brain in unhealthy states. Cannabis and cannabinoid are studied in different medical conditions. The therapeutic potentials of both cannabis and cannabinoid are related to the effects of THC, CBD and other cannabinoid compounds. However, the "high" effect of THC in cannabis and cannabinoid may limit the clinical use, particularly, the study on the therapeutic potential of THC alone is more limited. This review emphasizes the therapeutic potential of CBD and CBD with THC. CBD has shown to have benefit in a variety of neuropsychiatric disorders including autism spectrum disorder, anxiety, psychosis, neuropathic pain, cancer pain, HIV, migraine, multiple sclerosis, Alzheimer disease, Parkinson disease, Huntington disease, hypoxic-ischemic injury and epilepsy. CBD is generally well tolerated. Most common adverse events are diarrhea and somnolence. CBD also shows significantly low abuse potential.

Key words: cannabidiol (CBD), cannabinoid, cannabis, delta-9-tetrahydrocannabinol (THC)

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HISTORY

Cannabis sativa was cultivated and was used medicinally for more than 4000 years in China. The medical conditions ranged from menstruation to absentmindedness and eventually more than 100

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ailments[1]. The Chinese used mainly the seeds of cannabis for medical purposes[2,3]. Then cannabis was widely used in India, Persia, Assyria. The use of cannabis spread to the middle east, Africa, Europe and America. In the midst of 19th century, William B. O'Shaughnessy served in India introduced Cannabis sativa to England. In 1839, he published the work "on the preparations of the Indian hemp or Gunjah" that described various successful human experiments using cannabis preparation for rheumatism, convulsions, and mainly for muscular spasms of tetanus and rabies[4,5]. In the second half of the 19th century and early 20th century, over 100 scientific articles were published in Europe and the United States about the therapeutic value of cannabis[3].

Physiology, metabolism and mechanism of action

Cannabis plant has the scientific name called Cannabis sativa L. Cannabis plant has many species, but there are three main species including Cannabis sativa, Cannabis indica and Cannabis ruderalis.

Over 500 compounds have been isolated from cannabis species. At least 70+ of which are compounds known as cannabinoids, a molecule with 21-carbon terpenophenolic skeleton[6,7].

Cannabinoids in the cannabis plant are called phytocannabinoids. They produce over 100 naturally occurring chemicals. The most abundant chemicals are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), others include terpenes and flavonoids. THC is psychotropic chemical that makes people feel "high" but CBD is non-psychotropic chemical[8]. The discovery of THC led to identify the signaling pathways. The evidence that THC was interacting with a particular mammalian target was uncovered in murine neuroblastoma cells which expressed upregulated adenylate cyclase in response to exposure to the compound or its synthetic analogues. This finding led the way for the isolation and cloning of a G protein-coupled receptor that subsequently named the cannabinoid receptor type 1 (CB1)[9]. Later on, another cannabinoid receptor type 2 (CB 2) was isolated from human leukemia cells[10]. The identification of these receptors led to the hypothesis that endogenous ligands may also exist. The first endogenous cannabinoid ligand known as endocannabinoids was isolated from pig brain and named N-arachidonoylethanolamine or anandamide [11]. The second endogenous ligand was also isolated from intestinal tissue and named 2-arachidonoylglycerol (2-AG)[12,13]. Both are arachidonic acid derivatives produced from phospholipid precursors through activity-dependent activation of specific phospholipase enzymes[14]. Later on, a number of other endogenous ligands have been discovered, including N-arachidonoyldopamine, N-arachidonoylglycerolether and O-arachidonoylethanolamine[15].

Endocannabinoid chemicals that are produced by the mammalian body are endogenous lipid-based retrograde neurotransmitters[16,17]. They bind to G-protein coupled cannabinoid receptors CB1 and CB2. CB1 receptors are particularly abundant in the frontal cortex, hippocampus, basal ganglia, hypothalamus and cerebellum, spinal cord[8,18] and peripheral nervous system[18]. They are present in both inhibitory GABA-ergic neurons and excitatory glutamatergic neurons[18].

CB2 receptor is most abundantly found on cells of the immune system, hematopoietic cells[19] and glia cells[8]. CB2 is mainly expressed in the periphery under normal healthy condition, but in conditions of disease or injury, this upregulation occurs within the brain, and CB2 is therefore expressed in the brain in unhealthy states[16]. CB1 and CB2 receptors are also widely distributed in the cardiovascular system[20].

Endocannabinoids also bind with other G-protein-couplet receptors (GPCRs): GPR55, GPR18, GPR3, GPR6, GPR12; Transient Receptor Potential (TRP) channels: TRPVanilloid1-4, TRPAnkyrin1, TRPM8; Peroxisome Proliferator-activated receptors: (PPAR2, PPARy); Monoamine Transporters: NE, DA, 5HT1A; Fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), transport fatty acid-binding proteins (FABPs); adenosine equilibrative nucleoside transporters (ENTs), glycine receptor $\alpha 1$ and $\alpha 3$[17].

Lastly, cannabinoids that are produced in the laboratory to structurally or functionally mimic the endocannabinoids or phytocannabinoids are synthetic cannabinoids. Most synthetic cannabinoids have been designed based on THC of the natural cannabinoids. They strongly bind to CB1 receptor, which is linked to the psychoactive effects or "high" of cannabis. There are at least 142 synthetic cannabinoids reported by the European Monitoring Center for Drugs and drug addiction[21].

They are typically consumed through smoking or in a concentrated liquid form. They are marketed as herbal incense or herbal smoking blends. The street names like K2, Spice and synthetic marijuana. The negative effects of synthetic cannabinoids include palpitations, paranoia, intense anxiety, nausea, vomiting, confusion, poor coordination and seizures. People develop withdrawal syndrome and persistent craving[21].

THC is metabolized in the liver by microsomal hydroxylation and oxidation catalyzed by enzymes of cytochrome P450 (CYP) complex primarily CYP2C and CYP3A. The plasma half-life of THC is approximately 1-3 days infrequent cannabis users and 5 - 13 days in chronic cannabis users[22]. The average plasma clearance rates have been reported to be 36 L/hour for naïve cannabis users and 60 L/hour for regular cannabis users[23]. More than 65% of cannabis is excreted in the feces and approximately 20 % is excreted in urine[24].

Cannabidiol (CBD) extracted from phytocannabinoids is non-psychotropic chemical. CBD acts as immuno-modulators at CB2 receptors manifesting as anti-inflammatory[25]. CBD can either enhance or inhibit activation of its binding site targets: it blocks the activation of equilibrative nucleoside transporter, GPR55, and transient receptor potential cation channel subfamily, Glycine receptors M member 8 (TRPM8), among others and enhances, for example, the activity of serotonin receptors (i.e. 5-HT1A), α1, α3 and TRPA1[19]. CBD has high lipophilicity. It rapidly distributes in the brain, adipose tissues and other organs[19,25]. CBD is highly protein bound. It is hydroxylated to 7-OH-CBD by cytochrome P450 (CYP3A [2/4] and CYP2C [8/9/19]) family of isoenzyme. This metabolite then undergoes significant further metabolism in the liver, and the resulting metabolites are excreted in feces and much lesser extent in the urine. The half-life of CBD is estimated at 18-32 hours[19,26].

Pharmacology and Therapeutic Aspects in Human

Cannabis and cannabinoids (CBN) are studied in different medical conditions. The therapeutic potentials of both cannabis and cannabinoid are related to the effects of THC, CBD and other cannabinoid compounds. However, the "high" effect of THC in cannabis and cannabinoid may limit the clinical use, particularly, the study on the therapeutic potential of THC alone is more limited. Central nervous system effects of THC include disruption of psychomotor behavior, short term memory impairment, stimulation of appetite, anti-nociceptive and antiemetic effects[27]. There were also known risks with long-term use of cannabis included: diminished IQ and brain mass, lower cognitive function. low motivation, poor judgment. It could hasten, worsen, unmask psychosis and chronic bronchitis[28].

The cardiovascular effects of THC are also shown in the chronic users of cannabis. It was found to increase risks of stroke and heart attack. Wolff, et al. revealed 50 case reports of Cannabis- related stroke. Mean age was 33 years. Male:Female was 4.9:1. It was concluded that 83% of the case were ischemic stroke. It was found more frequent in chronic users[29]. The mechanism was that THC extracted from phytocannabinoids was shown to activate platelets via CB1 and CB2 receptors, leading to increased GPllb-llla expression and activation of factor Vll, a potent thrombogenic protein resulting in stroke and heart attack[30,31].

Therefore, most research studies emphasize the therapeutic potentials of CBD due to non-psychotropic chemical of CBD, and the combination of CBD with THC

There are clinical research studies of CBD in variety of neuropsychiatric disorders. including, autistic spectrum disorder[32,33], anxiety disorder, schizophrenia, , neuropathic pain, migraine multiple sclerosis, Parkinson disease, Huntington disease, Alzheimer disease, and hypoxic-ischemic injury and epilepsy[19,34].

Autism spectrum disorder

Researchers have found what they believe to be a potential link between autism and CB2 receptors within the endocannabinoid system. One study found that the cell mutations in the brain that have been previously associated with autism block the action of molecules that act on CB2 receptors that CBD acts upon[35].

A similar study also found that mice with autistic-like behavioral issues possessed upregulated CB2 receptors[36].

Another study discovered this same prevalence in the upregulation of CB2 but in human subjects[37]. Autistic children display immune system dysregulation and show an altered immune response of peripheral blood mononuclear cells (PBMCs). This study investigated

the involvement of cannabinoid system in PBMCs from autistic children comparing to age-matched normal healthy developing controls (age ranging 3-9 years). The mRNA level for CB2 receptors was significantly increased in PBMCs of autistic children and protein level of CB2 receptors were also significantly increased in autistic children comparing to healthy subjects.

These findings indicated CB2 receptor as potential therapeutic target for the pharmacological management of the autism care[37]. This led to the possibility of treating autism by CBD.

A retrospective study assessed tolerability and efficacy of cannabidiol-rich cannabis in 60 children with autism spectrum disorder and severe behavioral problems (age=11.8±3.5, range 5.0-17.5; 77% low functioning: 83% boys). These children were treated with oral CBD and THC at a ratio of 20:1 The dose was up-titrated to effect (maximal CBD dose - 10 mg/kg/day). Following the cannabis treatment, behavioral outbreaks were much improved or very much improved on the Caregiver Global Impression of Change (CGIC) in 61% of patients. The anxiety and communication problems were much or very much improved in 39% and 47% respectively. Disruptive behaviors were improved by 29% from 4.74±1.82 as recorded at baseline on the Home Situations Questionnaire-Autism Spectrum Disorder (HSQ-ASD) to 3.36±1.56 following treatment. Parents reported less stress as reflected in the Autism Parenting Stress Index (APSI) scores, changing by 33% from 2.04±0.77 to 1.37±0.59. Adverse events included sleep disturbances (14%) irritability (9%) and loss of appetite (9%). This study supports the feasibility of CBD based medical cannabis as a promising treatment option for refractory behavioral problems in children with autism spectrum disorder[32].

Anxiety

In human studies, CBD has been shown to reduce anxiety in a simulated public-speaking task[38]. Neural mechanisms under the anxiolytic actions of CBD have been visualized using imaging techniques such as functional magnetic resonance imaging and single-photon emission computed tomography. These imaging techniques have revealed decreased blood flow to the left mesial temporal lobe and decreased left amygdala activity after CBD administration. The opposite of effects that have been seen with THC use[12].

Recent retrospective case series at a psychiatric clinic involving clinical application of CBD for anxiety and sleep complaints as an adjunct to usual treatment. The final sample consisted of 72 adults presenting with primary concerns of anxiety (47) or poor sleep (25). Anxiety scores decreased within the first month in 57 patients (79.2%) and remained decreased during the study duration. Sleep score improved within the first month in 48 patients (66.7%) but fluctuated over time. CBD was well tolerated in all but 3 patients[39].

Psychosis

CBD has been shown to have activity in both the dopamine-mediated and of glutamate-mediated pathways relevant to psychosis. A study compared CBD efficacy to that of standard antipsychotic, amisulpride in 33 patients over 4 weeks. Both groups showed similar improvement from baseline in the primary outcome measure (Positive and Negative symptom Scale), but only the CBD-treated patients showed improvement in the negative symptoms[40]. CBD may also potentiate some of THC's beneficial effects as it reduces the psychoactivity of THC to enhance its tolerability and widen its therapeutic window[41]. CBD may counteract some of the functional consequences of CB1 activation in the brain[42], possibly by indirect enhancement of adenosine A1 receptors activity through the equilibrative nucleoside transporter inhibition. This may partly explain why users of cannabis preparations with high CBD: THC ratio are less likely to develop psychotic symptoms than those that consume preparation with low CBD:THC ratio[43]. Therefore, CBD has been proposed as a potential treatment for psychosis[40,44].

Neurogenic pain and cancer pain

Vaporized cannabis has been shown to have analgesic efficacy. A study compared two doses of vaporized cannabis: low (1.29%) and medium (3.53%) dose to treat neuropathic pain. Both doses showed analgesic efficacy comparing to placebo. Psychotropic effects were minimal[45]. Another study showed that patients who inhaled cannabis-extract cigarettes with 3.56% THC in TID for 5 days reduced chronic daily pain by 34% (median reduction) vs 17% with placebo and greater than 30% reduction in pain was reported by 52%. in cannabis group

vs 15 % with placebo[46]. A study compared the efficacy of THC:CBD extract, THC extract with Placebo by comparing mean Pain Numerical Rating Scale. It showed improvement in THC:CBD group vs placebo group (-1.37 vs -0.69) while THC group showed no significant improvement vs placebo (-1.01 vs -0.69)[47]. Long-term use of THC/CBD oromucosal spray (nabiximols or Sativex) was generally well tolerated with no evidence of a loss of effect for the relief of cancer-related pain. Furthermore, patients who kept using THC/CBD oromucosal spray did not seek to increase their dose of this or other pain-relieving medication overtime[48]. Another randomized double-blind, placebo-controlled, graded-dose study of nabiximols as add-on analgesic for patients with opioid-refractory cancer pain demonstrated efficacy and safety at low (1-4 spray per day) and medium dose (6-10 spray per day) doses[49]. Another double-blind, placebo-controlled crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain also showed better efficacy than placebo[50]. A synthetic THC that was approved by FDA called dronabinol (Marinol) to treat anorexia and weight loss in HIV/AIDS and cancer patients. dronabinol closely mimics the action of cannabis sativa L, a naturally occurring compound activated in the central nervous system by CB1 receptors. It exerts its effects by directly acting on the vomiting and appetite control centers in the brain[51]. The common side effects of dronabinol are drowsiness, euphoria, dry month and tachycardia. Another synthetic THC that were approved by FDA was nabilone (Cesamet). It is used as an antiemetic to treat nausea and vomiting caused by cancer drug and as an adjunct analgesic for neuropathic pain, fibromyalgia[52]. The most common side effects of nabilone include euphoria, drowsiness and dizziness[53].

Migraine

There was a number of studies on the use of cannabis to treat migraine headache. Most reports studied a small number of cases. A retrospective chart review of 121 adults with migraine, who use prescribed medical marijuana to treat or prevent migraine had migraine frequency decrease from 10.4 to 4.6 headache per month ($p< .0001$) Most participants used more than one form of marijuana daily for prevention. The study showed decreased frequency of migraine headache in 24 patients (19.8%) and aborted migraine headache in 14 patients (11.6%). The most common side effects were somnolence and difficulty controlling the effects of marijuana related to timing and intensity of the dose; edible marijuana products caused more negative effects [54].

The therapeutic effects of cannabis in migraine were possibly related to endocannabinoid. The study showed that AEA produced serotonin receptor responses consisting of 89% potentiation of 5-HT1A and 36% inhibition of 5-HT2A[55], the periaqueductal gray matter is a putative migraine generator in which AEA is tonically active, producing analgesia when administered or hyperalgesia when CB1 is pharmacologically blocked[56]. AEA diminished blood vessel dilation in the dura mater induced by calcitonin gene-related peptide (CGRP) 30%, capsaicin 45%, and nitric oxide (NO) 40%. Additionally, AEA acted presynaptically to prevent release of NO by CGRP in dural artery smooth muscle. AEA also was released in tonic manner and displayed modulatory activity in the trigeminovascular system[57].

In an animal model of migraine, AEA reduced nitroglycerin-induced neuronal activation in the nucleus trigeminalis caudalis and area postrema, the latter being an emetic chemoreceptor. There was likewise an induction of expression of the immediate early gene transcription factor Fos in the hypothalamic paraventricular and supraoptic nuclei, in the parabrachial nucleus, and in the brainstem periaqueductal gray matter of the brainstem. These findings reinforce an important role of the endocannabinoid system in generation of migraine episodes[58]. An additional study showed that 2-AG and AEA levels were both profoundly reduced in the platelets of patients with episodic migraine without aura (N=20) and CM (N=20) versus controls (N=20) ($p<0.0001$)[59].

In the study of chronic migraine (CM), AEA levels in cerebrospinal fluid of 15 chronic migraineurs showed reduced AEA levels. This supported the hypothesis of the failure of this endocannabinoid system in chronic migraine, which seems to be related to increased CGRP and NO production in this pathological condition. This finding might be due to a failure of the inhibitory role of the endocannabinoid AEA on the trigeminovascular system activation[60].

A survey study of 139 patients with cluster headache

found that 45.3% had history of cannabis use and 19.4% had tried cannabis to treat cluster headache. Only 25.9% of self-reported users had relief after inhaling cannabis[61]. The possible explanation is that the hypothalamus is thought to be the region of activation in cluster headache and other trigeminal autonomic cephalalgias, and there is a dense concentration of CB1 in the hypothalamus[61].

Multiple sclerosis

Early studies of cannabinoid in experimental mouse models of multiple sclerosis revealed a reduction in motor symptoms with stimulation of the CB1 and CB2 receptors and a concordant exacerbation of symptoms with their antagonism[62]. Endocannabinoid was found to be upregulated during the spasticity phases of disease progression, and inhibiting the activity of their metabolizing enzymes reduced the spasticity. Together, these findings suggest that the endocannabinoid may work to counteract symptoms of multiple sclerosis and a role for therapeutic cannabinoid use in the alleviation of these symptoms[34]. Nabiximols, THC/CBD oromucosal spray, was found to alleviate neuropathic pain, spasticity, overactive bladder and other symptoms of multiple sclerosis[63]. Recently, a meta-analysis of 17 randomized, placebo-controlled studies on medical cannabis for multiple sclerosis was reviewed. The select trials comprising 3,161 patients compared the effect of cannabinoids taken orally or oromucosally and identified significant findings for spasticity, pain and dysfunction bladder. Patients in the trials used a number of different cannabinoid-containing drugs including oral cannabis extracts containing THC and CBD, oromucosal cannabis extracts nabiximols (Sativex), dronabinol (Marinol) and nabilone (Cesamet) and synthetic oral versions of THC. The meta-analysis found the drugs provided mild relief from spasticity, pain and bladder dysfunction and overall the drug was well tolerated. Patients taking medical cannabis had a higher risk for dizziness or vertigo, dry mouth impaired balance and memory impairment compared with patients on placebo[64]. Another recent study compared and evaluated pain modulation and thermal/pain threshold of patients with multiple sclerosis by using quantitative sensory testing and laser-evoked potentials for pain modulation before and after 1 month of nabiximols therapy. The results indicated that nabiximols therapy provided pain relief in multiple sclerosis patients and suggested that it might modulate peripheral cold-sensitive transient receptor potential (TRP) channels[65].

Parkinson disease

Many studies examining the efficacy of cannabis in Parkinson disease are limited to questionnaires and observation in patients actively consuming cannabis either prescribed or recreational cannabis[66]. A majority of patients with Parkinson disease treated with cannabis reported improvement in overall symptoms, specifically reduction of tremor, muscle stiffness and pain, and improvement of depressed mood[67]. However, a large percentage of patients also reported having at least adverse event including confusion, anxiety, hallucination, amnesia, psychosis, cough, dizziness, unsteadiness and breathlessness[68]. It is interested that dopaminergic neurons have no cannabinoid receptors, but molecular studies suggest modulation of dopaminergic neurons occurs in response to cannabinoids[69]. Other studies have also shown that cannabinoid modulates dopamine signaling[34]. The mechanism shows that CB1 receptor is found in high concentration on noradrenergic neurons in the basal ganglia, specially the caudate, putamen, substantia nigra, globus pallidus, hippocampus and molecular layer of the cerebellum. This specific localization of CB1 may explain the impact of cannabis on cognitive and motor activity[70]. Furthermore, CB1 receptor levels are diminished in the basal ganglia, but not other regions, of postmortem of Parkinsonian human brain[71]. Another study shows that loss of upstream noradrenergic neurons that innervate dopaminergic neurons causes Parkinson-like effects in animal models[72,73]. It is concluded that the effects of cannabis on tremor and motor symptoms is likely through effects on dopaminergic and noradrenergic transmission at some level[73]. However, the existing evidence is still limited and not conclusive and requires further clinical study. Another explanation is by direct laboratory measurement of AEA level of CSF in untreated Parkinson's disease patients demonstrated a doubling of AEA levels over age-matched controls ($p<0.001$), irrespective of disease stage. The authors posited this as a compensatory mechanism in the striatum of Parkinson's disease patients in an effort to alleviate dopamine depletion. Subsequently, another study demonstrated the

role of the endocannabinoid system in synaptic long-term depression in motor circuits in Parkinson's disease. The motor deficits present in rodents with dopamine lesions were reversed by combining a D2 agonist with an endocannabinoid reuptake inhibitor. This finding suggests that progressive dopamine loss in Parkinson's disease in striatal circuits may decrease endocannabinoid tone and that the elevations in anandamide in Parkinson's disease patients may be an attempt to compensate for this loss[74].

CBD was studied in an exploratory double-blind trial in patients with Parkinson's disease showed the improvement of the quality of life in Parkinson's disease[75]. CBD may be effective, safe and well tolerated for the treatment of the psychosis in Parkinson's disease[76]. CBD demonstrated relief for tremor, psychosis and problem sleeping in patients with Parkinson's disease. An explanation of the effect of CBD in Parkinson's disease is related to GPR6. GPR6 is considered orphan receptor because there is no confirmed endogenous agonist for it. However, GPR6 is phylogenetically related to the cannabinoid receptor. In this study, the activities of endocannabinoids and phytocannabininoid were tested on GPR6 using a B-arrestin2 recruitment assay. Among the variety of cannabinoids tested. CBD significantly reduced B-arrestun2 recruitment to GPR6. In addition, the inhibitory effects of CBD on B-arrestin2 recruitment were concentration -dependent for GPR6. These results demonstratethat GPR6 novel moleculars for CBD. CBD acts as a novel inverse agonist on GPR6 indicates that some of the potential therapeutic effects of CBD on Parkinson's disease may be mediated through this receptor[77].

Huntington disease

A study showed that rats intoxicated with 3-nitro-propionate (3NP) as rat models of Huntington disease were given combination of THC and CBD in a ratio of 1:1 as in Sativex attenuated 3 NP-induced GABA deficiency, loss of nissl-stained neurons. Down-regulation of CB1 receptor and IGF-1 expression, and up-regulation of calpain expression, whereas it completely reversed the reduction in superoxide dismutase-1 expression. Similar responses were generally found with other combination of THC and CBD suggesting that these effects are probably related to the antioxidant and CB1 and CB2 receptor-independent properties of both phytocannabinoids[78].

Another study demonstrates the efficacy of CBD with THC in a transgenic murine model of Huntington disease, i.e. R6/2 mice, in which the activation of both CB1 and CB2 receptors has already been found to induce beneficial effects[79,80]. Recent clinical study demonstrated that cannabinoids, CBD with THC, improved the UHDRS motor score and the dystonia subscore of patients with Huntington disease[81]. However, there are human clinical trials addressed Huntington disease using cannabinoids, but the results of these studies have been conflicting[34].

Neonatal hypoxic-ischemia encephalopathy

Neonatal hypoxic-ischemia encephalopathy is resulted from the deprivation of oxygen during childbirth. The only available treatment is therapeutic hypothermia for asphyxiated infants but only provides neuroprotection in infant with mild neonatal hypoxic ischemia encephalopathy[82]. There is evidence that CBD has been known to have neuroprotection, because CB2 receptors are somehow involved in neuroprotective effects of CBD in immature brain. The neuroprotective effect is related to the modulation of excitotoxicity, oxidative stress and inflammation, as CBD normalizes the release of glutamate and cytokines as well as the induction of iNOS and COX2. It is also found that possible adverse effects of excessive CB1 signaling in the developing brain of newborn mice counterbalance the neuroprotective effects[83]. CBD is therefore a promising compound because it does not stimulate the CB1 receptor but CBD acts at CB2 receptor that is somehow involved in neuroprotective effects of CBD in immature brain including restored motor ability that is sustained over the long term in rodent models of injury[84]. Another study demonstrates that the administration of CBD after hypoxic ischemic insult in newborn pigs also reduces immediate brain damage by modulating cerebral hemodynamic impairment and brain metabolism derangement and preventing the appearance of brain edema and seizures. These neuroprotective effects are not only free from side effects but also associated with some beneficial cardiac, hemodynamic and ventilatory effects. These protective effects restore neurobehavioral performance in the following 72 hours post hypoxic ischemic brain damage. Furthermore, the therapeutic window of opportunity for intervention with CBD is

longer, 12 hours, than that of the existing hypothermic approach[85].

Epilepsy

Experimental and human studies have provided evidence for the anticonvulsant properties of CBD. In generalized seizure model in animal studies, CBD blocked maximal electroshock (MES), pentylenetetrazole (PTZ), 6Hz, 60 Hz, picrotoxin, isonicotinic acid, bicuculline, hydrazine, limbic kindling (electrical) and strychnine. In partial seizure model in animal studies, CBD blocked penicillin induced. CBD at high doses has an indirect antagonistic effect of CB1 resulting in the anticonvulsant properties[12]. CBD believes to act on other non-endocannabinoid signaling systems. A Cochrane review examined available data for CBD in epilepsy which consisted of four trials evaluating only responder rate and safety of THC, CBD and other cannabinoids and owing to the paucity of data concluded that there is insufficient body of evidence to recommended using marijuana to treat epilepsy[86]. However, since 2013, several epilepsy centers have been collecting data on children and young adults with severe epilepsy to better understanding the potential application of cannabidiol as part of a study authorized by the FDA. On reviewing the pharmacokinetics of CBD, CBD has low water solubility, absorption leads to variable pharmacokinetics if given as capsules. CBD given in oil product and by oral-mucosal/sublingual delivery through spray/lozenges has less variability. Furthermore, most CBD oil products in the markets are not standardized. GW Pharmaceutical/Greenwich Biosciences manufactures the CBD oil in a controlled standardized way to produce a medicine that is highly pure CBD with high safety standards. This purified extract of cannabis contained 99% CBD and less than 0.1% of THC called Epidiolex (GW Pharmaceuticals). GW Pharmaceuticals then proceeded with randomized controlled trials for use of Epidiolex in Dravet's syndrome and Lennox-Gastaut Syndrome. Results for the use of CBD oral solution to treat seizures associated with Dravet syndrome have been previously reported with patients taking 20 mg per kg per day experiencing a 39% drop in seizure frequency compared to a 13% drop experienced by those taking placebo[87]. Long-term cannabidiol treatment in patients with Dravet syndrome demonstrated an acceptable safety profile and led to sustained, clinically meaningful reductions in seizure frequency in patients with treatment-resistant Dravet syndrome[88,89]. Another study randomized 225 patients with refractory Lennox Gastaut Syndrome. The patients were currently taking an average of 3 antiepileptic drugs to which the cannabidiol or placebo were added. 149 were in CBD group (76 patients took 20 mg/kg/day and 73 patients took 10 mg/kg/day and 76 in placebo group) Duration of study was 14 weeks. Sensitivity analyses confirmed that the treatment effects of CBD were established during the first month of treatment and sustained over entire treatment period patients taking CBD 20 mg/kg/day had a 41.9% reduction in seizure frequency ($p=0.005$) or those taking CBD 10 mg/kg/day had 37.2% reduction in seizure frequency ($p=0.002$). Those treated with CBD reported more improvement on subjective impression of change questionnaires compared to placebo ($p<0.05$ for those doses). It was concluded that adjunctive CBD resulted in greater reduction in drop attacks than placebo. CBD oral solution has been generally well tolerated in both trials[90]. A small study of 18 of 56 patients with tuberous sclerosis who had intractable epilepsy were treated with Epidiolex from 5 mg/kg/day to maximum 50 mg/kg/day. Nine of these 18 patients or 50% showed mean seizure reduction. However, 12 of 18 patients (66.7%) showed adverse events including drowsiness (N:8) 44.4%, ataxia (N:5) 27.8%, diarrhea (N:4) 22.2%[91]. Another study on long-term safety and treatment effect of cannabidiol in 25 children and adults with treatment-resistant epilepsies treated with median CBD dose 25 mg/kg/day showed that proportion of patients with ≥50%, ≥75% and 100% reductions in convulsive seizures were 52%, 31% and 11% respectively, at 12 weeks, with similar rates through 96 weeks. CBD was generally well tolerated, most common adverse events were diarrhea (29%) and somnolence (22%)[92]. A study monitored drug interaction between CBD and other antiepileptic drugs. Increasing doses of CBD raise serum levels significantly of topiramate, zonisamide, rufinamide, desmethylclobazam active metabolite of clobazam, and eslicarbazepine. CBD has no significant interaction with valproate, levetiracetam, lacosamide and perampanel. But AST/ALT levels were significantly higher in participants taking concomitant valproate[93]. This study emphasizes the importance of monitoring serum antiepileptic drug levels and liver function tests during the treatment with CBD.

In conclusion, although CBD has shown to have benefit in a variety of neurological disorders particularly epilepsy, the risk and benefits should be carefully weighed. Long-term safety effect of THC has been reported, but long-term safety of CBD has not been known. A recent study showed significantly low abuse potential of CBD at 750 mg therapeutic doses in a highly sensitive population of polydrug users[94]. However, the therapeutic dosage of CBD is not standardized among various neurological disorders. Epidiolex has been approved as a drug by FDA, but there are CBD oil products that are extracted by other manufactures and are used as herbal supplement. They are not standardized in purification and dosage. Patients should be cautioned against getting CBD from unreliable sources until FDA can find a better solution in this matter.

Potential conflicts of interest

The author has no conflicts of interest to declare

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