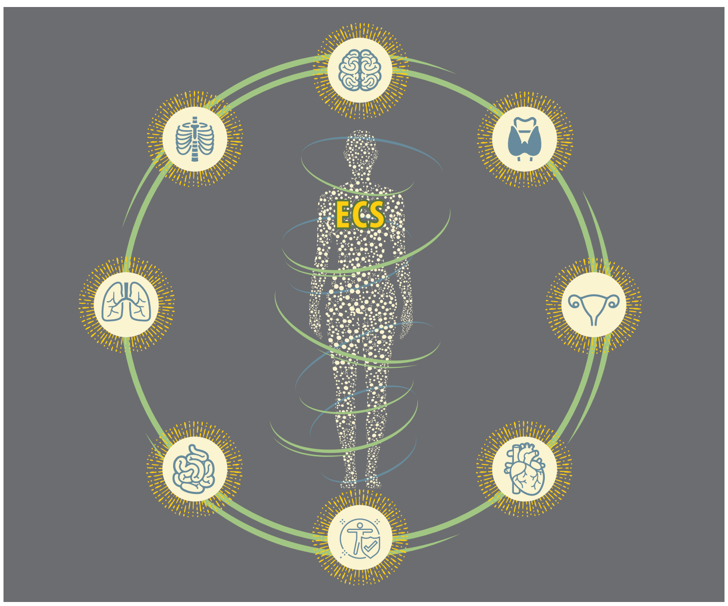
The Endocannabinoid System

Introduction

The endocannabinoid system, or ECS, is an important physiological system involved in regulating and balancing numerous functions and processes in the human body, including brain plasticity, learning and memory, stress and emotions, immune response, inflammation, appetite and food intake, bone and muscle health, digestion, metabolism, and energy balance (Figure 1).[1] An imbalanced, prolonged alteration in the ECS—such as clinical endocannabinoid deficiency, which occurs when there are changes in function or density of cannabinoid receptors and/or endogenous cannabinoids levels—may negatively impact many aspects of health.[2,3] Therefore, supporting and nourishing the function of the ECS is essential for maintaining the health of the mind and body.

Figure 1: The ECS and its role in regulating and balancing many physiological processes



Research highlights

- ✓ The ECS plays a critical role in regulating and balancing a range of physiological functions in the body to help maintain homeostasis.[1]
- ✓ Suboptimal function of the ECS (e.g., clinical endocannabinoid deficiency [CED]) is linked to many pathophysiological states, adversely impacting overall health.[2,3]
- ✓ Lifestyle approaches, such as stress management and targeted nutritional interventions, may help support ECS functions, which mediate homeostasis in multiple organ systems involved in various aspects of physical, psychological, and emotional health.[4-11]
- ✓ Utilization of plant-derived cannabinoids and terpenoids is a rapidly expanding research area, and emerging data suggest their potential in supporting the function of the ECS.[12-16]

Mechanisms of action

The ECS consists of three main components: a widespread network of cannabinoid receptors throughout the body including cannabinoid receptor type 1 and type 2 (CB1 and CB2), endogenous cannabinoids or endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and various endocannabinoid metabolic enzymes including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).[2]

When facing a challenging condition that disturbs homeostasis, endocannabinoids are produced and released from phospholipid precursors and activate the cannabinoid receptors, leading to a variety of physiologic processes involved in maintaining homeostasis.[2] CB1 receptors are primarily localized in the central nervous system, and their activation results in a robust suppression of neurotransmitter release into the synapses. CB2 receptors, on the other hand, are mostly located in immune cells and, when activated, can modulate immune cell migration and cytokine release.[18]

Two important scenarios, stress response and immune response, are described below to illustrate how the ECS adapts swiftly to challenging conditions.

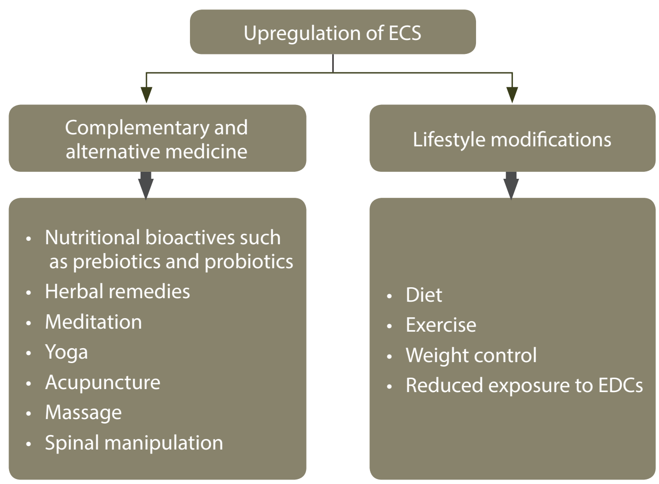
- **Stress response:**
  The ECS is both a regulator and a target of stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis. Under steady-state conditions the ECS constrains HPA axis activity, while exposure to stress induces changes in functional roles of endocannabinoid signaling.[17] Specifically, exposure to stress reduces AEA levels and increases 2-AG levels.[18] The reduction in AEA signaling contributes to the activation of the HPA axis and manifestation of anxiety behavior, while the increase in 2-AG contributes to termination of the HPA axis activity and drives habituation of the stress response. Additionally, exposure to chronic stress causes a downregulation or loss of CB1 receptors.[18] Therefore, impairment in the ECS may correlate with dysregulated stress-related behaviors like anxiety and depression, and elevating endocannabinoid signaling can modulate the stress response.[18]
- **Immune response:**
  Cannabinoid receptors, primarily CB2, and circulating endocannabinoids are extensively involved in regulating immune and inflammatory responses.[19] Endocannabinoids mediate the inflammatory response by a) regulating cytokines at different steps throughout the inflammatory response (e.g., AEA suppresses proinflammatory cytokines and enhances anti-inflammatory cytokines in both innate and adaptive immune responses mostly via CB2 binding); b) suppressing immune cell activation, proliferation and migration, and the activation of immune cell apoptosis.[20,21] The crosstalk between the immune system and ECS is tightly regulated, and a dysregulation in this crosstalk has potential to negatively influence the body's immune response.[19]

Lifestyle approaches and ECS support

Various pathological states such as migraine, posttraumatic stress disorder (PTSD), and inflammatory bowel disease (IBD) are associated with clinical endocannabinoid deficiency.[3] On the other hand, an overactive ECS is associated with conditions like obesity and diabetes.[3] Certain lifestyle approaches may help support ECS functions, which mediate homeostasis in multiple organ systems involved in various aspects of physical, psychological, and emotional health.

- **Stress management:** Chronic stress negatively impacts the ECS by altering levels of AEA and 2-AG and CB1 receptor signaling.[3] Osteopathic manipulative treatment, massage, meditation, yoga, and breathing techniques may be helpful in attenuating the effects of stress on endocannabinoid signaling and supporting ECS function.[4,5]
- **Diet and exercise:** A healthy diet along with moderate intensity aerobic exercise has been shown to improve endocannabinoid signaling.[22] In human and animal research, obesity has been shown to overstimulate the ECS by increasing levels of endocannabinoids and CB1 receptor expression. It has been suggested that weight loss via caloric restriction or fasting may beneficially modulate the ECS.[3]
- **Specific dietary changes:** Animal studies have shown that adequate intakes of dietary omega-3 fatty acids are important for functional endocannabinoid signaling.[9,10] Preliminary evidence from animal studies shows that probiotics and prebiotics may restore proper expression of CB receptors.[11] In addition, endocrine-disrupting chemicals (EDCs) used in pesticides and food packaging can alter normal ECS function. Therefore, practices aimed at reducing exposure to EDCs (e.g., eating more organic foods and less processed foods) may also promote endocannabinoid homeostasis.[3]
- **Plant bioactives:** Preliminary studies have shown that plant-derived compounds such as phytocannabinoids and terpenoids modulate the ECS and affect a variety of physiological processes influenced by the ECS. For example:
  - A human clinical study showed that cannabidiol (CBD) enhanced endocannabinoid signaling by suppressing FAAH activity, thereby increasing concentrations of the anti-inflammatory endocannabinoid AEA.[23]
  - In animal models another phytocannabinoid, cannabigerol (CBG), regulated endocannabinoid signaling and demonstrated antioxidant and anti-inflammatory properties, leading to neuroprotection.[24,25]
  - β-caryophyllene, one of the known terpenes found in many plants and spices such as pepper and cloves, exerts anti-inflammatory and antioxidant effects through activation of the CB2 receptor.[26]

Figure 2: Potential clinical interventions for supporting ECS function



Adapted from McPartland JM et al. *PLoS One*. 2014;9:e89566.[3]

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