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The Endocannabinoid System and Medical Marijuana in 15 Minutes

In order to fully appreciate the health effects of marijuana, it is essential that one has knowledge of the endocannabinoid system, the components of the cannabis plant and how the components of the cannabis plant interact with the endocannabinoid system.

What is the endocannabinoid system?

The endocannabinoid system (ECS) is an internal homeostatic system present in all vertebrates. The ECS plays a critical role in the nervous system and regulates multiple physiological processes including digestion, mood, coordination, sensory integration, and other processes. The ECS also influences immunomodulation, cardiovascular functions, fertility, tumor surveillance, bone physiology, appetite, the hypothalamic-pituitary-adrenal axis, neural development, and intraocular pressure. *This homeostatic system was only discovered within the last few decades and was referred to as the endocannabinoid system because it is an endogenous system whose components interact with or resemble delta-9-tetrahydrocannabinol (THC), a compound derived from the cannabis plant. (1-8)*

What are the components of the endocannabinoid system?

The ECS is comprised of three main components: endocannabinoids, receptors, and regulatory enzymes. (5,6)

Endocannabinoids (also called endogenous cannabinoids) are compounds produced by the body. Endocannabinoids are agonists of the cannabinoid receptors found within the body. A key point is that exogenous cannabis-derived compounds, such as THC, bind to these same receptors. What are two of the most well studied endocannabinoids?

N- arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG) are the most well studied cannabinoids. Both AEA and 2-AG play a role in multiple physiological systems. These endocannabinoids are synthesized on demand, and when they are produced, they travel in a retrograde fashion across a synapse to inhibit neurotransmitter release. (5,9,10)

What are the receptors of the endocannabinoid system?

There are two well-known cannabinoid receptors: cannabinoid receptor-1 (CB1) and cannabinoid receptor-2 (CB2). Some endocannabinoids and some cannabis-derived compounds bind to receptors other than the CB1 and CB2 receptors, including the TRPV1 and GPR55 receptors. (5,8)

The CB1 receptor is a G protein receptor that serves as a target for both endocannabinoids and phytocannabinoids (compounds derived from the cannabis plant). Where are CB1 receptors expressed? When CB1 receptors are activated, what physiological processes are affected?

CB1 receptors are highly expressed throughout the central nervous system (CNS). In fact, in humans, the CB1 receptor is 10 times more prevalent in the CNS, as compared to the μ-opioid receptor. In addition to the CNS, CB1 receptors are abundant throughout the gastro-intestinal system, on mast cells, macrophages, epidermal keratinocytes, adipose, skeletal muscle and other tissues. (1,6,8, 10-16)

CB1 receptors are the primary psychoactive cannabinoid receptors and mediate numerous physiological processes, including cardiovascular function, energy homeostasis and reproduction. Activation of CB1 receptors also affects pain modulation, cognition and memory, reward sensation and emotional behavior, sensory perception, motor control, and other functions. (1,6,8, 10-16)

Similar to CB1, CB2 is a G protein receptor that serves as a target for both endocannabinoids and phytocannabinoids. What are the main functions of CB2 receptors?

The CB2 receptors are primarily immunomodulatory and anti-inflammatory. They are expressed on the cell membranes of B cells, T cells and macrophages. When signaled, CB2 receptors are generally inhibitory to immune cell activation, and proinflammatory cytokine production is inhibited. Expression of CB2 receptors is inducible and the number of receptors is increased by inflammation. (17-20)

What are phytocannabinoids (also referred to as cannabinoids)?

Scientists have identified > 400 chemical compounds produced by the cannabis plant. Of these compounds, more than 100 are unique to the cannabis plant and interact with endocannabinoid receptors or otherwise affect the endocannabinoid system via a non-receptor mediated pathway. These cannabis-specific compounds are called phytocannabinoids. Examples of phytocannabinoids include delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabigerol (CBG). (8,21,22)

The terms cannabis, marijuana and hemp are often used interchangeably; however, the terms have different meanings. What is cannabis? What is marijuana? What is hemp? Is the hemp plant a cannabis plant?

Cannabis is a genus of flowering plants belonging to the family Cannabaceae. Within the genus are various related plants, and these related plants have the names C. sativa, C. indica, C. ruderalis, and hemp. Other than differences in appearance, cannabis varieties differ by their specific profile of components (phytocannabinoids, terpenes and other phytochemicals). (23,24,25)

Marijuana is defined as a substance composed of parts of the plant Cannabis sativa, including the leaves, flowers, seeds, and the resin extracted from any part of the plant. Marijuana contains the psychoactive phytocannabinoid THC along with other phytocannabinoids. (23,24,25)

Hemp is a genetic variant of Cannabis sativa, which has been bred to maximize its fiber content and minimize its phytocannabinoid content, especially of THC. "The term `hemp' means the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol (THC) concentration of not more than 0.3 percent on a dry weight basis." (26,27)

What are terpenes (also called terpenoids)?

Terpenes are aromatic hydrocarbons and just like the phytocannabinoids, terpenes are manufactured in the glands of the cannabis flower. Terpenes may influence the uptake and effects of phytocannabinoids. The terpenes found in cannabis include limonene, pinene, myrcene, delta-3-carene, eucalyptol and humulene. (28)

What are the health effects of THC?

Briefly, THC is the cannabinoid responsible for many of marijuana's psychoactive effects, including the "high" and it is also responsible for many of the other health effects reported to be associated with marijuana use. THC's effects include reduction of nausea and vomiting, stimulation of appetite, reduction of pain and inflammation, and increase in muscle relaxation. Some of THC's potential adverse effects include dizziness, somnolence, dry mouth, disorientation, anxiety, and acute psychosis. (23)

The overdose of opioids or benzodiazepines may lead to respiratory depression. Does an overdose of cannabinoids lead to respiratory depression?

Cannabinoid use is NOT associated with respiratory depression because CB1 receptors are not located in the midbrain, the part of the brain responsible for respiratory drive. (29)

In 2017, the National Academies of Sciences, Engineering and Medicine (NASEM) published The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. According to this document, do cannabinoids have therapeutic value?

Yes, for some conditions. The research committee found that there is conclusive or substantial evidence that cannabinoids are effective for...

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