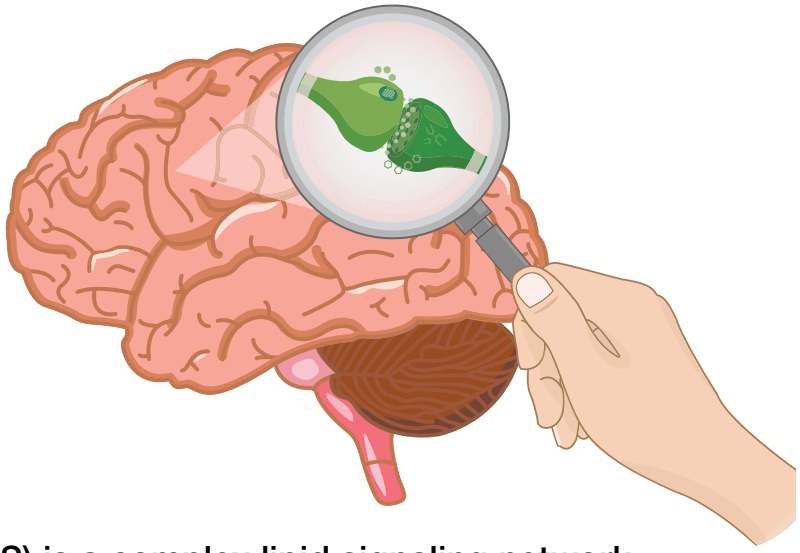
Endocannabinoids: Beyond hemp/CBD

by Kristen McPhee



The endocannabinoid system (ECS) is a complex lipid signaling network involved in regulating and balancing physiological processes in the body.[1,2] This biological system comprises endogenous endocannabinoids, enzymes and cannabinoid receptors.

Endocannabinoids are ligands, or lipid molecules, synthesized enzymatically from dietary omega-6 and omega-3 essential fatty acids (EFAs). Two primary endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), bind to and subsequently activate or inhibit cannabinoid receptors.[3]

Similar to endocannabinoids, two primary cannabinoid receptors exist within the ECS. Cannabinoid receptor type 1 (CB1) receptors are concentrated in the central nervous system (CNS), but are also present in the peripheral nervous system, cardiovascular system, adipose tissue and liver. Cannabinoid receptor type 2 (CB2) receptors are predominant in the brain, blood and immune cells, lymph nodes, spleen and thymus.[2]

Prolonged stress and inflammation alter AEA and 2-AG endocannabinoid levels and CB1 and CB2 cannabinoid receptor expression, resulting in an overactive ECS. When homeostasis of the biological system is disrupted, pathophysiological conditions arise. Visceral obesity and cardiac dysfunction are associated specifically with elevated AEA levels and CB1 expression.[2] Metabolic disorders, including obesity and type 2 diabetes, as well as cardiovascular disease and hyperglycemia, are associated with an overactive ECS.[2,4]

Many sufferers turn to hemp (*Cannabis sativa*)-based products for support; however, research suggests dietary modifications may address the underlying cause of an overactive ECS. Also, a number of plant constituents and phytocannabinoids are emerging as promising candidates for proper ECS support.

Consumption of omega-6 EFAs has reached an all-time high in the standard American diet, while few meet the recommended daily allowance of omega-3 fats. Since dietary sources of fats are precursors to the ECS, researchers evaluated the effects of differing proportions of omega-6 and omega-3 EFAs—namely docosahexaenoic acids (DHA) and eicosapentaenoic acid (EPA)—on ECS function.

A 2019 study identified a growing class of omega-3 fatty acid endocannabindoids derived from dietary omega-3 EFAs, and evaluated their potential physiological influences.[3] Of significance, two omega-3 endocannabinoids (docosahexaenoyl ethanolamide [DHA-EA] and eicosapentaenoyl ethanolamide [EPA-EA]) showed that their anti-inflammatory effects occur by modulating the inflammatory cascade via the oxygenase pathway.

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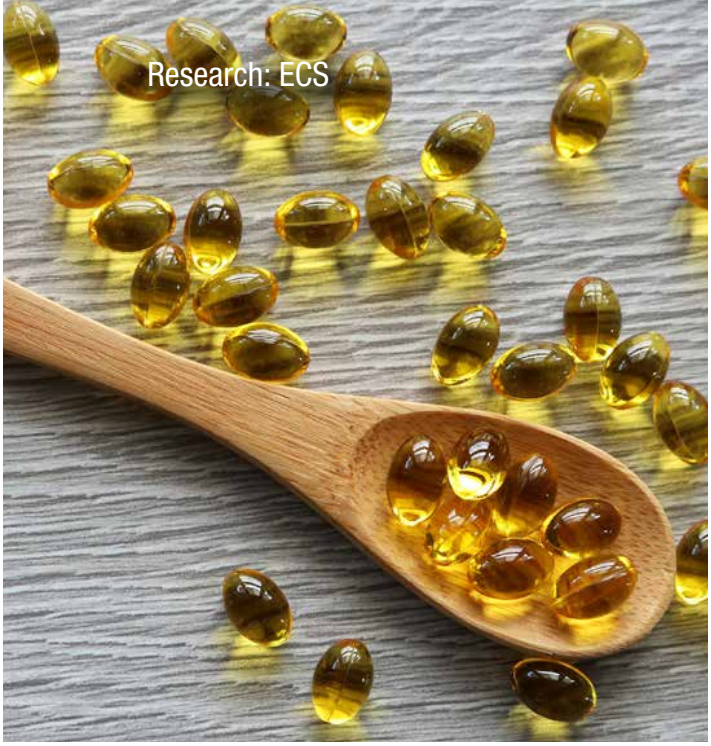

In a 12-week, randomized clinical trial, 55 participants with daily chronic headaches who consumed a high omega-3 and low omega-6 EFA diet showed significant increases in the omega-3 EFA derivatives, DHA-EA and 2-docosahexaenoylglycerol (2-DHG) by 99% and 65%, respectively, and a significant reduction in the omega-6 EFA derivative 2-AG by 25%.[5] The diet-induced changes in the endocannabinoid derivatives correlated with reduced physical pain and psychological distress.

The benefits of the dietary omega-3 EFA DHA were also seen in mice fed a semi-purified diet containing DHA (~5 g per day) for 118 days.[4] The intervention group's diet consisted of 5.9% DHA of total fatty acids, or a 10.5:1 omega-6 to omega-3 ratio. The control group's diet consisted of 0.2% DHA of total fatty acids, or a 298:1 omega-6 to omega-3 ratio. The intervention group showed that the increased dietary DHA altered ECS gene expression by antagonizing CB1 activation and reducing downstream endocannabinoid and inflammatory markers. Also, the DHA-fed mice showed significantly higher lean mass, lower fat mass and lower epididymal fat mass compared to control.

In another study involving mice, the effects of the dietary omega-6 EFA, linoleic acid, on the ECS and obesity were studied.[6] The proportions used were reflective of the increase in dietary omega-6 essential fatty acid consumption in the American diet. Increased dietary intake of linoleic acid (LA) from 1% to 8% energy was associated with obesity and an overactive ECS. The 8% LA-fed group also showed increased plasma LA concentrations and AEA and 2-AG endocannabinoid levels compared to the 1% LA-fed group. Further, adding 1% energy of omega-3 EFAs (DHA and EPA) to the group fed 8% LA reduced AEA and 2-AG endocannabinoid levels and reversed several markers associated with obesity.

Although both omega-6 and omega-3 EFAs are necessary for a healthy diet, the proportions in which they are consumed impacts ECS response, as well as overall health.[7] When consumed in excess, omega-6 EFAs may increase AEA and 2-AG endocannabinoid levels, activate CB1 receptors, and subsequently result in an overactive ECS associated with multiple pathophysiological conditions. Conversely, omega-3 EFAs may increase levels of omega-3 EFA endocannabinoid derivatives such as DHA-EA, EPA-EA, 2-DHG, among others. An emphasis on dietary omega-3 EFAs' usefulness in correcting an imbalanced system may have the most clinical relevance, given the magnitude of individuals affected by chronic stress and inflammation, excessive dietary omega-6 EFA consumption and omega-3 EFA deficiency.

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Similar to omega-6 and omega-3 EFAs, palmitoylethanolamide (PEA) is also present in numerous foods and acts indirectly on the ECS. PEA is also produced endogenously and is from the family of bioactive lipids known as N-acylethanolamine (NAE), along with AEA and 2-AG endocannabinoids, making them structurally related. Although widely studied for anti-inflammatory, analgesic and neuroprotective effects, its mechanisms of action are not fully understood. However, PEA is thought to indirectly act on cannabinoid receptors through directly activating peroxisome proliferator-activated receptor (PPAR)-gamma and orphan G protein-coupled receptor (GPR55), as well as indirectly activating transient receptor potential vanilloid type 1 (TRPV1).[8]

Human clinical studies involving various models of pain have evaluated the anti-inflammatory and analgesic efficacy of PEA. A systematic review and meta-analysis of 10 randomized controlled trials including 1,298 total participants determined PEA supplementation was associated with a significant reduction of acute and chronic pain.[9] The doses used were 300 to 1,200 mg/d, and the duration of the studies was 10 to 180 days. More recently, PEA (as Levagen from Gencor) improved muscle recovery in 28 healthy, young male participants exposed to a series of leg press exercises in a double-blind, randomized, placebo-controlled study.[10] The main findings were reduced myoglobin and blood lactate concentrations and increased protein kinase B phosphorylation.

The lesser discussed underachieving ECS is seen in neuropsychiatric and mood disorders, including depression and post-traumatic stress disorder.[2,11] As such, the anti-depressant potential of PEA was studied in 54 patients diagnosed with major depressive disorder who were prescribed the widely used antidepressant citalopram in a six-week, double-blind, randomized, placebo-controlled study.[11] Co-administration of PEA and citalopram significantly improved depressive symptoms compared to citalopram alone in as early as two weeks. Some of the possible PEA mechanisms included anti-inflammatory effects exhibited through PPAR-gamma or GPR55 receptors, among others.

Preclinical studies have examined the potential of plant-derived phytocannabinoids that either directly interact with cannabinoid receptors, are structurally similar to hemp cannabinoids, or both. For example, beta-caryophyllene from mastic tree (*Pistacia lentiscus*) essential oil is also a primary constituent in hemp and present in numerous foods. A single, oral dose of beta-carophyllene administered to rats before reperfusion prevented increases in oxidative stress, inflammation and ECS activity.[12] The mechanisms of the sesquiterpene included activating CB2 and PPAR-gamma receptors, demonstrating both direct and indirect actions.

In addition to PEA, other fatty acid derivatives from the NAE family are present in chocolate (*Theobroma cacao*), echinacea (*Echinacea angustifolia*) and carrot (*Daucus carota*). Plant-derived NAEs do not directly interact with cannabinoid receptors, but exert cannabimimetic effects by inhibiting the fatty acid amide hydrolase (FAAH) enzyme or AEA endocannabinoid transport, according to in vitro studies highlighted in a special cannabinoids issue of the British Journal of Pharmacology.[13]

Among the findings detailed was in vitro research finding the polyphenols trans-resveratrol (from grape, *Vitis vinifera*), curcumin (from turmeric, *Curcuma longa*) and epigallocatechin 3-0-gallate (from tea, *Camellia sinensis*) showed negligible effects in vitro. Interestingly, several flavonoids, including genistein, kaempferol, 7-hydroxyflavone and 3,7-dihydroxyflavone inhibited FAAH, albeit at relatively high concentrations and with limited bioavailability. The publication further noted rutamarin (from rue, *Ruta graveolens*) and 3,3-diindolylmethane (from cruciferous vegetables, Brassicaceae) bind weakly to the CB2 receptor in vitro.

Both omega-3 EFAs and PEA are present in foods and have indirectly modulated the ECS in human clinical studies, demonstrating anti-inflammatory, analgesic and neuroprotective effects. Much remains to be elucidated as to how select plant constituents and phytocannabinoids affect the ECS and whether they have beneficial effects in humans. ✦

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