

# The Endocannabinoid System and Medical Marijuana in 15 minutes!

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In order to fully appreciate the health effects of marijuana, it is essential that one has knowledge of the endocannabinoid system and cannabis. Therefore, this primer includes a discussion of the endocannabinoid system, 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 that plays a critical role in the nervous system and regulates multiple physiological processes, including appetite, digestion, mood, coordination, and other processes. The ECS also influences immunomodulation, cardiovascular functions, sensory integration, tumor surveillance, fertility, bone physiology, 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**. (Key Point!)

### What are the components of the endocannabinoid system?

The **endocannabinoid system** is comprised of three main components: **endocannabinoids**, **receptors** and **regulatory enzymes**.

Endocannabinoids (also called endogenous cannabinoids) – These compounds are endogenous agonists of the receptors to which THC, a plant derived compound, also binds. (VERY important!)

### What are two of the most well studied endocannabinoids?

- ❖ N-arachidonylethanolamine (also called **anandamide** or AEA)
- ❖ 2-arachidonoylglycerol (**2-AG**)

Both endocannabinoids play a role in multiple physiological

systems, and they are synthesized on demand, meaning that there is no evidence for their storage inside vesicles. When these endocannabinoids are produced, they travel in a retrograde fashion across a synapse to inhibit neurotransmitter release.

### What are the receptors of the endocannabinoid system?

There are two well-known cannabinoid receptors:

- ❖ Cannabinoid receptor-1 (**CB1**)
- ❖ Cannabinoid receptor-2 (**CB2**)

Some endocannabinoids and some cannabis-derived (plant) compounds bind to receptors other than CB1 and CB2, including the TRPV1 receptor and the GPR55 receptor.

### Describe cannabinoid receptor-1 (CB1).

The CB1 receptor is a G protein receptor that serves as a target for both endocannabinoids and phytocannabinoids (compounds derived from the cannabis plant), including THC. The CB1 receptor is very highly expressed throughout the brain. In humans, the CB1 receptor is 10 times more prevalent in the central nervous system, as compared to the  $\mu$ -opioid receptor.

CB1 receptors are the primary psychoactive cannabinoid receptors, and mediate numerous physiological processes, including cardiovascular function, energy homeostasis and reproduction. The activation of CB1 receptors also affects pain modulation, cognition and memory, reward sensation and emotional behavior, sensory perception, motor control, and other functions.

Continued...

**Some cannabinoid-based medicines are used to treat chemotherapy-induced nausea/vomiting. Have cannabinoid-based medicines been shown to be effective in the treatment of post-operative nausea/vomiting?**

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## Describe cannabinoid receptor-2 (CB2).

Similar to CB1, CB2 is a G protein receptor that serves as a target for both endocannabinoids and phytocannabinoids (compounds derived from the cannabis plant). 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.

## Respiratory depression is associated with the overdose of opioids or benzodiazepines. Is respiratory depression associated with an overdose of cannabinoids?

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

## What are phytocannabinoids (also referred to as cannabinoids)?

Scientists have identified over 400 chemical compounds produced by the cannabis plant. Of these compounds, at least 104 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 (or cannabinoids). Examples of phytocannabinoids include delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabigerol (CBG).

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

**Cannabis**, a genus of flowering plants belonging to the family Cannabaceae, has been cultivated for thousands of years and used for various purposes. 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 and terpenes).

**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 tetrahydrocannabinol (THC) along with other phytocannabinoids.

**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." Hemp plants can be useful as sources of fiber from their stalks, and of foodstuffs from their seeds.

## 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.

## Briefly discuss the health effects of delta-9-tetrahydrocannabinol (THC).

**THC** is the cannabinoid responsible for many of marijuana's psychoactive effects, including the "high," and it is also responsible for many other health effects reported to be associated with marijuana use. Research suggests that 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.

## 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*. Did the results of the research indicate that cannabis-based products are effective?

Yes, for some conditions. The research committee found that there is conclusive or substantial evidence that cannabis-based products are effective :

- ❖ For the treatment of **chronic pain** in adults
- ❖ As antiemetics in the **treatment of chemotherapy-induced nausea and vomiting** (oral cannabinoids)
- ❖ For improving patient-reported **multiple sclerosis spasticity symptoms** (oral cannabinoids)

Importantly, after the publication of the NASEM report, scientific evidence from a double-blind randomized placebo-controlled trial showed that cannabidiol (CBD) is effective in **reducing motor seizures in children with Dravet syndrome**, a severe type of epilepsy.

Note: In June 2018, the U.S. Food and Drug Administration (FDA) approved Epidiolex (cannabidiol) oral solution for the treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome in patients 2 years of age or older, and in July 2020, the FDA approved Epidiolex for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients one year of age and older.

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