Endocannabinoids, Phytocannabinoids, Palmitoylethanolamide and Their Fascinating Role in Pain Management

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Chronic pain is one of the most common complaints affecting modern society with an estimated 25.3 million US adults (11.2%) suffering from this health concern.[1] Furthermore, almost 40 million adults (17.6%) have severe levels of chronic pain.[1] One of the most severe forms of chronic pain is neuropathic pain, which results from damage to the central or peripheral nervous systems.[2] This damage can result from physical trauma such as accidents, surgery, and stroke, diseases such as diabetes, cancer, and immune disorders, and medications such as cancer chemotherapy drugs.[2] Neuropathic pain is also often associated with accompanying mental health disorders such as depression, anxiety, sleep problems, and reduced social interactions.[3]

Standard first-line treatments for neuropathic pain (such as tricyclic antidepressants and selective serotonin norepinephrine reuptake inhibitors) are often not completely effective on all types of neuropathy.[4] In fact, at least 50% of people with neuropathic pain do not notice any clinically meaningful pain relief from their medications.[2] Some medications used for neuropathic pain are accompanied by side effects including dizziness, sedation, depression, and sleep disorders,[2] making them a bad choice for many people.

Another widespread source of chronic pain is osteoarthritis of the knee or hip. Osteoarthritis is the most frequent cause of joint problems in the United States.[5] An estimated 10% of men and 13% of women aged 60 years or older have knee osteoarthritis.[5] In a society where people spend excessive amounts of time staring down at their cell phones or looking at their computer, it's not surprising that neck pain is another common disorder that annually affects 30% to 50% of the general population.[6] Furthermore, at any given time, 31 million people in the US experience low back pain.[7]

Opioids are commonly prescribed to treat chronic pain, either as a first or second line of treatment. Sales of opioid drugs nearly quadrupled from 1999 to 2014.[8] However, opioid drugs are addictive, and overdose of this medication is common. According to Centers for Disease Control and Prevention statistics, drug overdoses killed 63,632 Americans in 2016 and almost two-thirds (66%) of those deaths were the result of a prescription or illicit opioid.[9]

An abundance of research indicates that phytocannabinoids—substances such as cannabidiol (CBD) derived from cannabis and hemp plants – may be effective alternatives. Phytocannabinoids exert much of their actions through the endocannabinoid system, which is involved in pain control. This article will discuss in detail the role of the endocannabinoid system in pain management, how two common phytocannabinoids (THC, the psychoactive component of cannabis and CBD, the non-psychoactive component) differ in their effects on pain, and how a relative newcomer in the realm of natural pain management supplements known as palmitoylethanolamide (PEA) works with the endocannabinoid system to control pain.

The Endocannabinoid System and Pain

Endocannabinoids produced within the body, including anandamide (arachi-donylethanolamide) and 2-arachidonylglycerol (2-AG), are able to activate receptors in the endocannabinoid system. Two important receptors in this system that are involved in pain management are CB_1 and CB_2.[10] In the central nervous system, CB_2 receptor mRNA is not present in the neuronal tissue of human or rat brains.[11] However, it *is* found in brain cells known as microglia when they are activated.[11] Microglia can become activated in states of inflammation and activated microglia themselves can produce pro-inflammatory molecules. The presence of CB_2 in activated microglia indicates it may be involved in blocking the effect of

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painful stimuli in inflammatory processes of the nervous system.[11] Activation of CB_2 receptors blocks the pain response to thermal and mechanical stimuli,[12,13] thermal and tactile hypersensitivity produced by peripheral inflammation,[13-15] and neuropathic pain.[16] The effects of CB_2 receptors on neuropathic pain and inflammation are particularly noteworthy as those conditions are often resistant to treatment, as noted earlier.

Although CBD's ability to inhibit neuropathic pain is only half that of THC, CBD can be given in higher doses without the psychoactive effects that occur with THC.

An extensive amount of evidence points to the endocannabinoid system's role in pain control. According to preclinical studies in animal models, activation of CB_1 or CB_2 receptors leads to a reduction in chemotherapy-induced allodynia (a pain response from stimuli that don't normally cause pain.)[17] Further evidence that the endocannabinoid system is involved in pain regulation is the similarity between endocannabinoids and the pain reliever acetaminophen. The acetaminophen metabolite and endocannabinoid reuptake inhibitor AM 404 indirectly activates CB_1 receptors, which may be responsible for analgesia induced by acetaminophen.[18] Likewise, some non-steroidal anti-inflammatory drugs (NSAIDs) are able to influence the cannabinoid system. The inflammatory enzyme COX-2 breaks down anandamide, an endocannabinoid involved in the regulation of pain perception.[11,19] NSAIDs inhibit the action of the enzyme COX-2, which in turn prevents anandamide destruction.[11,19] Furthermore, clinical studies revealed altered endocannabinoid signaling in patients with chronic pain.[20]

Endocannabinoids control pain in a way that is much safer compared with opioids, although they can indirectly work through the same receptors. CB_2 receptors indirectly stimulate opioid receptors found in primary afferent pathways.[21] Furthermore, CB_1 expression is weak in the areas of the brain stem that regulate respiration. This suggests that respiratory depression, a potentially fatal adverse effect of opioid drugs, would not occur when using cannabinoids as painkillers.[10] Additionally, CB_1 receptor agonists (substances that enhance the activity of CB_1) work differently on neurotransmission pathways compared with opioids to induce analgesia.[22]

This difference in pathways may explain why in animal models of neuropathic pain cannabinoid receptor agonists last longer compared with morphine.[23]

Researchers are beginning to look beyond the classical CB_1 and CB_2 receptors as potential mediators of some of the beneficial effects of endocannabinoids and phytocannabinoids. For example, 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.[17] Other undiscovered cannabinoid receptors may exist, and these receptors may partly mediate some of the analgesic effects associated with cannabinoids.[24,25]

THC vs. CBD in Neuropathic Pain

CB_1 receptors inhibit pain signaling pathways.[10] CB_2 receptors, on the other hand, reduce pain via anti-inflammatory effects.[10] THC directly acts on CB_1 receptors of the endocannabinoid system,[26] which are primarily expressed in the brain, and it can also act on CB_2 receptors.[27]

CBD, although it has a low affinity for CB_1 and CB_2 receptors, indirectly acts on the CB_1 receptors by suppressing the enzymatic breakdown of the endogenous cannabinoid anandamide, increasing the duration of time anandamide stays in the system.[28] As noted earlier, anandamide is involved in the regulation of pain perception.

CBD's effects on the CB_1 receptor counteract the psychoactive effects of THC.[29] In most studies, CBD has thus been shown to inhibit adverse effects of THC including intoxication, sedation, and tachycardia.[29] CBD also acts on the CB_2 receptor, and therefore exerts anti-inflammatory effects important for pain control.[10] The ability of THC or CBD to act on CB_2 receptors blocks activation of the brain cells known as microglia, thereby preventing the development of neuropathic pain.[27]

A number of animal studies indicate CBD alone can reduce neuropathic pain. A mouse model of neuropathic pain caused by injury found that CBD alone had beneficial effects on pain reduction.[30] Although CBD's effects were less powerful than THC, CBD administration was not associated with the psychoactive side effects that accompanied THC.[30] In a rat model of sciatic nerve pain and inflammatory pain, oral treatment with CBD (2.5-20 mg/kg for neuropathic sciatic pain and 20 mg/kg for inflammatory pain) or intraplantar injection from a week to 14 days post-injury reduced the sensitization to painful stimuli.[31] Cannabidiol administration also correlated with a lower level of several inflammatory mediators, such as prostaglandin E(2) (PGE(2)), lipid peroxide, and nitric oxide (NO).[31] In this study, CBD's beneficial effects on pain appeared to be due to its actions on the vanilloid receptors rather than CB_1 or CB_2. The authors concluded, "The results indicate a potential for therapeutic use of cannabidiol in chronic painful states."

CBD has also been shown to be effective in a mouse model of diabetic neuropathy. In diabetic mice, moderate or high doses of cannabidiol administered intranasally, beginning at onset of diabetes, or high doses of CBD given through an intraperitoneal route were associated with a reduction in the development of two measures of diabetic neuropathy: sensitivity to heat and increased pain after being touched (tactile allodynia).[27] This effect lasted during cannabidiol treatment and for the additional four assessments over two months after CBD was discontinued. CBD had no effect on neuropathic pain that was present prior to CBD treatment. One other benefit of CBD was that mice given either medium or high doses of intranasal/intraperitoneal CBD at diabetes onset had lower densities

of microglia in the dorsal spinal cord, an indication of reduced microglia activation.[27]

Rodent models of neuropathy caused by chemotherapy drugs indicate CBD is useful in this instance as well. In a mouse model of neuropathy caused by the chemotherapy drug cisplatin, CBD or THC reduced but did not prevent neuropathy symptoms.[32] In another mouse study, both CBD and THC alone reduced mechanical allodynia caused by the chemotherapy medication paclitaxel.[33] CBD also reduced pain associated with the chemotherapy drug oxaliplatin but not vincristine, while THC significantly reduced vincristine-associated pain but not pain associated with oxaliplatin.[33] Doses of CBD or THC that were too low to be effective when given separately, when given together were effective against pain caused by oxaliplatin but not vincristine.[33]

Although CBD's ability to inhibit neuropathic pain is only half that of THC, CBD can be given in higher doses without the psychoactive effects that occur with THC.[2] Furthermore, long-term use of CBD has been associated with improved efficacy in regards to pain control compared with short-term administration.[2]

With the promising results achieved in animal studies, it is surprising that clinical trials investigating the use of CBD alone on neuropathic pain are lacking. All of the clinical studies have evaluated the use of CBD combined with THC. Many of these studies have found the combination of the two phytocannabinoids to be effective in neuropathic pain.[34-36]

Joint Pain and Phytocannabinoids

Endocannabinoids and phyto-cannabinoids are able to affect pain pathways in the joints. Cannabinoid receptors, including CB_1, CB_2, GPR55, PPARα, and PPARγ, have been found on human articular cartilage from patients with symptomatic osteoarthritis (OA).[37] According to one group of researchers, "Chondrocytes from OA joints were shown to express a wide range of cannabinoid receptors even in degenerate tissues, demonstrating that these cells could respond to cannabinoids."[37] OA leads to a combination of inflammatory, nociceptive, and neuropathic pain. The endocannabinoid system has been shown to reduce all of these types of pain.[38]

CBD was studied for its effects on experimental osteoarthritis in rats. After administration of peripheral CBD (100-300 µg) to rats with end-stage OA, there was a dose dependent decline in joint afferent firing rate.[39] Furthermore, although 100 or 200 µg of CBD did not produce any benefits, 300 µg CBD was associated with increased withdrawal threshold and weight bearing. Local CBD administration also alleviated acute, transient joint inflammation. Prophylactic administration of CBD blocked the development of subsequent joint pain and nerve damage. The researchers concluded, "These findings suggest that CBD may be a safe, useful therapeutic for treating OA joint neuropathic pain."

In collagen-induced arthritis (CIA), a model for rheumatoid arthritis, CBD at 5 mg/kg per day i.p. or 25 mg/kg per day orally resulted in clinical improvement associated with protection against severe joint damage.[40] CBD led to a reduction in IFN-gamma production and decreased synthesis of tumor necrosis factor by knee synovial cells. In vitro, CBD induced a dose-dependent inhibition of lymphocyte proliferation, both mitogen-stimulated and antigen-specific, and suppression of Zymosan-triggered reactive oxygen burst by peritoneal granulocytes.[40] In mice, CBD blocked the rise in serum tumor necrosis factor caused by lipopolysaccharides.[40] According to the authors, "Taken together, these data show that CBD, through its combined immunosuppressive and anti-inflammatory actions, has a potent anti-arthritic effect in CIA."

Despite promising preclinical studies and reports from clinical practice as well as a great deal of in vitro justification as to why cannabinoids likely support joint health,[41] there is a paucity of human studies investigating the effects of cannabinoids on joint pain.[41]

Phytocannabinoid Use in Other Forms of Pain

Phytocannabinoids have been studied for their effects on other forms of pain. In a randomized, double-blind, placebo-controlled trial, the semisynthetic THC analog nabilone was shown to reduce pain and improve quality of life and sleep in people with fibromyalgia.[42] In another study, kidney transplant patients experiencing pain were given CBD.[43] The study included seven patients who were given an initial dose of up to 100 mg/day of CBD. Two participants experienced complete improvement of pain, four had a partial response in the first 15 days, and one subject experienced no change.

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. Cannabidiol has been shown to improve mental health in a number of studies. We addressed the evidence supporting CBD's role in mental health in greater detail in an article in the *Townsend Letter* earlier this year.

The Role of Palmitoylethanolamide (PEA) in Pain Management

A promising new strategy for resolving pain is to use palmitoylethanolamide (PEA) in combination with CBD. When in pain, the body produces PEA, which acts as a natural painkiller.[46] PEA is also found in foods such as egg yolks, peanuts, and soybeans. It is not found in cannabis and is not classified as an endocannabinoid. However, it acts on the endocannabinoid system by helping the body use anandamide more effectively.[46]

Accumulating evidence points to the role of neuroinflammation, characterized by infiltration of immune cells, activation of mast cells and glial cells, and synthesis of inflammatory mediators in the peripheral and central nervous systems, in chronic pain.[46] PEA is an anti-inflammatory and pro-

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resolving lipid mediator that reduces mast cell activation and regulates glial cell behaviors.[46-48]

A meta-analysis of 12 double-blind, controlled, and open-label clinical trials found that PEA supplementation leads to a progressive decrease in pain intensity that is substantially greater compared to the controls.[46] The pain reduction in PEA-treated patients was 1.04 points every two weeks with a 35% response variance explained by the linear model. Conversely, in the control groups, pain reduction intensity was 0.20 points every two weeks with only 1% of the total variance explained by the regression. Pain scores on the Kaplan-Meier estimator was ≤ 3 in 81% of patients given PEA whereas only 40% of control subjects had a score ≤ 3, 60 days after the beginning of the trial. The researchers concluded, "These results confirm that PEA might represent an exciting, new therapeutic strategy to manage chronic and neuropathic pain associated with neuroinflammation."

Conclusion

Chronic pain is a debilitating condition that is widespread among the population. Regulating the endocannabinoid system through the use of phytocannabinoids and PEA is an alternative to other pain control approaches associated with potentially dangerous side effects. The use of these agents is associated with improvements in pain caused by various forms of neuropathy, joint problems, and other pain disorders. The benefits are achieved through modulation of not only the endocannabinoid system but also indirect influence on opioid receptors.

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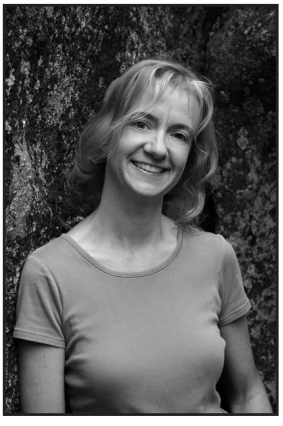

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