REVIEWING THE MANY APPLICATIONS OF CANNABINOID-RIC GUT-BRAIN AXIS

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This is the third and final installment of a series of articles discussing cannabinoid-rich hemp oil and a new certification program for dietary supplement manufacturers and healthcare practitioners offered by the International Center for Cannabis Therapy (ICCT). As Chief Medical Officer–USA of the ICCT, a Czech Republic-based partnership of qualified doctors and scientists who specialize in the medical application of cannabis, Dr. Meletis is an expert on the clinical applications and research supporting the use of cannabinoid-rich hemp oil and its effects on the endocannabinoid system. Last month, we

discussed the endocannabinoid system, its role in health, and how the endocannabinoid system interacts with the adrenals, sex hormones, and gut. We also shared pre-clinical and clinical research and Dr. Meletis' observations about the use of cannabinoid-rich hemp oil in clinical practice, with an emphasis on the management of pain and inflammation and how to balance the endocannabinoid system without overwhelming its receptors. In this article, we'll address the use of cannabinoid-rich hemp oil in applications such as Alzheimer's disease, depression, anxiety, irritable bowel syndrome, stroke, schizophrenia, autoimmunity, and epilepsy, among other uses. We'll also discuss the role of cannabinoids in the gut-brain axis.

Healthcare practitioners who want to delve deeper into the benefits of cannabinoid-rich hemp oil, understand the legal ramifications of prescribing it, and become certified as a respected hemp oil expert who understands proper dosing and other nuances of hemp oil use, can sign up for the ICCT online medical certification program at www.icctcertification.com.

A Brief Review of the Endocannabinoid System

Endogenous endocannabinoids that are produced within the body including anandamide (arachidonylethanolamide) and 2-arachidonylglycerol (2-AG) are able to activate receptors in the endocannabinoid system. Phytocannabinoids such as Δ9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa*, and cannabidiol (CBD), a non-psychoactive component, are also able to activate endocannabinoid receptors. Two of the main receptors in the endocannabinoid system are CB1 and CB2. CB1 is the primary receptor in the nervous system. It is also found in the adrenal gland, adipose tissue, heart, liver, lungs, prostate, uterus, ovary, testis, bone marrow, thymus, and tonsils. CB2 is primarily expressed in the immune system. Endocannabinoids and phytocannabinoids also act upon other receptors to achieve some of their beneficial effects. When the endocannabinoid system is stressed, there is a loss of homeostasis; and a number of diseases can result. For more detail about endocannabinoids and their receptors as well as supporting references, we recommend you read part two of this article.

The Endocannabinoid System and Neurological Diseases

An impaired endocannabinoid system may play a role in neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's disease. Endogenous cannabinoid signaling performs many functions in the central nervous system (CNS), such as modulating neuroinflammation and neurogenesis, as well as regulating synaptic plasticity, and the response to stress.[1,2] Furthermore,

upregulation of type-2 cannabinoid (CB2) receptors is associated with many neurodegenerative disorders. Consequently, influencing CB2 receptor signaling may be neuroprotective.[2]

Endocannabinoids possess a broad-spectrum of activity,[2] which is advantageous in neurodegenerative diseases where neural dysfunction is caused by a combination of different factors including protein misfolding, neuroinflammation, excitotoxicity, oxidative stress, and mitochondrial dysfunction.[2] The endocannabinoid signaling system is thought to regulate each of these factors.[2] The endocannabinoid system also modulates brain tissue homeostasis during aging and/or neuroinflammation.[2]

CB2 receptors exert neuroprotective properties through their ability to suppress inflammation.[3] Activation of CB2 receptors regulates the production of cytokines, proteins that play a significant role in immune function and inflammatory responses.[4] Conversely, rather than inhibiting neurodegenerative diseases via an immunological pathway, the CB1 receptor suppresses cell death through protecting against excitotoxicity, overstimulation of excitatory receptors and simultaneous calcium release.[2]

In the neurons of healthy brains, there is a lower expression of CB2 receptors. However, a significant increase in expression of these receptors is noted in reactive microglia and activated astrocytes during neuroinflammation.[5,6] Microglia are cells in the brain and spinal cord. When they become reactive, it is associated with neurodegenerative diseases. Activated microglia modulate inflammatory responses to pathogens and injury by signaling the synthesis of pro-inflammatory cytokines. Similarly, diseases that impact the central nervous system activate astrocytes. The fact that CB2 receptors are highly expressed when both these types of cells are activated may indicate they are needed to combat inflammation. This led researchers to conclude, “Therefore, the CB2 receptors have the potential to restrain the inflammatory processes that contribute to the declines in neural function occurring in a number of neurodegenerative disorders.”[2]

The involvement of CB2 receptors in Alzheimer’s disease was demonstrated in a number of human studies. Inspections of postmortem brains from individuals with Alzheimer’s disease showed that CB2 receptors are upregulated in cells that are linked to amyloid beta (Aβ)-enriched neuritic plaques.[7-10] The deposition of amyloid beta plaques in the brain are involved in Alzheimer’s disease pathology. Other researchers found markedly higher CB2 receptor levels in individuals with severe Alzheimer’s disease compared with age-matched controls or people with moderate Alzheimer’s.11 Activation of the CB2 receptor has resulted in beneficial effects in Alzheimer’s disease, including the inhibition of microglial activation in mice.[12]

Further support for the role of the endocannabinoid system in Alzheimer’s is provided by preclinical studies showing that cannabidiol, the non-psychoactive component of *Cannabis sativa*, may be beneficial in Alzheimer’s. In one of these studies, mice inoculated with Aβ then injected with CBD (2.5 or 10 mg/kg) for seven days had anti-inflammatory and neuroprotective effects as evidenced by its

ability to suppress a marker of activated astrocytes.13 A rat model of Alzheimer's-related neuroinflammation further elucidated the role CBD may play in Alzheimer's. In this study, adult male rats were inoculated with human Aβ42 in the hippocampus.[14] Then, for 15 days, they were given 10 mg/kg CBD either with or without a PPAR-γ or PPAR-α receptor antagonist. CBD counteracted many of the pathogenic mechanisms of Aβ, and its effects involved the regulation of PPAR-γ. This makes sense since PPAR-γ receptors are increased in people with Alzheimer's disease.

Parkinson's Disease

The progressive loss of dopaminergic neurons primarily in the substantia nigra (SN) is the distinguishing characteristic of Parkinson's disease. This dopaminergic neuron loss impairs the basal ganglia leading to bradykinesia (slowness of movement), rigidity, and tremors. Inflammation is a prominent player in Parkinson's disease pathogenesis. Post-mortem evaluations of Parkinson's disease patients observed microglia activation in the SN.[15] Structural brain imaging studies have also shown that activated microglia and an increase of proinflammatory cytokines occur in the nigrostriatal system of Parkinson's disease patients.[16,17] A post-mortem study indicated that individuals with Parkinson's disease have increased expression of CB2 receptors in microglial cells of the SN.18 This and other evidence suggests that targeting the CB2 receptor may serve as an anti-inflammatory approach in Parkinson's.[2]

In support of the idea that modulating the endocannabinoid system is beneficial in Parkinson's disease are a number of small studies investigating the use of cannabidiol in this group of patients. In a double-blind, placebo-controlled study of 21 Parkinson's patients without dementia or comorbid psychiatric conditions, 300 mg/day cannabidiol enhanced well-being and quality of life.19 In an open-label pilot study, six Parkinson's disease outpatients (four men and two women) who suffered from psychosis for at least three months received CBD starting with an oral dose of 150 mg/day for four weeks combined with their usual therapy.[20] CBD intervention resulted in a marked decline in psychotic symptoms as measured by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire. CBD also lowered the total scores of the Unified Parkinson's Disease Rating Scale. Furthermore, cannabidiol significantly reduced the frequency of sleep behavior disorder (RBD) in four patients with Parkinson's disease.[21]

Anxiety and Post-Traumatic Stress Disorder

The endocannabinoid system regulates stress and anxiety, and modulation of the endocannabinoid system has been found to reduce anxiety. Repeated injections of cannabidiol to mice exposed to

chronic unpredictable stress reduced anxiety in the animals. This effect was mediated by CB1, CB2, and serotonin (5HT1A) receptors. In a double-blind randomized trial investigating subjects with generalized social anxiety disorder not receiving medication, 600 mg of cannabidiol reduced anxiety and cognitive impairment caused by simulated public speaking and improved the participants' comfort level in their speech performance.[23] Another study of 10 individuals with generalized social anxiety disorder observed that 400 mg of cannabidiol was associated with markedly reduced subjective anxiety.[24] Furthermore, advanced imaging studies indicate that the endocannabinoid system is underactive in post-traumatic stress disorder.[25] Preliminary studies in humans have observed that cannabinoids may improve PTSD symptoms such as sleep quality and hyperarousal.[26] Nabilone, a synthetic cannabinoid, reduced PTSD-related nightmares in a small group of Canadian military personnel.[27] In an animal model, cannabinoids given shortly after experiencing a traumatic event blocked the development of a PTSD-like phenotype.[26]

For more information about the interaction between the endocannabinoid system and anxiety, we recommend you enroll in the ICCT medical certification program at www.icctcertification.com. This is a vast topic that cannot be addressed in one article alone.

Depression

Dysregulation of the endocannabinoid system may be involved in the development of depression. Suppressing the CB1 receptor results in a phenotypic state that is comparable to melancholic depression, with identical symptoms such as decreased appetite, increased anxiety, arousal, and wakefulness, an inability to release aversive memories, and increased sensitivity to stress.[28] Furthermore, some antidepressant medications enhance endocannabinoid activity.[28]

One mechanism by which CBD reduces depression may be via its ability to protect against the effects of stress. Stress can lead to anxiety and depression. In animal models, CBD lowers autonomic indices of stress and behavioral effects of depression and anxiety and improves the delayed emotional consequences of stress via mechanisms that involve serotonin receptors.[29,30] CBD is also thought to reduce depressive symptoms by enhancing hippocampal neurogenesis. Ongoing administration of CBD in mice undergoing chronic unpredictable stress improved depressive- and anxiety-like behaviors and triggered hippocampal progenitor proliferation and neurogenesis.[31]

CBD is thought to stimulate neurogenesis by elevating hippocampal levels of the endocannabinoid anandamide (AEA). A clinical study found that higher serum concentrations of AEA were associated with reduced anxiety in patients with major depression, although in this group of patients AEA levels were not associated with major depressive symptoms.[32] Conversely, in people with minor depression, AEA concentrations were elevated compared to controls, suggesting that these levels might be raised as the body's way to compensate for the depression and that they may have a neuroprotective role in

patients with less severe depressive symptoms.

The role of cannabinoids in depression is a vast topic, and we recommend that you enroll in the ICCT medical certification program to understand how phytocannabinoids can be safely used in depression.

Gut-Brain Axis and Endocannabinoids

The gut-brain axis refers to the bidirectional interplay between the gut microbiota and the nervous system whereby the gut microbiota can impact behavior and cognition and the central nervous system can influence enteric microbiota composition. The gut-brain axis is thought to explain the association between chronic inflammatory bowel disease and depression.[33]

Accumulating evidence points to the endocannabinoid system's important role in both normal gastrointestinal function and gastrointestinal pathology.[34] The endocannabinoid system is involved in the regulation of motility, gut-brain-mediated fat intake and hunger signaling, and inflammation and gut permeability.[34] The endocannabinoid system also works together with the gut microbiota to maintain gut health.[34] Additionally, cannabinoids help recruit immune cells to the site of intestinal inflammation.[35] In models of colitis, cannabidiol also has been shown to suppress the synthesis of pro-inflammatory cytokines, such as TNF-α and IFN-γ.[35-38] This anti-inflammatory role in gut health was also reflected in a study where intestinal tissues of individuals with ulcerative colitis had concentrations of the endocannabinoid PEA that were 1.8 fold higher compared with healthy patients, likely in an attempt to help heal the inflammation.[39] The anti-inflammatory effect of cannabinoids in the gastrointestinal system may be mediated by the gut microbiota. In mice, dysbiosis of the microbiota caused by antibiotics resulted in a general inflammatory state and altered endocannabinoids in the gut.[33] (The concept of an endocannabinoidome will be addressed in much further detail in the ICCT certification program). Mitochondrial transport in enteric nerves may also be controlled by CB1 receptors, further lending support to the role of cannabinoids in gut health.[40]

The interplay between the gut, the brain, and the endocannabinoid system is involved in the development and progression of inflammatory bowel disease and irritable bowel syndrome. CB1 receptors in sensory ganglia modulate visceral sensation. During ongoing psychological stress, epigenetic pathways change the transcription of CB1 receptors, a mechanism which may explain the link between stress and abdominal pain.[41] Furthermore, in rodent models, the endocannabinoid system is altered by early-life stress, leading to the development of irritable bowel syndrome (IBS).[42,43]

In tissue from humans with inflammatory bowel disease, there is elevated epithelial CB2-receptor expression.[44] This indicates that CB2 receptors modulate immunity in this disorder.[45] The CB2 receptors impact mucosal immunity and act together with CB1 receptors in the colonic epithelium to encourage epithelial wound healing.[44]

Research suggests that type 1 vanilloid receptors (TRPV1) may regulate some cannabinoid effects. One study observed a 3.5-fold increase in TRPV1-immunoreactive nerve fibers in biopsies from IBS sufferers compared with controls.[45] This elevation may promote visceral hypersensitivity and pain in IBS.[45] One scientist concluded, “Thus, a rationale exists for therapeutic interventions that would boost AEA levels or desensitize TRPV1, such as cannabidiol (CBD), to treat the condition [IBS].”[25]

Cannabinoids, Autoimmunity, Strokes, Epilepsy, and Other Disorders

Cannabidiol may have a role to play in autoimmune health. Animal models indicate it exerts beneficial actions in a number of autoimmune disorders including multiple sclerosis (MS), type 1 diabetes, and autoimmune myocarditis.[46,47] Autoimmune disease develops due to transformed subsets of T cells into autoreactive memory T cells. These cells are falsely directed to target the body’s own cells resulting in tissue degeneration and autoimmune disease development such as type 1 diabetes, rheumatoid arthritis, and MS.[46] CBD is able to modulate autoreactive T cell function.[46] In one study it weakened the function of encephalitogenic Th17 cells.[46] CBD also increased anti-inflammatory actions in activated memory T cells including enhanced synthesis of the anti-inflammatory IL-10 cytokine.[48] Furthermore, CBD produced anti-inflammatory effects in animal models of T cell-mediated collagen-induced arthritis,[49] autoimmune diabetes,[50] and autoimmune hepatitis.[51] It also has reversed the development of type 1 diabetes mellitus in mice.[52] Most of the human studies showing cannabinoids are beneficial in multiple sclerosis have used a pharmaceutical combination of THC and CBD.[53,54]

Cannabinoids are important to other aspects of immunity. Specifically, they possess strong antibacterial activity. All five major cannabinoids (cannabidiol, cannabichromene, cannabigerol, Delta (9)-tetrahydrocannabinol, and cannabinol) significantly inhibited a number of methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[55] THC use by itself, however, was associated with increased susceptibility of mice to infection with the pathogen *Legionella pneumophila*.[56]

Another application of CBD may include protection against stroke.[57] In vivo and in vitro stroke models indicate cannabidiol reduces infarct size.[57] A study of human brain microvascular endothelial cells and human astrocyte co-cultures suggests that CBD can prevent permeability changes in the blood brain barrier.[57]

Another promising role for cannabidiol is in the improvement of schizophrenia. Modulating the endocannabinoid system using THC, the main psychoactive component in cannabis, can cause acute psychotic effects and cognitive impairment in schizophrenia patients.[58] Conversely, CBD may possess antipsychotic actions and may have a role to play in supporting schizophrenia patients. Evidence to this effect is emerging thanks to small-scale clinical studies with CBD for the treatment of patients with psychotic symptoms.[59] The results demonstrated that CBD is effective, safe, and well-tolerated in

patients with schizophrenia, although large randomized clinical trials are needed.[59]

Cannabidiol has also been used successfully in clinical practice and in human studies in patients with epilepsy. It has been found to improve brain tumor-related seizures.[60] Additionally, patients with Sturge-Weber syndrome, a disorder characterized by medically refractory epilepsy, stroke, and cognitive impairments, experienced up to a 50% reduction in seizures after supplementation with cannabidiol.[61] It's important to note that CBD supplementation can alter the serum levels of certain anti-epilepsy medications. This is not always a bad thing as CBD may reduce the side effects of some epilepsy medications by lowering their dosage.[62] However, the blood levels of these pharmaceuticals should be monitored when taking CBD.

Dr. Meletis will discuss these and other clinical applications of CBD in the ICCT medical certification course and will also talk about the proper dosing to ensure that doctors who suggest CBD aren't doing more harm than good. This is especially important in regard to seizures as too much CBD may actually cause seizures.

Dosing, Side Effects, and Drug Interactions

Cannabidiol is a safe substance, with a half-life of 18-32 hours,[63] but it can have minor adverse effects in some people. Potential side effects are dry mouth, low blood pressure, light-headedness, drowsiness, tiredness, diarrhea, and changes of appetite or weight.[62,64] There is also cross-reactivity between medical marijuana and certain foods as well as molds, dust mites, plants, and cat dander.[65] It's unclear whether these same reactions occur with cannabidiol. In fact, one mouse study indicated CBD in a dose-dependent manner markedly reduced inflammatory reactions associated with delayed-type hypersensitivity reactions.[66] These are allergic reactions that develop days after exposure to the offending substance.

It is also important to keep in mind that cannabidiol can affect levels of medications. This is indicated by the fact it is an inhibitor of multiple cytochrome P450 enzymes, which are involved in the metabolism of drugs.[67]

The issues of potential side effects, proper dosing, and how to balance the endocannabinoid system without overwhelming its receptors are complex topics that Dr. Meletis and other scientists and doctors at the ICCT discuss in the certification program.

Conclusion

This three-part series began with an article discussing the ICCT's certification for cannabinoid-rich

hemp oil manufacturing facilities and products and how American Nutritional Products was the first company in the US to become ICCT-certified. It also discussed a new medical certification program for healthcare practitioners. This certification program is essential for any doctor recommending cannabinoid-rich hemp oil who wants to be aware of the legal ramifications and develop a greater level of trust among patients. The second part of the series discussed the endocannabinoid system's interaction with the adrenals, sex hormones, and gut with an emphasis on the management of pain and inflammation. Finally, we wrapped up our discussion in this article with many of the clinical applications for cannabidiol.

Cannabinoid-rich hemp oil is being used successfully for a number of conditions. But we want to leave you with the caution that, as noted in the first part of this series, many manufacturers are producing inferior-quality products contaminated with pesticides. Healthcare practitioners who enroll in the certification program at https://www.icctcertification.com/international-cannabinoid-therapy-clinical-mastery/ will know how to differentiate between these poor quality products and ones that are more likely to benefit patients in a safe and effective manner.

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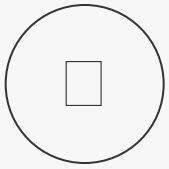

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