The Endocannabinoid System

The means by which cannabis derivatives (e.g. cannabinoids) can exert their effects on the human body involves the endocannabinoid system, a complex cell-signaling network that involves neural, immune, enzyme-driven, and other physiologic processes. While evidence for the endocannabinoid system has existed for nearly a century, a clear understanding as to the underlying structure and function of the endocannabinoid system remains elusive. In recent years, as increasing attention has been directed towards cannabinoids such as cannabidiol, research interest has increased as well. For example, a search of Google scholar using the term 'cannabidiol' reveals 107 articles published in 1980. This dropped to 71 articles in 1990, but then grew to 249 and 1240 articles in the years 2000 and 2010, respectively, before exploding to 6650 articles in 2020. This increased attention that cannabidiol (CBD) – just one of many derivatives of cannabis – is receiving in the research arena is encouraging and indicates tremendous potential for better understanding both the physiological involvement of cannabidiol and all cannabis derivatives as well as how these compounds may provide important health benefits.

How did our understanding of cannabis derivatives and the endocannabinoid system develop?

Evidence indicates that human interaction with cannabis goes back over 11,000 years (Pisanti & Bifulco, 2019). Specific to medical use, cannabis – which directly interacts with the endocannabinoid system – has been used for its anti-inflammatory effects as far back as 1500 BC (Crocq 2020).

While the medicinal effects of cannabis have been utilized for thousands of years, investigation into the mechanisms of how cannabis exerts its effects on our body has only been studied for the past hundred or so years. Tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, has by far received the main attention of researchers (Chang 2020) – likely due to its known psychoactive properties. Despite the research emphasis into THC, cannabidiol was actually isolated from cannabis first – in 1940 – while THC was not isolated until 1964 (Mechoulam & Gaoni 1965, Pertwee 2006).

Once individual compounds were isolated from cannabis, attention turned toward how our body interacts with those compounds. Still, it was not until 1988 that a cannabinoid receptor was recognized to exist within the brain (Devane et al 1988). Later, in 1992, the first endocannabinoid was found – arachidonoylethanolamide (AEA) (Devane 1992).

What components make up the endocannabinoid system?

As a whole, the endocannabinoid system is comprised of endogenous cannabinoids, cannabinoid receptors – which are capable of binding to both endogenous and exogenous cannabinoids, and those cell structures (e.g. enzymes) responsible for the transport, synthesis, and degradation of endocannabinoids.

What is the function of the endocannabinoid system?

A clear understanding of the function of the endocannabinoid system remains elusive. At present, our understanding of the endocannabinoid system indicates a role in several physiological events such as learning, memory, pain control, motor function, thermogenesis, and reproduction, among others (Mecccariello 2016). Simplistically, the endocannabinoid system can be thought of as a cascade of physiological events that are triggered by deviations from homeostasis. Athletic trainers often treat patients/athletes/clients reporting common conditions such as musculoskeletal pain, inflammation, anxiety or disordered sleep. Considering how each of these conditions in isolation, or in combination, represent deviations from homeostasis, it stands to reason why interventions like cannabis or cannabinoids that affect the endocannabinoid system, would be effective in modulating symptoms.

What are endocannabinoids?

The term "cannabinoid" originally represented those compounds found within the cannabis sativa plant, but has evolved to the point where it now represents a group of molecules which mimic the physiologic actions of plant cannabinoids (Schurman & Lichtman 2017). Endogenous cannabinoids, or 'endocannabinoids', are lipid molecules produced within the body which serve to bind to and activate cannabinoid receptors (Lu & Mackie 2020). Endocannabinoids are located within all tissues that have been investigated (Hillard 2017), and are synthesized by the body as needed (Kendall 2017) via metabolism of phospholipid precursors (Guindon & Hohmann 2009).

Endocannabinoids have long been known to play a significant role in modulation of nociceptive signaling events (Karst et al 2010). However, evidence also indicates that endocannabinoids have a much broader influence including roles in metabolism (Hillard 2017), stress and anxiety (Skosnik et al 2016), and even cardiovascular disease (Matthews 2015) among other events.

What is the link between cannabinoids and endocannabinoids?

As mentioned earlier, cannabinoids were originally those compounds produced within the cannabis plant. However, cannabinoids are now considered any compound capable of binding to cannabinoid receptors. Whereas those cannabinoids produced within the body are considered as endogenous cannabinoids, either endogenous cannabinoids or cannabis-derived cannabinoids are capable of binding to – and causing a subsequent effect from – the body's cannabinoid receptors (Alger & Tang 2012).

Where are cannabinoid receptors found within the body?

Cannabinoid receptors are protein-based molecules located on the surface of a cell and which are capable of binding to exogenous (e.g. phytocannabinoids) and endogenous (e.g. endocannabinoids) molecules (Schurman & Lichtman 2017). The human body contains two known cannabinoid receptors – cannabinoid receptor type-1 (CB1) and type-2 (CB2). The CB1 receptor is predominantly found throughout the central nervous system (i.e. brain and spinal cord) and function to regulate many of the psychotrophic as well as behavioral effects that are commonly associated with cannabis (Ye et al 2019). More specifically, CB1 is found predominantly within areas of the brain such as the hippocampus and cerebral cortex – areas that are responsible for memory, learning, and movement (Schurman & Lichtman 2017) as well as within all areas of the brain related to the processing of pain (Starowicz & Finn 2017). The CB1 receptor can also be found at low levels in other tissue such as the liver, muscle, heart, lung, and even sperm cells (Lu & Potter 2017). In contrast, the CB2 receptor is found in highest concentrations within tissues associated with the immune system such as the spleen, tonsils, and even leukocytes (Kendall & Yudowski 2017, Ye et al 2019) but can also be found in non-immune tissue including the brain (e.g cerebellum, brain stem) (Piomelli 2003), reproductive and cardiovascular cells (Derbenev 2004), as well as cells within muscle, liver, intestinal, and fat tissue (Garcia-Bueno & Caso 2016). Despite this widespread presence of CB2 receptors, endocannabinoids actually have a greater general affinity for the CB1 receptor than the CB2 receptor (Tabrizi & Baraldi 2017).

How do cannabinoid receptors function?

CB1 receptors are classified as retrograde messengers. Unlike most receptors in the body that cause actions to happen further down a signaling pathway, CB1 receptors function through the inhibition of upstream signaling events. Endocannabinoids involved with CB1 activity such as 2-arachidonoylglycerol (2-AG) and anandamide are released at the post-synapse and travel 'backward' to the pre-synapse where they bind to CB1 receptors (see Figure 1). The CB1 receptor then undergoes its own signal transduction cascade to inhibit any additional pre-synapse transmitter release (Lu & Potter 2017). Chemically, the actions that endocannabinoids ultimately trigger include inhibition of adenylate cyclase enzyme activity as well as decreasing cyclic adenosine monophosphate (cAMP) levels (Pertwee 2008). These collective actions serve to inhibit further neurotransmitter release. Therefore, endocannabinoids can be considered as capable of serving to terminate certain physiological events due to the inhibitory action of their receptors (as opposed to excitatory action which would cause a receptor to initiate a physiological event).

CB2 receptors are less well-understood than CB1 receptors. In fact, not much is currently known about how CB2 receptors work (Lu & Potter 2017). It is suspected that the CB2 receptor plays a role in helping to regulate inflammation within the liver. This in turn suggests an overriding role for the CB2 receptor as a protective agent for the body (Mallat & Teixeira-Clerc 2011). In addition, bone remodeling is suspected to be controlled in part by the action of CB2 receptors (Tam et al 2006), and there appears to be some interplay between CB2 receptors and disease states. For example, the brain is known to be quite low in CB2 receptors yet certain diseases such as Alzheimer's and Huntington's disease have been shown to significantly elevate the level of CB2 receptors (Palazuelos 2009).

Furthermore, it is thought that CB2 may be involved in controlling CNS-associated diseases such as depression and substance abuse. This association between CB2 receptors and disease may explain the purported effects that endocannabinoids such as CBD can have on neurological-based conditions including epilepsy, seizure, Parkinson's, multiple sclerosis, and Alzheimer's, among others (Marcu 2016).

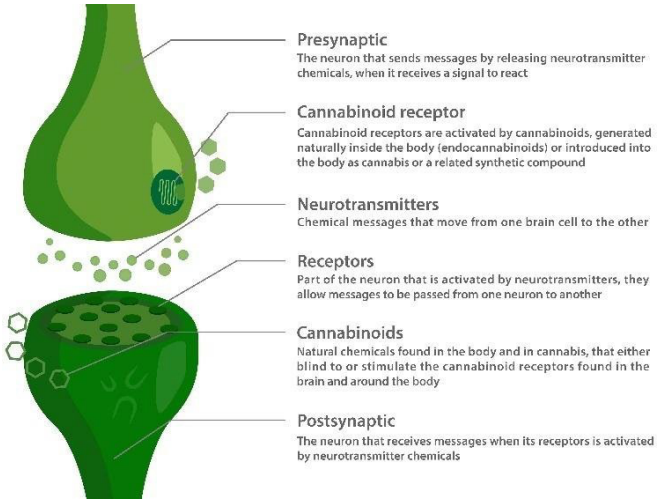

Figure 1. Cannabinoids associated with CB1 function occur through retrograde activation. Cannabinoids released from the post- synaptic terminal travel 'backwards' to inhibit subsequent neurotransmitter release.

Take Home Message:

1. The ECS is a complex cell-signaling system that was not well-described until the late 20th century and remains poorly understood.

2. The ECS can be influenced by both endocannabinoids and exogenous cannabinoids, meaning the naturally occurring substances that affect the ECS of all people, irrespective of cannabis or cannabinoid use, and external substances like cannabis and other cannabinoid products.

3. Cannabis and cannabinoid products affect the body by modulating activity at the CB1 and CB2 receptors.

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