An Introduction to the Endocannabinoid System

A description of the lipid signaling system essential to health, healing, and homeostasis, long excluded from the medical school curriculum

By Dustin Sulak, D.O.

Adapted from a class for doctors entering the field of Cannabis-based Medicine.

You may be wondering why, as a clinician, you’ve never learned about the endocannabinoid system (ECS) during any of your training. The discovery of this system is relatively new, but it’s been around for 20 years, and a huge body of evidence and peer-reviewed research has been published on various aspects of the endocannabinoid system.

There are two different cannabinoid receptors, the CB1 and CB2, which are very similar in structure. They follow the classic pattern of the G protein-coupled receptor with seven passes through the cell membrane.

CB1 and CB2 are 7-transmembrane G-coupled receptors. Lipophilic ligands outside the cell (top) activate structures within the hydrophobic layer of the membrane, leading to a response within the cell (bottom).

CB1 receptors are located primarily in the nervous system, but also in reproductive tissues, connective tissues, adipose tissues, and other glands and organs. The CB2 receptors are found primarily in cells of the immune system, but during situations of injury or inflammation, the CB2 receptors can also be created and up-regulated in other tissues where they’re not normally found.

The cannabinoid system is extremely old. Phylogenetic studies suggest the cannabinoid receptors evolved some 600 million years ago. Insects don’t have any cannabinoid receptors.

Very primitive animals like sea squirts and nematodes have a cannabinoid receptor that’s almost identical to the human CB1 receptor. This high level of evolutionary conservation suggests that this receptor and receptor system is very important for the function of life.

G protein receptors

G protein-coupled receptors can open or close the ion channels and they can inhibit or stimulate the formation of adenylyl cyclase, which will have other downstream effects in the cell.

“Agonist trafficking” means that the function of the cannabinoid receptor depends on which agonist actually activates that receptor, which adds another layer of complexity to the ECS. This is analogous to an assortment of keys opening the same lock. But depending on which key is used, the door will open into different rooms.

CB1 receptors (scans at left) are distributed throughout the central nervous system, with highest densities shown in red. CB2 receptors (scans at right) are found throughout the periphery, with especially high density in the liver.

Endogenous Cannabinoids and Their Targets

The endogenous (endo-) cannabinoids are molecules our bodies make to interact with the cannabinoid receptors.

The two most well-known are anandamide and 2-arachidonyl glycerol (2-AG). Anandamide is named after the Sanskrit word ananda, which means bliss.

The endocannabinoids are arachidonic acid derivatives synthesized on demand from precursors in the cell membrane. They act as “retrograde messengers.” Elsewhere in the body these endocannabinoids function as autocrine (within cells) and paracrine (cell-to-cell) mediators.

When the endocannabinoids have finished their signaling role, they’re degraded by enzyme hydrolysis; FAAH (fatty acid amide hydrolase) degrades anandamide and MAGL (monoacylglycerol lipase) degrades 2-AG.

Several other cannabinoid receptors have been identified, but G protein receptors are nuclear membrane receptors located inside the cell that are also targets of endocannabinoids. They regulate the translation of genes that are involved in metabolism, energy homeostasis, cell differentiation, and inflammation.

Endocannabinoids can control voltage-gated ion channels and ligand-gated ion channels.

Cannabinoid function in the nervous system

The CB1 receptor is the most common G-protein receptor found in the human brain. The highest densities of CB1 are found in the hippocampus, the cerebral cortex, the cerebellum, the amygdala, and the basal ganglia — areas of the brain involved with short-term memory, cognition, mood and emotion, motor function, and nociception.

Cannabinoid receptors are virtually absent in brainstem cardiorespiratory centers. This is why there is no lethal overdose of cannabinoids.

Below is a simplified diagram of the “retrograde signaling” activity of cannabinoids in the nervous system. At the top you see the presynaptic cell with neurotransmitters inside of vesicles. Upon nerve depolarization, these neurotransmitters are released, and they move across the synapse to stimulate a receptor on the postsynaptic cell. Cannabinoids follow the opposite path. They’re produced on the cell membrane of the postsynaptic cell and travel retrograde across the synapse to interact with the CB1 receptor on the pre-synaptic nerve terminal.

“Let’s look at the mechanism of retrograde signaling in a little more depth, beginning with depolarization-induced suppression of excitation (D I S E )...”

Neuroplasticity

The function of the endocannabinoid system in the nervous system is more than just homeostatic prevention of too much excitation or too much inhibition. There is a significant protective and repair function, and the endocannabinoid system is heavily involved in neuroplasticity.

Neuroplasticity involves the sprouting and pruning of synapses, changes in dendritic spine density, and changes in neurotransmitter turnover in response to changes in conditions in the synaptic cleft. Neuroplasticity includes the conscious act of gaining a new skill, and the unconscious acquisition of a new emotional response. It is also involved in pathological processes such as central sensitization to pain.

There are multiple mechanisms by which cannabinoids modulate neural plasticity, including neurogenesis (the formation of new neurons), long-term potentiation and long-term depression. Research in humans has shown that the administration of endocannabinoids can cause neuroplastic changes. One study that looked at volunteers who were heavy cannabis users found neuroplastic changes in the nucleus accumbens and amygdala. These are two areas of the brain that are involved in the enjoyment of activities such as eating and sex, and also involved in addiction.

...continued on next page
Other studies have shown that cannabinoids can enhance a process called fear extinction. Fear extinction is a neuroplastic event that’s essential for preventing and recovering from post-traumatic stress.

Anandamide and 2-AG are also endogenous neuropro- tective agents, produced by the nervous system in re- sponse to both chemical and mechanical trauma. Other phytocannabinoids and synthetic cannabinoids have been shown to decrease glutamate excitotoxicity in a situation of a seizure or a stroke.

When neurons become injured or ill, they tend to release their contents. Excessive extracellular release levels of gluta- mate that become toxic to the surrounding cells, and we see a domino effect of excitotoxicity. Cannabinoids have been shown to halt that process.

The United States Department of Health and Human Services actually owns a patent on the use of cannabinoids as anti-oxidants and neuroprotectants. The authors of this patent discuss the potential benefit of using cannabinoids in neurodegenerative conditions such as multiple sclerosis, Alzheimer’s, Parkinson’s, Huntington’s, and more.

Cannabinoids also affect autonomic tone. In the sym- pathetic nervous system, CB1 receptor stimulation will inhibit noradrenaline release. It will dampen sympathetically mediated pain and modulate the hypothalamic-pituitary-adrenal axis and the hypothalamic-limbic-neuropeptide axis.

Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

Cannabinoid receptors also have peripheral activities that affect autonomic tone: For example, myocardial CB1 re- ceptors, when activated, cause vagally mediated biphasic effects on heart rate and cardiac contractility. Depending on the situation, stimulation of the CB1 receptors could increase or decrease heart rate and contractility.

In vascular tissues CB1 activation causes vasodilation, which leads to an anti-hypertensive effect that has been demonstrated in humans.

Some rodent studies suggest that cannabinoid receptor activation has a protective role in myocardial ischemia. The parasympathetic nervous system also has CB1 re- ceptors, which will reduce parasympathetic activity when stimulated. And this is likely providing the anti-emetic ef- fect of cannabinoids.

Pain signaling

The endocannabinoid system is heavily involved in pain signaling. Preclinical models have shown that endocan- nabinoid activation causes antinociceptive effects in the three major types of pain: acute pain, persistent inflamma- tory pain, and neuropathic pain.

The peripheral antinociceptive effects of cannabinoids involve many mechanisms in different parts of the body, including the central nervous system’s periaqueductal gray, ventro- posterior lateral nucleus of the thalamus, and rostral ven- tromedial medulla, as well as the spinal cord, the periph- eral nervous system, and the peripheral tissues.

One mechanism by which cannabinoids are able to de- crease nociception and decrease the perception of pain in- volves the descending pain inhibitory pathway depicted below. This pathway has components in the mid-brain, the medulla, and the spinal cord that decrease the nociceptive signals that make it to pain areas in the brain.

In the dorsal horn of the spinal cord there are inhibitory interneurons that release GABA and actually suppress this descending pain inhibitory pathway. Cannabinoids will suppress these GABA neurons thereby enabling the descending pain pathway to do its work in decreasing the amount of pain experienced.

Cannabinoids also decrease pain associated with injury via a homomostatic mechanism. When we experience an injury, activators and sensitizers cause pe- ripheral sensitization including hyperalgesia and eventual- ly allodynia. These activators and sensitizers come from a variety of sources including the damaged tissue itself, the leukocytes, leukocyte-activated platelets, the neighbor- ing autonomic nerves, and the nociceptive nerves them- selves. All can activate activators and sensitizers, leading to peripheral sensitization, which elicits a homeostatic re- sponse by the endocannabinoid system.

As peripheral sensitization begins after an injury, the function of the endocannabinoid system provides the first line of defense against pain. CB1 receptors will decrease the release of activators and sensitizers from the injured peripheral cell.

As noted, CB2 receptors are found not only in immune cells but also in other tissues, especially during situations of injury. CB2 receptors have been found, for example, in painful neuromas. And CB2 agonists produce anti-noci- ceptive effects in pre-clinical models of inflammatory and nociceptive pain.

Cannabinoid-opioid interaction

Opioids and cannabinoids share several pharmacolog- ical effects including antinociception. In animal studies, the crosstalk between these two signaling pathways has shown a promise for combination pain therapy and novel treatments for opioid addiction and abuse.

The spinal administration of various cannabinoids with morphine produces a greater-than-additive antinocicep- tive effect in mice. The “tail-flick test” enables research- ers to assess pain levels. The rodent is positioned with its tail on a hot plate and the heat is gradually increased until the animal finally pain and flinches its tail.

Various doses of morphine can be given to rodents to plot the dose response curve of antinociception in the tail flick test. When very low doses of THC — doses that are marginally active in a tail-flick test — are added to mor- phine, the dose response curve of morphine shifts to the left by four-to-10-fold.

The same is true in the opposite experiment. When low doses of morphine are added to the THC trial, we see the dose response curve shifting to the left again. This points to an analgesic synergy beyond just the additive effects of morphine plus THC.

Adding cannabinoids to opioids will poten- tiate analgesia but will not increase the risk of cardio-respiratory suppression or fatal overdose.

THC has also been shown to trigger the release of en- dogenous opioids, which stimulate both the delta and kappa opioid receptors. Combination treatment with can- nabinoids and opioids is surprisingly safe. The cannabi- noid and opioid receptors are both found in areas of the brain and spinal cord that control pain signaling. But be- cause the cannabinoid receptors have such low densities in the brainstem’s cardio-respiratory center, adding can- nabinoids to opioids will potentiate the analgesia but will not increase the risk of cardiorespiratory suppression or fatal overdose. Therefore, combination therapy actually increases the therapeutic index of opioids.

We all know that, clinically, treating chronic pain with opioids is a major problem due to tolerance building and the potential for dose escalation. Cannabinoids, when co- administered with opioids, can prevent tolerance building to the opioids. Opioid receptor proteins are upregulated in the spinal cord of animals treated with both can- nabinoids and opioids. Mice treated with low doses of THC and morphine in combination showed avoidance of toler- ance to the opioids while retaining their anti-nociceptive effects.

CB1 and MU opioid receptors are also co-localized in the areas of the brain that are important for morphine ab-stinence, such as the ventral tegmental area.

Endocannabinoids and connective tissue

In bone, both osteoblasts and osteoclast produce anan- dadamide and 2-AG, and both express the CB2 receptor. Stimulation of the CB2 receptor leads to increased osteoblast activity and increased osteoblast activity, thus increasing bone formation.

There are CB1 receptors on the sympathetic nerve termi- nals close to the osteoblasts. These nerves release norepi- nephrine, which restrains bone formation. Retrogade CB1 signal will inhibit the release of the norepinephrine and alleviate this tonic sympathetic restraint, thus allowing bone to form.

In cells together connective tissues — fibrobasts, myo- fibroblasts, chondrocytes, and synoviocytes — express both CB1 and CB2 receptors, and the enzymes used to metabo- lize endocannabinoids.

CB1 receptors have been found to be upregulated after exposure to inflammatory cytokines and equiaxial stretch- ing of fibroblasts in models of stress.

Cannabinoids also modulate fascia remodeling via fibro- blast focal adhesions.

Cannabinoids have been shown to prevent cartilage de- struction by inhibiting chondrocyte expression of cyto- kines and metalloproteinase enzymes.

Cannabinoids have also been shown to decrease con- nective tissue inflammation. Animal models of athero- sclerosis demonstrate that CB2 receptor activation on macrophages within atherosclerotic plaques can decrease atherosclerosis.

ECBs in the immune system

In contrast to the drug war propaganda that cannabi- noids are immunosuppressive, there now appears to be sound science that cannabinoids modulate the immune system, just as they modulate other bodily systems. Cannabinoids have been shown to decrease Th1 cytokine levels, increase the levels of Th2 cytokines, and decrease certain subsets of B, T, and NK (natural killer) cells.

Phytocannabinoids also have other immune-mediating mechanisms that are separate from cannabinoid receptors. For example, THC, the acidic form of THC, can inhibit the release of tumor necrosis factor-alpha from macro- phages.

Neuropain

As clinicians, when we think of cannabinoids and cancer, we tend to think of the management of cancer symptoms and the side effects of chemotherapy. Many clinicians are surprised to discover that cannabinoids also have direct oncologic effects.

The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle.

Cannabinoids have been shown to inhibit tumor growth in multiple cell lines. This is a hot area of research. Nu- merous human cancer cells lines have been xenografted to immunosuppressed rodents and treated with cannabinoids. The animals treated with cannabinoids tend to have much slower growing tumors than the animals treated with a control vehicle. Cannabinoids affect neoplasia via mul- tiple mechanisms of action, including cytostasis, apoptosis, antiangiogenesis, and anti metastasis.

Cannabinoids are effective anti-tumor compounds that can kill cancer cells without injuring healthy cells at the same dosage. This makes cannabinoids much less toxic than traditional chemotherapy agents.

Cannabinoids in embryony

Cannabinoids are also heavily involved in embryology and cell growth and differentiation. CB1 receptors have been detected in mouse embryos as early as the second day of gestation. Blastocyst implantation into the endome- trium, which is thought of as the first suckling function, requires suitable levels of cannabinoids.

The proliferation and differentiation of neural stem cells are shaped by extracellular cues provided by endocanabbini- noids. Adult neurogenesis is regulated by many of these.
Endocannabinoid System from previous page

same embryonic endocannabinoid mechanisms. Endocannabinoids

Gastrointestinal System

In the digestive system, CB2 receptors are found in the lamina propria, the plasma cells, activated macrophages, and in the myenteric plexus and submucosal ganglia in the

CB2 receptor signaling likely involves the inhibition of inflammation, visceral pain, and intestinal motility in the inflamed gut.

The Endocannabinoid System In The Liver

The liver expresses both CB1 and CB2 receptors at low levels. The CB1 receptors are mostly found in endothelial cells and hepatocytes, and the CB2 receptors are mostly found in Kupffer cells.

Anandamide and 2-AG are present at substantial levels in the liver, along with the enzymes needed to break down the endocannabinoids.

Liver injury is associated with an increased endocannabi-
noid tone in several pathologic settings. During injury or inflammation, CB1 receptors are induced in hepatocytes, hepatic myofibroblasts, and endothelial cells. CB2 recep-
tors are induced in Kupffer cells as well as the hepatic myofibroblasts. Levels of 2-AG also increase in hepatic stellate cells and hepatocytes during liver injury. The Kupffer cells are involved in our response to early liver injury via the production of tumor necrosis factor-
alpha. This signals the stellate cells to synthesize collagen and cause fibrosis. Fibrosis will eventually lead to cirrho-
sis or loss of liver function.

As we can expect from a signaling system that has ho-
meostatic properties, the cannabinoid system can both in-
crease and decrease fibrosis through different mechanisms.

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naling in myofibroblasts and inhibited by CB2 signaling in the same cells.

The endocannabinoid system also helps control hunger and feeding. Human breast milk contains endocan-
nabinoids, and newborn mice that are given a CB1 recep-
tor antagonist stop suckling and die.

The endocannabinoid system modulates cellular me-
tabolism via many other hormones and neuropeptides, includ-
ing orexin and adiponectin. In obesity, adipocytes produce excessive levels of endocannabinoids which can drive CB1 receptors into a feed-forward dysfunction, contribut-
ing to its homeostatic role in a more balanced manner.

Effects of Exogenous Cannabinoids

Delta-9 THC is the most well known phytocannabinoid. It mimics the activity of anandamide and 2-AG by act-

CB1 and CB2 receptors have opposite effects on liver fibrosis (see figure below). At the top of the figure we have three typical liver insults: a high fat diet, alcohol, and a virus such as hepatitis C. Early liver injury leads to steatosis, which is enhanced by CB1 receptor activation on hepatocytes and on adipocytes, but inhibited by CB2 receptor activation on the Kupffer cells. Prolonged ste-
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A Discovery By Inference
By Fred Gardner

While studies reported in journals help keep scientists and health care providers on recent trends, conferences offer a preview of ongoing research and a chance to ques-
tion and network with the investigators. Scientists who
attend meetings of researchers in other fields remark the
unusual non-competitive, collegial openness at get-to-
gathers of cannabinoid researchers.

The International Association for Cannabinoid Medi-
cines grew out of a group founded in 1997 by a German
physician, Franjo Grotenhermen, the “Association for
Cannabis as Medicine.” Similarly, the C-word in the
International Cannabinoid Research Society’s name has
been changed from “Cannabis.”

At the September 2013 IACM meeting in Cologne,
Raphael Mechoulam recounted a hypothesis published
by Pal Pacher and George Kunos in 2005: “A Discovery
By Inference.”

Mechoulam reported on an analysis of data from an the
then-newly discovered CB1 cannabinoid receptor.

Mechoulam linked the findings to the idea that, while the CB1 receptor is best known for its role in analgesia,
other effects may also occur, such as anxiolysis, antiepi-
lepsy, and anti-inflammation. He speculated that the
role played by the cannabinoid system in these other
conditions may help explain the variety of therapeutic
benefits seen in cannabis.

Mechoulam described the analysis as an “inference” of
the data, rather than a direct observation, because it
 prohibited from directly proving the existence of the
CB1 receptor. However, he argued that the results sup-
sported the hypothesis, as they showed consistency with
other findings in the field.

Mechoulam went on to discuss the potential for
complementary therapies that leverage the CB1 recep-
tor’s role in the endocannabinoid system, which plays a
role in the body’s pain response, mood, and appetite.

He noted that cannabis has been shown to down-regulate
the CB1 receptor, potentially reducing its activity. This
could explain some of the observed therapeutic effects
of cannabis, such as its ability to reduce pain and stress.

Mechoulam also highlighted the potential for further
research to explore the role of the CB1 receptor in
therapies and the development of new treatments.

A slide provided a partial list of conditions involving the endocan-
nabinoid system:

- Inflammatory bowel disease
- Multiple sclerosis
- Nausea
- Pain
- Psychosis
- Seizures
- Spinal cord injury
- Stroke

Mechoulam concluded by suggesting that the study of
the CB1 receptor and the endocannabinoid system
holds promise for future research and treatment.

Pharmacology is not the only route to the truth, although as “hard science,” it commands more respect than the clini-
cian’s craft.

Another IACM presentation that Tod anticipated, in a
recent talk, was a discussion of the potential for cannabi-
sclinicians.org.

An IACM poster by Dutch researcher Martin Perescis de-
scribed a study in which he and his team treated 200 rats
with either an antagonist drug or placebo for six months.

“Severe muscle contractions developed in 15% of animals
with the drug treatment,” Tod said. “The drug treatment
was effective in reducing muscle contractions.”

Tod noted that the results of this study, and others like it,
highlight the potential for cannabinoids to treat a wide
range of conditions. However, he emphasized the need for
further research to fully understand the mechanisms
behind these effects.

Tod concluded by sharing his perspective on the future
of cannabis research and treatment. He expressed
optimism about the potential for cannabinoids to offer
new insights into the treatment of chronic pain and
inflammation, as well as other conditions.

A slide provided a partial list of conditions that may be
affected by cannabinoids:

- Arthritis
- Cancer
- Chronic pain
- Depression
- Epilepsy
- Insomnia
- Multiple sclerosis
- Neurodegenerative diseases
- Parkinson’s disease
- Rheumatoid arthritis

Tod concluded his talk by emphasizing the need for
continued research and collaboration between scientists
and clinicians to fully understand the role of cannabinoids
in human health.

Pharmacology is not the only route to the truth, although as “hard science,” it commands more respect than the clini-
cian’s craft.
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