1. The Endocannabinoid System

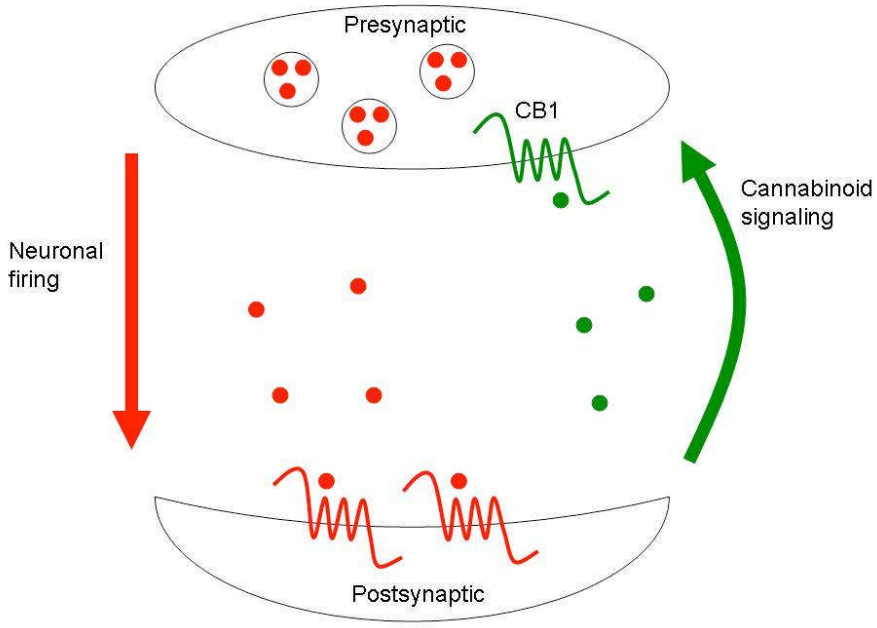
By Kevin Baiko, M.D.

We start with the endocannabinoid (pronounced “en-doe-can-NAB-i-noid”) system. It was discovered in the early 1990’s that the human body has receptors that respond to a set of at least 60 compounds found in the cannabis plant – called cannabinoids. (We actually positively respond to other compounds in the plant too – terpenoids & flavenoids - more on all these compounds in another post.) THC (short for delta-9-tetrahydrocannabinol) is the best known of these cannabinoids – mostly for its psychoactive, but also medicinal effects. But there are others similar in structure with differing, modulating and probably even more profound healing effects, including CBD (cannabidiol), CBG (cannabigerol), CBC (cannabichromene), to name a few. It was later discovered that our bodies manufacture compounds that bind to these receptors. These are called endocannabinoids (eCBs), and at least 2 of them, named anandamide, 2AG (2-aracidonylglycerol) are found in the human body. It turns out that all chordates (including all animals with a spine) have cannabinoid (CB) receptors, and even more animals synthesize anandamide for some purpose, leading scientists to estimate that CB receptors evolved over 600 million years ago and anandamide even further back. Considering that the cannabis plant first shows in the fossil record around 25 million years ago (McPartland *et al*), it’s likely that the plant evolved its peculiar set of phytocannabinoids to its own survival advantage in a world full of animals that respond to them. Regardless, cannabis plant or no, our bodies have CB receptors and create the eCBs that trigger these receptors, which leads us to an obvious line of questioning... What happens when eCB binds to CB receptor? And even bigger in scope... What does the endocannabinoid system do?

To better address these questions, we should explore where these receptors – CB1 & CB2 (the two most studied) - are found. CB1 receptors are primarily found throughout the nervous system, while CB2 receptors are primarily found throughout the immune system. These two systems are central to adaptation and survival, and arguably regulate and influence every other system in the body. The eCB system appears to play a key role in modulating these two systems, serving as a pro-homeostatic (maintaining balance) system for stress recovery and adaptation, facilitating our ability to relax, eat, rest, forget and protect ourselves (Di Marzo *et al*). Keep this in mind when people scoff at the capacity of the cannabis plant to treat so many different disease complaints and states of illness. The eCB system literally exerts effect, directly or indirectly, on every other system of the body. That this rudimentary system has been preserved throughout much of the animal kingdom means that animal models work well to predict effects on humans, when our human overlords actually allow such research to take place.

We can start to appreciate how the endocannabinoid system is so special when we look at how eCBs modulate the nervous system. Nerves transmit signals throughout the body, and like individual lanes in a highway, individual nerves only transmit signals in a specific direction. (Like from brain to hand or from toe to spinal cord.) When a nerve releases its neurotransmitter (NT) into the synapse (space between it and the next nerves down the highway lane) NT binds to receptors on the other nerves and trigger a response

on the post-synaptic nerve. Imagine the pre-synaptic nerve as the pitcher and the post-synaptic nerve as the catcher. The baseball is the neurotransmitter, and it only travels from pre-synapse (pitcher) to post-synapse (catcher) because the pre-synaptic nerve lacks the appropriate receptors on its side of the synapse. But counter to this model, eCBs are released and received in the opposite direction. Post-synaptic nerves release an eCB when they been sufficiently stimulated, and the eCBs cross the synaptic space, binding to CB1 receptors on the pre-synaptic nerve, signaling it to stop releasing its NT. This picture depicts this process... The red dots are the neurotransmitters being released at the endplate of one nerve, diffusing across the synaptic cleft and attaching to their receptor on the next nerve downline. When this second nerve has had enough of the NT, it releases some eCB (green dots) from its cell membrane, they diffuse across the cell in retrograde direction, attach to the CB1 receptor on the first nerve, signaling it to stop the NT release...



In other words, eCBs provide a direct negative feedback in nerve signalling, keeping its cellular stress in check at the synaptic level. That eCBs are the only known neurotransmitters to perform this retrograde neuroregulation suggests their primary role in keeping the nervous system – and therefore all other systems – in a healthy balance (homeostasis).

Considering the direct effects of endocannabinoids on both the nervous system - especially the brain centers thought to most influence emotional processing (amygdaloid nucleus, hippocampus & prefrontal cortex) and the immune system (including white blood cells and glands like the adrenal), it follows that eCBs directly influence emotional health. In fact, there is an inverse relationship between 2-AG levels in the hypothalamus and blood levels of cortisol (stress hormone released by adrenal gland) (Hill & Tasker). In other words, eCBs help us deal with small spurts of emotional stress, whereas chronic emotional stress inhibits our ability to maintain emotional balance – leading to a

spectrum of unpleasant and even pathological emotional states. This inverse relationship works both ways, as demonstrated when an emotionally stressed individual uses some cannabis and homeostasis is restored.

Dysregulation of the endocannabinoid system is being linked to a growing list of medical conditions. Di Marzo's research team has described how the eCB system's plasticity (ability to normalize cellular stress) is compromised a chain reaction of neuro-inflammation, excitotoxicity (under regulated nerves) and production of free radicals begins, leading researchers to believe that over time abnormal plasticity causes disease in organs and organ systems. Too little plasticity has been linked to epilepsy, Alzheimer's dementia, depression and certain forms of cancer. Too much plasticity in the wrong cell or at the wrong time has been linked with obesity and ensuing metabolic disorders (diabetes & dyslipidemia), propensity to addictions, and Parkinson's disease. Too much plasticity at the wrong receptor has been linked to osteoporosis, atherogenic inflammation and atherosclerosis. Even from only these primary findings we get the point... A properly working eCB system in crucial to health. Cannabis supplementation in itself probably goes a long way in helping this system to keep our many body's cells & systems healthfully working in concert with one another, but there is obviously much more going on in the many ways the eCB system can go out of whack, which begs for more research on this subject.

One area of research which scientists, cannabis cultivators and patients are only just beginning to explore is the effect of many cannabinoids themselves. Not only do the cannabinoids effect the body in different ways, but different ratios of these cannabinoids effect the body in different ways. But that is an entire discussion in itself.

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