Insights from the International Center for Cannabis Therapy, Part 2:

Evidence for the Clinical Use of Cannabinoid-Rich Hemp Oil in the Management of Pain, Inflammation, and Stress

by Chris D. Meletis, ND, and Kimberly Wilkes

In last month's *Townsend Letter,* Dr. Chris Meletis discussed the International Center for Cannabis Therapy (ICCT) cannabinoid certification programs for dietary supplement manufacturers and healthcare practitioners. As the 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. In this article, we will talk about the endocannabinoid system, its role in health, and how the endocannabinoid system interacts with the adrenals, sex hormones, and gut. We'll also share 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. The next part of this article in a future issue of *Townsend Letter* will address the use of cannabinoid-rich hemp oil in applications such as epilepsy, stroke, irritable bowel syndrome, depression, anxiety, and psychosis, among other uses.

These articles can only touch the surface of everything there is to know about the endocannabinoid system and hemp oil. 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.

The endocannabinoid system is a fascinating regulator of many aspects of our health. Endogenous endocannabinoids that are produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), are able to activate receptors in this system. Phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC), the psychoactive component of *Cannabis sativa*, and cannabidiol (CBD), a non-psychoactive component, are also able to activate endocannabinoid receptors. Additionally, synthetic cannabinoids have been synthesized and have an effect on endocannabinoid system pathways.

Two of the main receptors in the endocannabinoid system are CB_1 and CB_2. CB_1 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.[1] Its expression is weak in the areas of the brain stem that regulate respiration, which is why respiratory depression, a potentially fatal adverse effect of opioid drugs, does not occur when using phytocannabinoids as painkillers.[1]

The CB_2 receptor is typically not expressed in neurons, which is why it was originally called the peripheral cannabinoid receptor. The immune system is the primary site of its expression. However, its presence has been detected in dorsal root ganglia, a cluster of cells in spinal nerves.[2] CB_2 receptors can also be expressed in bone, the gastrointestinal tract, and in activated microglia in the central nervous system.[2] Microglia are cells found in the brain and spinal column that defend the central nervous system against immune assaults. Because antibodies are too large to penetrate the blood brain barrier, microglia serve as the last defense against pathogens that enter the brain. Activated microglia, sometimes referred to as reactive microglia, create an inflammatory response linked to diseases of the brain.[3] The presence of CB_2 receptors in activated microglia indicate they may be involved in blocking the effect of painful stimuli in inflammatory processes of the nervous system.[4]

Different phytocannabinoids have different effects on endocannabinoid receptors. THC directly acts on CB_1 receptors of the endocannabinoid system,[5] which are primarily expressed in the brain. CBD indirectly acts on the CB_1 receptors by suppressing the enzymatic breakdown of the

endogenous cannabinoid anandamide, increasing the duration of time it stays in the system.[6] CBD's effects on the CB_1 receptor counteract the psychoactive effects of THC.[7] CBD thus inhibits adverse effects of THC including intoxication, sedation, and tachycardia.[7] CBD also acts on the CB_2 receptor, which is expressed in the periphery and is involved in immunity.[8]

From Fetus to Newborn: The Endocannabinoid System's Important Role

The endocannabinoid system plays an important role in our health long before we are born. The endocannabinoid system has been observed in cell types that play a role in male reproduction.[9] Endocannabinoids and cannabinoid receptors have been detected in testicular tissue, including Sertoli and Leydig cells and spermatozoa.[10] The endocannabinoid system also is involved in the hypothalamus-pituitary-gonadal (HPG) axis.[10] The anandamide-degrading enzyme FAAH regulates key steps in sperm biology pathways, and this action involves the CB1 receptor.[10]

Furthermore, the endocannabinoid system is important and highly expressed during fetal development. Too much cannabinoid resulting in the over expression of anandamide could lead to negative outcomes such as ectopic pregnancy.[11] Therefore, anandamide concentrations in the uterus must be tightly regulated for conception to occur.[12] During vaginal birth, the newborn's exposure to high endocannabinoid levels assists with the transition from fetus to becoming an infant. During birth, the levels of anandamide and an anti-inflammatory fatty acid amide known as palmitoylethanolamide (PEA) are markedly higher in vaginally delivered babies compared with infants delivered by cesarean section,[13] indicating that vaginally born infants would have a naturally higher degree of protection against pain and inflammation.

Another rodent study serving as a good example of the importance of the endocannabinoid system in prenatal and postnatal health involved female rats who were subjected to dietary restriction involving 20% fewer calories than a normal diet during pre-gestation and gestation. At birth, a significant decline in the levels of anandamide, 2-AG, and PEA were detected in the hypothalamus of the offspring of the calorie-restricted rodents. As adults, these offspring were more likely to gain excessive weight and body weight and be overweight as well as have increased anxiety-related responses.[14]

Furthermore, endocannabinoids have been detected in breast milk, and activation of CB_1 receptors was found to be critically important for milk sucking by newborn mice, helping them to develop oral-motor musculature.[15] This means that if a baby is delivered by C-section and then is bottle fed, he or she may be seriously depleted in endocannabinoids and may be at a disadvantage both as infants and later in life both mentally and physically. CB_1 receptors are temporarily present in white matter regions of the pre- and postnatal nervous system.[15] This implies that CB_1 receptors have a part to play in brain development and endocannabinoid deprivation in newborns can therefore be especially concerning.

The importance of the endocannabinoid system to infants is supported by a study showing that anandamide was neuroprotective against lesions induced in perinatal rodents.[16] Another study demonstrated that in rats that receive poor rearing during the neonatal timeframe, the neuroendocrine response to early life stress is reduced. Increasing anandamide levels ameliorates these stress-induced changes in glucocorticoid synthesis in these rats.[17]

Beyond CB_1 and CB_2 Receptors

Research is beginning to look beyond the classical CB_1 and CB_2 receptors as potential mediators of some of the beneficial effects of phytocannabinoids. Other receptors targeted by phytocannabinoids include G-protein coupled receptors (GP- CRs: GPR_{18}, GPR_{55} and GPR_{119}). Both GPR_{18} and GPR_{55} may recognize the phytocannabinoid CBD. Evidence indicates this phytocannabinoid serves as a GPR_{55} antagonist, as well as a weak partial agonist.[1] GPR_{18} is expressed primarily in immune cells while GPR_{55} is expressed in several brain regions as well as in the dorsal root ganglia in neurons with larger diameters, the hippocampus, frontal cortex, cerebellum, striatum, and hypothalamus. GPR_{55} may also be expressed in the immune system as well as in the microglia and bone.[1]

Research suggests that type 1 vanilloid receptors ($TRPV_1$) may regulate some cannabinoid effects. The $TRPV_1$ receptor has been identified in neurons that play a role in pain signaling.[18] Other undiscovered cannabinoid receptors may exist, and these receptors may partly mediate some of the analgesic effects associated with cannabinoids.[19,20]

Interaction of CBD Receptors and Other Physiological Pathways

The role of endocannabinoids and phytocannabinoids in mood enhancement and reduction of pain and inflammation cannot be completely explained by their effects on CB_1 and CB_2 receptors alone as well as the other receptors mentioned above. Cannabinoids influence other pathways and their effects on these pathways may play a role in their myriad health benefits. Peroxisome proliferator-activated receptor gamma (PPAR-gamma) is one of those pathways. PPAR-gamma is a nuclear receptor whose actions include regulation of glucose homeostasis and inflammatory processes and connective tissue health.[21] Mice experiencing a loss of PPAR-gamma function in fibroblasts were more likely to suffer from skin fibrosis.[21] Some endocannabinoids and associated signaling lipids as well as certain natural and synthetic cannabinoids can activate PPAR-gamma including THC and CBD.[22] The anti-inflammatory effects of anandamide and 2-arachidonoylglycerol are mediated by PPAR-gamma.[22]

Moreover, CBD blocks microglial activation in vitro through a mechanism that involves the activation of PPAR-gamma.[23] This effect was mediated by the inhibition of the inflammatory nuclear kappa factor beta (NF-KB)

➤

➤

pathway.[23] The ability of cannabinoids to target both CB receptors and PPAR-gamma may explain their regulation of a number of processes including neuroprotection, inflammation, immunomodulation, and vascular responses.[24]

Cannabinoids also interact with 5HT1A serotonin receptors. It has been shown that the anxiety-reducing effects of CBD are dependent upon neurotransmission that is mediated by 5HT1A.[23] It is thought that CBD indirectly influences the 5HT1A receptors through interactions with the receptor binding site and/or modulating intracellular pathways.[23] CBD's effects on stress-reduction and anxiety as well as its mood-enhancing abilities are also mediated through the 5HT1A receptor.[23] Furthermore, CBD's ability to reduce brain tissue damage in mice caused by cerebral artery occlusion is blocked when 5HT1A receptors are inactivated.[25] The fact that CBD interacts with multiple receptors was shown in an animal study where CBD's ability to prevent hypoxic-induced brain damage was dependent upon both 5HT1A and CB2 receptors.[26]

CB_2 receptors themselves are able to indirectly stimulate opioid receptors located in primary afferent pathways, and this may be a means by which CBD inhibits pain.[27]

Endocannabinoid System Burdens

A number of factors can interfere with the proper functioning of the endocannabinoid system, throwing the body out of homeostasis. For example, obesity is associated with an over activated endocannabinoid system in adult subjects.[28] Moreover, offspring of female rodents that consumed a high-fat diet during pregnancy were obese with fat cell hypertrophy and buildup of lipids in brown adipose tissue.[29] These effects correlated with alterations in the endocannabinoid system of the rat pups. In male offspring of mothers fed a high-fat diet, CB_1 and CB_2 receptor levels declined in subcutaneous adipose tissue. In female offspring of mothers fed a high-fat diet, visceral CB_1 levels increased while subcutaneous concentrations decreased. CB_1 concentrations increased in brown adipose tissue from both male and female offspring of mothers that consumed the high-fat diet.

Toxins can serve as another disrupter of the endocannabinoid system. For example, the mechanism by which BPA causes fatty liver is thought to involve up-regulation of the endocannabinoid system.[30]

An imbalance of the gut microbiota known as dysbiosis is another threat to the optimal functioning of the endocannabinoid system. A rodent study found that dysbiosis of the gut microbiota led to changes in the endocannabinoid system.[31] In this study, researchers administered antimicrobials to mice for two weeks in order to cause dysbiosis. Afterward, the animals were given 10^9 CFU/day of *Lactobacillus casei* DG or a placebo for up to a week. Antimicrobial administration resulted in dysbiosis of the microbiota. At the same time, there was a general inflammatory state and changes in some aspects of the endocannabinoid system in the gut. These changes were accompanied by behavioral alterations, including increased immobility in the tail suspension test (an indicator of depression), as well as biochemical and functional changes in the brain such as neuronal firing in the hippocampus and rearrangements of non-neuronal cells in brain regions controlling emotional behavior. Probiotic intake eliminated most of these changes.

Sex Hormones and Cannabinoids

The association between the endocannabinoid system and estrogen indicates that declining estrogen levels with menopause may disrupt this system. The endocannabinoid system has an under-recognized role in male and female health. Cannabinoids and sex hormones influence common molecular pathways involved in cell proliferation.[32] Furthermore, estrogen plays an important role in the endocannabinoid system expression in the female reproductive tract.[12] Administering the estrogen estradiol to ovariectomized rats caused a marked increase in CB_1, CB_2, the anandamide-degrading enzyme fatty acid amide hydrolase (FAAH), and COX-2 expression.[12] These effects were estrogen-receptor dependent. Anandamide levels also increased in the plasma after estradiol treatment. According to the study authors, "Thus, estradiol may have a direct regulatory role in the modulation of ECS [the endocannabinoid system] in female reproductive tissues."

These findings may explain anecdotal reports of CBD oil reducing hot flashes and other symptoms of surgically induced menopause in women.

Endocannabinoid Imbalance and Psychological Stress

One characteristic of an imbalanced endocannabinoid system is the inability to cope with stress.[33-35] That's why this system is often dysfunctional in people with post-traumatic stress disorder. Stimulation of the endocannabinoid system inhibits the activation of the hypothalamus-pituitary-adrenal axis that occurs after stress.[33-35] In this way, this system helps us recover from anxious experiences and brings us back to homeostasis. In male rodents, when the CB_1 receptor is blocked, it takes longer for the HPA axis to recover from stress.[36]

Significant concentrations of nitric oxide (NO) are found in the brain and adrenal glands and NO may be involved in the stress response. During stress, anandamide suppresses the activity of the nitric oxide synthase enzyme, indicating that endocannabinoids may reduce stress by inhibiting the generation of NO in the hypothalamus and adrenals.[37]

An impaired endocannabinoid system may also be one of the reasons why stress impacts gastrointestinal function.[38] The endocannabinoid system in the gastrointestinal tract regulates motility, secretion, sensation, emesis, satiety, and inflammation. It also influences visceral sensation.

Beyond stress, there are many other consequences of a dysfunctional endocannabinoid system including pain, cognitive dysfunction, depression, epilepsy, and more. We will discuss some of these in further detail in this article while we will address others in next month's issue of *Townsend Letter*.

Improving Endocannabinoid System Function with Cannabinoid-Rich Hemp Oil

Cannabinoid-rich hemp oil is an ideal choice to optimize the endocannabinoid system. Throughout the remainder of this article and the next part of this article we will discuss the justification for using hemp oil in a variety of clinical applications. The primary cannabinoid in hemp oil is CBD. However, it also contains other phytocannabinoids as well as terpenes, which work with CBD to support endocannabinoid system function and therefore make hemp oil uniquely suited to enhance areas of health regulated by the endocannabinoid system. The entourage effect – sometimes called the "hemptourage effect" – refers to the ability of other more minor components of hemp oil such as the terpenes to support the activity of its main player, CBD. For example, the terpenes limonene, pinene, and linalool can provide a complementary action to CBD's cognitive-enhancing abilities by improving mood.[39] Pinene is also known to enhance mental clarity, thus acting synergistically to CBD.[39] The entourage effect is a fascinating aspect of cannabinoid therapy, and Dr. Chris Meletis explores this effect in more detail in the ICCT medical certification program.

Like so many herbals that are popularly used around the world, hemp has been employed for centuries with many health benefits. The moment we start eliminating certain constituents we may lose certain therapeutic benefits often attributed to the entourage or hemptourage effect. Yet, even with that said, we still don't fully know all the effects of the cannabinoids and terpenes either as standalone substances or in concert.

Cannabinoid-Rich Hemp Oil and Pain Control

As noted earlier, various receptors in the endocannabinoid system are involved in the regulation of pain including CB_1, CB_2, and $TRPV_1$. Pain is a common complaint among patients as evidenced by the fact sales of opioid drugs almost quadrupled from 1999 to 2014.[40] CB^2 indirectly activates opioid receptors, thus blocking painful stimuli.[41] In part through this mechanism, cannabinoids reduce inflammatory and neuropathic pain, which are notoriously difficult to successfully treat.[42] Animal models, human studies, and experience from clinical practice indicate that cannabinoid-rich hemp oil or CBD are useful in various types of pain. In a rodent model of osteoarthritis, CBD administered locally to the area surrounding the joint reduced the initial inflammatory response and thus subsequent pain and inflammation.[43] Furthermore, cannabinoid-rich hemp oil reduced body pain and improved other symptoms in girls who had an adverse reaction to the human papillomavirus (HPV) vaccine.[44] Other evidence indicates the oil of cannabis seeds reduces pain in patients with chronic musculoskeletal inflammation, an effect attributed to the ideal omega-3/omega-6 ratio content.[45]

Treating pain properly involves addressing more than just physical discomfort. Pain is a multidimensional problem that also encompasses impairments in mood, cognition, and function. This is one way where management of pain with opioids goes wrong as opioids can actually worsen all of these components of pain. Phytocannabinoids found in hemp oil, on the other hand, can improve all of these accompanying mental health factors as we will discuss in the next part of this article.

Proper Dosing Is Crucial

Before concluding this article, we want to caution that it is important to keep in mind proper dosing protocols when employing cannabinoid-rich hemp oil. CBD is less potent than THC and much higher doses may be needed for its beneficial effects on pain and inflammation. At the same time, it's crucial not to over activate the endocannabinoid system as scientists at the ICCT have found that overdosing on CBD can worsen certain conditions such as epilepsy. It's best to begin dosing at modest levels and then increase the dose slowly over two weeks.

Diligent education and a conservative approach to dose for each individual patient and the patient pool in general needs to be in the forefront of the prescriber. As Dr. Meletis has shared in the classroom setting as an associate professor of natural pharmacology, if a natural substance is strong enough to nudge a biochemical pathway towards optimized homeostasis, it also holds the potential to disturb homeostasis when not employed judiciously. Keeping up with the rapidly growing and burgeoning research field on hemp is critical. This is one reason why Dr. Meletis applauded the ICCT when they decided to create their certification programs. The medical certification program is a more precise way to establish the proper dose by using established ICCT protocols.

We also recommend that healthcare practitioners seek out hemp-oil manufacturers who are recommending the use of products that have been certified by the ICCT so as to avoid hemp oil products that may have contaminants or overly high concentrations of THC.

Conclusion

From long before birth, our bodies are dependent upon the homeostasis provided by the endocannabinoid system, which casts a wide net over various aspects of health including pain management and control of psychological stress, among many others. The endocannabinoid system functions through the activation of a number of receptors. Endocannabinoids as well as phytocannabinoids such as those found in hemp oil interact with these receptors. Consequently,

➤

➤

supporting the function of the endocannabinoid system is an under-recognized way to enhance virtually every aspect of health.

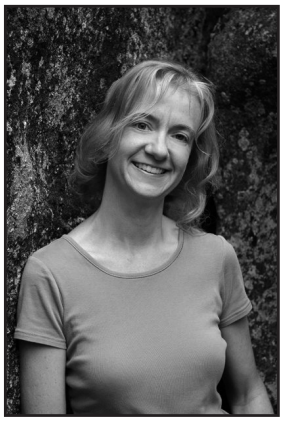
References

1. Miller RJ, Miller RE. Is cannabis an effective treatment for joint pain? *Clin Exp Rheumatol*. 2017 Sep-Oct;35 Suppl 107(5):59-67.
2. Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. *Br J Pharmaco*l. 2010 Jun;160(3):467-79.
3. Lowry JR, Klegeris A. Emerging Roles of Microglial Cathepsins in Neurodegenerative Disease. *Brain Res Bull*. 2018 Feb 15. [Epub ahead of print.]
4. Manzanares, J, Julian MD, Carrascosa A. Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes**.** *Curr Neuropharmacol*. 2006 Jul;4(3):239-57.
5. Bhattacharyya S, et al. Acute induction of anxiety in humans by delta-9-tetrahydrocannabinol related to amygdalar cannabinoid-1 (CB1) receptors. *Sci Rep*. 2017 Nov 3;7(1):15025.
6. Leweke FM, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012 Mar 20;2:e94.
7. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*. 2006;66(2):234-46.
8. Shannon S, Opila-Lehman J. Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report. *Perm J*. 2016 Fall;20(4):108-11.
9. du Plessis SS, Agarwal A, Syriac A. Marijuana, phytocannabinoids, the endocannabinoid system, and male fertility. *J Assist Reprod Genet*. 2015 Nov;32(11):1575-88.
10. Lewis SE, Maccarrone M. Endocannabinoids, sperm biology and human fertility. *Pharmacol Res*. 2009 Aug;60(2):126-31.
11. Gebeh AK, Willets JM, Marczylo EL. Ectopic pregnancy is associated with high anandamide levels and aberrant expression of FAAH and CB1 in fallopian tubes. *J Clin Endocrinol Metab*. 2012 Aug;97(8):2827-35.
12. Maia J, Almada M, Silva A. The endocannabinoid system expression in the female reproductive tract is modulated by estrogen. *J Steroid Biochem Mol Biol*. 2017 Nov;174:40-7.
13. Jokisch V, et al. Endocannabinoid Levels in Newborns in Relation to the Mode of Delivery. *Am J Perinatol*. 2015 Oct;32(12):1145-50.
14. Ramírez-López MT, et al. Maternal Caloric Restriction Implemented during the Preconceptional and Pregnancy Period Alters Hypothalamic and Hippocampal Endocannabinoid Levels at Birth and Induces Overweight and Increased Adiposity at Adulthood in Male Rat Offspring. *Front Behav Neurosci*. 2016 Nov 1;10:208.
15. Fride E. The endocannabinoid-CB(1) receptor system in pre- and postnatal life. *Eur J Pharmacol*. 2004 Oct 1;500(1-3):289-97.
16. Shouman B, et al. Endocannabinoids potently protect the newborn brain against AMPA-kainate receptor-mediated excitotoxic damage. *Br J Pharmacol*. 2006 Jun;148(4):442-51.
17. McLaughlin RJ, et al. Inhibition of anandamide hydrolysis dampens the neuroendocrine response to stress in neonatalrats subjected to suboptimal rearing conditions. *Stress*. 2016;19(1):114-24.
18. O'Hearn S, et al. Modulating the endocannabinoid pathway as treatment for peripheral neuropathic pain: a selected review of preclinical studies. *Ann Palliat Med*. 2017 Dec;6(Suppl 2):S209-14.
19. Breivogel CS, et al. Evidence for a new G protein-coupled cannabinoid receptor in mouse brain. *Mol Pharmacol*. 2001 Jul;60(1):155-63.
20. Hájos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. *Neuroscience*. 2001;106(1):1-4.
21. del Río C, et al. The cannabinoid quinol VCE-004.8 alleviates bleomycin-induced scleroderma and exerts potent antifibrotic effects through peroxisome proliferator-activated receptor-γ and CB2 pathways. *Sci Rep*. 2016 Feb 18;6:21703.
22. O'Sullivan SE. Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. *Br J Pharmacol*. 2007 Nov;152(5):576-82.
23. Campos AC, et al. Cannabidiol, neuroprotection and neuropsychiatric disorders. *Pharmacol Res*. 2016 Oct;112:119-27.
24. del Río C, Navarrete C, Collado JA. The cannabinoid quinol VCE-004.8 alleviates bleomycin-induced scleroderma and exerts potent antifibrotic effects through peroxisome proliferator-activated receptor-γ and CB2 pathways. *Sci Rep*. 2016; 6:21703.
25. Mishima K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke*. 2005 May;36(5):1077-82.
26. Pazos MR, et al. Mechanisms of cannabidiol neuro-protection in hypoxic-ischemic newborn pigs: role of 5HT(1A) and CB2 receptors. *Neuropharmacology*. 2013 Aug;71:282-91.
27. Ibrahim MM, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci U S A*. 2005 Feb 22;102(8):3093-8.
28. Engeli S, et al. Peripheral endocannabinoid system activity in patients treated with sibutramine. *Obesity (Silver Spring)*. 2008 May;16(5):1135-7.
29. Almeida MM, et al. Perinatal maternal high-fat diet induces early obesity and sex-specific alterations of the endocannabinoid system in white and brown adipose tissue of weanling rat offspring. *Br J Nutr*. 2017 Nov;118(10):788-803.
30. Martella A, et al. Bisphenol A Induces Fatty Liver by an Endocannabinoid-Mediated Positive Feedback Loop. *Endocrinology*. 2016 May;157(5):1751-63.
31. Guida F, et al. Antibiotic-induced microbiota perturbation causes gut endocannabinoidome changes, hippocampal neuroglial reorganization and depression in mice. *Brain Behav Immun*. 2018 Jan;67:230-45.
32. Dobavišek L, Hojnik M, Ferk P. Overlapping molecular pathways between cannabinoid receptors type 1 and 2 and estrogens/androgens on the periphery and their involvement in the pathogenesis of common diseases (Review). *Int J Mol Med*. 2016 Dec;38(6):1642-51.
33. Ganon-Elazar E, Akirav I. Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the conditioning and extinction of inhibitory avoidance. *J Neurosci*. 2009 Sep 9;29(36):11078-88.
34. Hill MN, et al. Suppression of amygdalar endocannabinoid signaling by stress contributes to activation of the hypothalamic-pituitary-adrenal axis. *Neuropsychopharmacology*. 2009 Dec;34(13):2733-45.
35. Patel S, et al. Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic-pituitary-adrenal axis. *Endocrinology.* 2004 Dec;145(12):5431-8.
36. Hill MN, et al. Recruitment of prefrontal cortical endocannabinoid signaling by glucocorticoids contributes to termination of the stress response. *J Neurosci*. 2011 Jul 20;31(29):10506-15.
37. Surkin PN, et al. Pharmacological augmentation of endocannabinoid signaling reduces the neuroendocrine response to stress. *Psychoneuroendocrinology*. 2018 Jan;87:131-40.
38. Storr MA, Sharkey KA The endocannabinoid system and gut-brain signalling. *Curr Opin Pharmacol*. 2007 Dec;7(6):575-82.
39. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011 Aug; 163(7):1344-64.
40. Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/data/prescribing.html Accessed March 2, 2018.
41. Ibrahim MM, et al. CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. *Proc Natl Acad Sci U S A*. 2005 Feb 22;102(8):3093-8.
42. Manzanares J, Julian MD, Carrascosa A. Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes. *Curr Neuropharmacol*. 2006 Jul;4(3):239-57.
43. Philpott HT, O'Brien M, McDougall JJ. Attenuation of early phase inflammation cannabidiol prevents pain and nerve damage in rat osteoarthritis. *Pain*. 2017 Dec;158(12):2442-51.
44. Palmieri B, Laurino C, Vadalà M. Short-Term Efficacy of CBD-Enriched Hemp Oil in Girls with Dysautonomic Syndrome after Human Papillomavirus Vaccination. *Isr Med Assoc J*. 2017 Feb;19(2):79-84.
45. Shaladi AM, et al. [Cannabinoids in the control of pain]. [Article in Italian, Abstract in English]. *Recenti Prog Med*. 2008 Dec;99(12):616-24.

◆

Dr. Chris D. Meletis is an educator, international author, and lecturer. His personal mission is "Changing America's Health One Person at a Time." He believes that when people become educated about their bodies, that is the moment when true change and wellness begins. Dr. Meletis served as dean of naturopathic medicine and chief medical officer for 7 years at National College of Natural Medicine (NCNM) and was awarded the 2003 Physician of the Year award by the American Association of Naturopathic Physicians.

www.DrMeletis.com



Kimberly Wilkes is a freelance writer specializing in health, science, nutrition, and complementary medicine. She has written more than 300 articles covering a variety of topics from the dangers of homocysteine to sugar's damaging effects on the heart. She is the editor of ProThera® Inc.'s practitioner newsletter and enjoys scouring the medical literature to find the latest health-related science.