Endocannabinoids

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Overview

Humans and animals alike naturally synthesize endocannabinoids, chemical compounds that activate the same receptors as delta-9-tetrahydrocannabinol (THC), the active component of marijuana (*Cannabis sativa*). Marijuana, as smoked in cigarettes, has many names both formal—cannabis, cannabis, hashish, hemp, sinsemilla—and informal—pot, dope, grass, weed, Mary Jane, bud, hash, bhang, kef, ganja, locoweed, reefer, doob, spliff, toke, roach.

Marijuana is famous for its significant psychoactive effects. Its ability to provide relief to chronic pain sufferers, to induce an increase in appetite, to alleviate nausea, and to ease anxiety are only some of the common uses for hemp. The interest in cannabis has risen in the United States since its medical and recreational use is now (2015) legal in 20 states.

Medical use of marijuana is allowed in the following 20 states (2015):

- Washington
- Oregon
- California
- Nevada
- Arizona
- New Mexico
- Montana
- Colorado
- Illinois
- Alaska
- Hawaii
- Michigan
- Maine
- Massachusetts
- Rhode Island
- Connecticut
- New Jersey
- Delaware
- Maryland
- Washington, DC

Recreational use of marijuana is allowed in the following two states (2015):

- Colorado
- Washington

Abbreviations

Abbreviations used in the discussion of cannabinoids and in this article are as follows:

- THC: Δ9-Tetrahydrocannabinol
- AEA: Anandamide
- 2-AG: 2-Arachidonoylglycerol
- AA: Arachidonic acid
- EC: Endocannabinoids
- ECS: Endocannabinoid system
- CB1-R: Cannabinoid binding receptor-1 (predominantly in brain)
- CB2-R: Cannabinoid-binding receptor-2 (predominantly in immune system)
- PE: Phosphatidylethanolamine
- NAT: *N* -acyltransferase
- NAPE: *N* -acyl-phosphatidylethanolamine
- NAPE-PLD: NAPE-specific phospholipase D
- MGL: Monoacylglycerol lipase
- FAAH: Fatty acid amide hydrolase

Further investigation

Endocannabinoids are crucial to bioregulation. Their main role is in cell-signaling, and, because they are hydrophobic, their main actions are limited to paracrine (cell-to-cell) or autocrine (same cell), rather than systemic, effects. Unique characteristics of the ECS are as follows:

- Lipid structure, making it lipophilic
- Hydrophobic with limited mobility in an aqueous environment
- Local cell-signaling (paracrine or autocrine)
- Retrograde transmission in the brain; travels backward from postsynaptic to presynaptic cells
- Formed from the internal lipid constituents of cellular membrane
- Synthesized “on demand” and not stored
- Very short half-life
- Degradation by FAAH may regulate ECS bioactivity
- Two G-protein–coupled receptors in the brain (CB1-R) and immune system (CB2-R)

With scientific evidence suggesting their role in inflammation, insulin sensitivity, and fat and energy metabolism, inhibition of endocannabinoids may be a tool in reducing the prevalence of metabolic syndrome and augmenting the benefits of physical exercise.[1, 2] Furthermore, modulation of the endocannabinoid system may be a cure for more chronic neurologic and immune conditions. Many questions are left unanswered about this relatively newly discovered regulatory system. Further investigation into this exciting field promises to shed insights into the mechanisms of health and disease and provide new therapeutic options.

History

History of endocannabinoid research

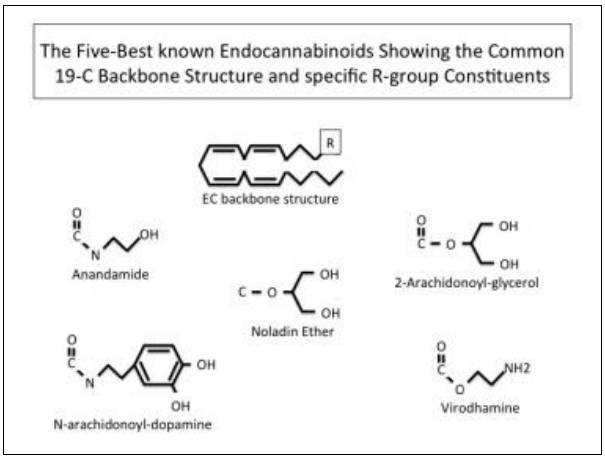
When Mechoulam and colleagues isolated THC in 1964, they made it possible to further understand the complex nature of the endocannabinoid system.[3] Other important events in endocannabinoid research are as follows:

- 2000-650 BCE: Cannabis (azaluu or gurgurru) mentioned in Assyrian pharmacopoeia at the library of Assurbanipal
- 1964: THC isolation and structure elucidation
- 1988: Cannabinoid-binding sites in rat brains identified
- 1991: Human CB1-R receptor successfully cloned
- 1992: Endogenous CB1-R ligand (EC), anandamide (based on Sanskrit for “supreme joy”), discovered in the brain
- 1993: CB2-R receptor found in the immune system successfully cloned
- 1995: Second EC, 2-AG discovered and more abundant in the brain than AEA

In the 21st century, new discoveries of other endocannabinoids, their site distributions, and roles are deepening our understanding of the endocannabinoid system.

Chemical Structure

Although the first EC to be identified was AEA, 2-AG is the most abundant in the brain.[4] Several other ECs have been identified, but their function and role in ECS physiology remains to be determined. Five of the best-known ECs are in the figure below. Note that all of them share the same 19-C backbone structure but differ in the R-group constituents.

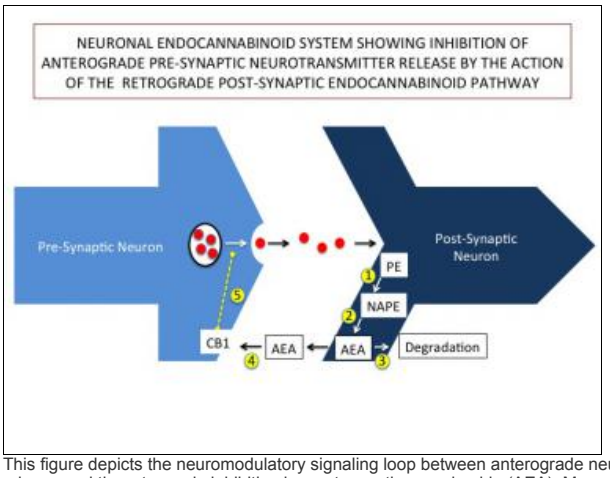


The five best-known endocannabinoids showing the common 19-C backbone structure and specific R-group constituents.

Endocannabinoid System Roles

Multiple human and animal studies support that endocannabinoids play a key role in memory, mood, brain reward systems, drug addiction, and metabolic processes, such as lipolysis, glucose metabolism, and energy balance.[5]

Several competing pathways for AEA biosynthesis have been described. The best-described pathway is shown in the figure below. AEA biosynthesis is initiated following a postsynaptic neuronal depolarization and an influx of calcium. The calcium then activates *N*- acylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD) and diacylglycerol (DAG) lipase, each of which forms AEA and 2-AG, respectively.[4, 6] The anterograde neurotransmitter transmission and retrograde EC modulation form the closed signaling loop depicted in the figure below.



This figure depicts the neuromodulatory signaling loop between anterograde neurotransmitter release and the retrograde inhibition by postsynaptic anandamide (AEA). More specifically, it shows the biosynthesis of AEA and activation of the cannabinoid binding receptor-1 (CB1-R) receptor pathway (2-arachidonoylglycerol [2-AG] pathway is similar but not shown here). The initiation of AEA biosynthesis differs from 2-AG. Important to note is that these two processes are mutually exclusively so that AEA and AG cannot be co-synthesized. The endocannabinoid system (ECS) steps shown are as follows: (1) the initiation of AEA biosynthesis starts with activation of N-acyltransferase (NAT), which transfers an acyl group to the membrane phospholipid, phosphatidylethanolamine (PE), forming N-acyl-phosphatidylethanolamine (NAPE); (2) a NAPE-specific phospholipase D (NAPE-PLD) next cleaves NAPE to produce AEA; (3) once synthesized, AEA is susceptible to degradation by fatty acid amide hydrolase (FAAH), possibly an important point of regulation; (4) the AEA that escapes FAAH degradation can diffuse across the synaptic cleft to activate the presynaptic G-coupled membrane bound CB1-R receptor; (5) this activation results in inhibition of anterograde neurotransmitter release. It is obvious that one of the purposes of this ECS is to enable postsynaptic neuron control over neurotransmitter action.

Owing to their lipophilic nature, the endocannabinoids act locally and are not synthesized until needed. Central nervous system messengers that act in a retrograde fashion, the endocannabinoids, are agonists to CB1-R and CB2-R.[7, 8]

Endocannabinoid receptors (CB1-R and CB2-R)

CB1-R and CB2-R are membrane-bound G-protein receptors that activate cyclic-AMP like other classic G-protein receptors. A non–CB1-R/non–CB2-R has been theorized based on indirect data but has yet to be characterized.

CB1-R and CB2-R are G-protein receptors. CB1-R receptors are abundant in the brain, specifically the mesocorticolimbic system, the spinal cord, and the peripheral neurons. CB1-R receptors are particularly concentrated on both gamma-aminobutyric acid (GABA)–releasing neurons (inhibitory neurons) and glutaminergic-releasing neurons (excitatory). Hence, activation of CB1-R leads to retrograde suppression of neurotransmitter release, which may be excitatory or inhibitory depending on the location in the brain.[7, 9] Interestingly, *CB1R* gene polymorphisms have been described but their functional effects are not well-characterized. Some are associated with anxiety and depression.[10]

CB2-R receptors are located peripherally, with a high density on immune-modulating cells, including microglia in the brain. It is believed the CB2-R may have a protective effect on autoimmunity and inflammation.[1, 10] CB2-R may have some relationship to depression based on animal studies and the finding of a high-incidence of CB2-R polymorphisms in a depressed Japanese population.[10]

Table. Comparison of EC Receptors CB1-R AND CB2-R Characteristics (Open

Table in a new window)

	CB1-R	CB2-R
Principal Endogenous Ligands	AEA and 2-AG	2-AG (AEA partial agonist)
Major Tissue Locations	Brain and peripheral nervous system	Immune system
Other Tissue Locations	Pituitary, thyroid, and adrenal glands; male and female reproductive system; liver, adipocytes, lungs, kidney	Spleen, tonsils, thymus gland, gastrointestinal tract, osteocytes
Cellular Location	Presynaptic glutamate and GABA neurons	Monocytes, macrophages, microglia, B-cells, and T-cells
Gene/Chromosome	*CNR1*/6q14	*CNR2*/1p36
General Action	Inhibits release of glutamate and GABA	Modulates cytokine release and immune response
Physiologic Actions		
Gastrointestinal System	Decreases gut motility	Reduces bowel inflammation
Peripheral Nervous System Analgesic Effects	Nociceptive interneurons in the dorsal horn of the spinal cord	Anti-inflammatory action mast cells in spinal cord
Reproductive System	Male – Leydig cells Female – Ovary, ducts, uterus, placenta, embryo implantation	Placenta, embryo, T-cell cytokine release
Liver	Promotes fibrosis, increases steatosis	Inhibits fibrosis, decreases steatosis
Cardiovascular System	Hypotension, bradycardia	Atherosclerotic plaque inflammation
Drug-Seeking Behavior	Stimulates	Reduces

CB1-R CB2-R physiologic and pathophysiologic roles in the body

Chronic stress

Although stress responses can be life-saving in the face of a threat, chronic stress often has negative health effects. The ECS is the central mediator of the stress response. The ECS regulates the release of stress-induced neurotransmitters including the systemic release of norepinephrine and cortisol. The ECS plays a role in the stress alterations of mood, cognition, and activation of the hypothalamic-pituitary-adrenal axis. The ECS may also mediate some of the dysmetabolic effects glucocorticoids on lipid metabolism, leading to hepatic steatosis and potentially contributing to the metabolic syndrome.[11] Therefore, the ECS is an important control point and therapeutic target to reduce the deleterious effects of chronic stress.[12]

Obesity

CB1-R is important for energy balance in the body. With fasting or starvation, anandamide and 2-AG levels increase in the limbic forebrain and, to a less significant extent, in the hypothalamus. CB1-R activation increases food intake and effects energy metabolism through coordination of the mesolimbic reward system and the hypothalamus' appetite control pathway.[9, 13] This receptor also promotes food intake by increasing odor detection via stronger odor processing in the olfactory bulb.[14]

Some obese people may have excess CB1-R activation. Obese and overweight individuals may have a mutation in FAAH, the enzyme that degrades AEA. This can lead to increased levels of AEA (15-fold increase in FAAH "knock-out" mice)

and stimulation of the hypothalamic appetite control center.[13]

It is uncertain if there is a regulatory feedback loop between the ECS and obesity. Wild-type mice that develop diet-induced obesity have a hyperactive ECS, with an increase in receptor availability and an increase in circulating ECs. In presatiated mice, an intrahypothalamic injection of AEA induced substantial hyperphagia. Inactivation of CB1-R receptors decreases plasma insulin and leptin levels, ultimately leading to more efficient energy metabolism.[15, 16]

Nervous system

The ECS obviously plays a significant role in the normal functioning of the brain, spinal cord, and peripheral nervous system. Therefore, the ECS can either cause or become altered by diseases of the neurologic system. For example, hyperactivity of the ECS reduces dopaminergic tone in the basal ganglia, contributing to the pathophysiology of Parkinson disease.[17] Other diseases with potentially significant ECS interactions include multiple sclerosis, seizure disorders, Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis, and psychiatric diseases such as schizophrenia.[18, 19]

Pain

Pain is already a well established and important therapeutic target for ECs. CB1-R agonists act on nociceptive interneurons in the dorsal horn of the spinal cord to alleviate pain. In addition, CB2-R–selective agonists have proven to be helpful in reducing inflammation and undoing established inflammation hypersensitivity involved in peripheral pain and skin disorders.[20, 1]

Heart and blood vessels

CB1-R activation aids in vasodilation and cardiac contractility, regulating blood pressure and improving left-sided heart function. CB2-R has been implicated in the inflammation in atherosclerotic plaques. In this regard, CB2-R activation is a therapeutic strategy for reducing atherosclerotic plaque inflammation and reducing vulnerability to rupture and thrombosis.[21]

Cancer

Both marijuana and ECs are anti-inflammatory, antiproliferative, anti-invasive, antimetastatic, and proapoptotic in most cancers, in vitro and in vivo, in animals. In some cancers, ECs are proproliferative and antiapoptotic, but in the majority they show cell cycle arrest, autophagy, apoptosis, and tumor inhibition. At present, cannabinoid cancer therapy is limited to nausea and pain, but future studies are needed to determine its full chemotherapeutic potential.[20, 22, 23]

Gastrointestinalsystem

Activation of CB-1 receptors and, to a lesser extent, CB2-R receptors, by AEA also reduces gastrointestinal motility and secretions. CB1-R receptor activation inhibits proinflammatory responses in the colon.[24, 25]

Liver

CB1-R receptors aid in modulating hepatic lipogenesis. Activation in the liver leads to fatty acid synthesis, causing hepatic steatosis and diet-induced obesity. In addition, the CB1-R promotes hepatic fibrosis and contributes to the hemodynamic abnormalities in cirrhosis. By reducing inflammatory cell infiltration and lipid peroxidation, CB2-R receptor activation is protective against hepatic ischemia-reperfusion injury. Targeting the hepatic ECS may have therapeutic potential in a variety of liver diseases.[26]

Reproductive system

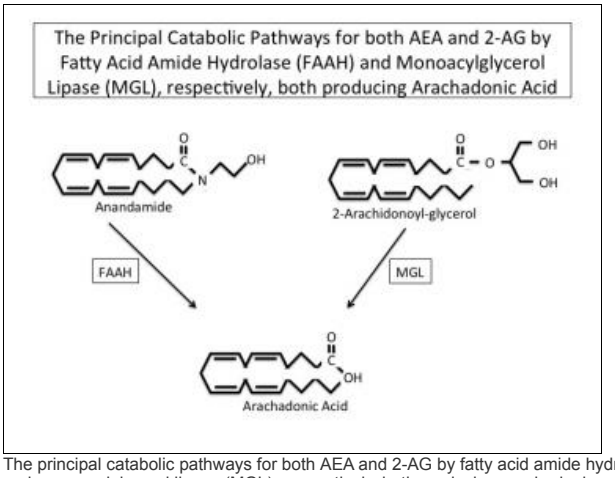
The ECS has a role in reproduction. The CB1-R is found in the male (Leydig cells) and the female (ovary, ducts, uterus). Furthermore, normal folliculogenesis and spermatogenesis may require the ECS. The CB1-R is also present in the placenta and is necessary for embryo implantation.[22] The use of cannabis is associated with implantation failure, spontaneous miscarriage, fetal growth restriction, and premature birth in humans. Future research efforts will be needed to unravel the full complexity of the ECS involvement in the process of reproduction.

Skeletal system

In addition to immunomodulatory pathways, CB2-R receptors are involved in maintaining proper bone mass.[27] CB2-R receptors are abundant in osteocytes, osteoclasts, and osteoblasts. CB2-R agonists enhance endocortical osteoblast reproduction and activation, while inhibiting osteoclastogenesis.

Endocannabinoid degradation

Endocannabinoids have a short life span. AEA and 2-AG are quickly degraded through transport protein reuptake and hydrolyzation by either FAAH or MAG lipase, respectively.[28] Degradation may be an important regulatory control point, since inactivation of FAAH results in 15-fold elevated AEA levels in genetic FAAH knock-out mouse brains. Furthermore, these enzymes, FAAH and MGL, have become therapeutic targets for pharmacologic interventions of the ECS. FAAH inhibition has shown the advantages of a lack of abuse potential or physical dependence compared with MGL.[6, 10, 25] See the figure below.



The principal catabolic pathways for both AEA and 2-AG by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), respectively, both producing arachadonic acid.

Other less important enzymatic pathways exist, demonstrating redundancy in EC degradation. Interestingly, the catabolite AA is a precursor for the cyclooxygenase (COX)–2 enzyme, leading to a number of bioactive eicosanoids (eg, prostaglandins, prostacyclin, thromboxane, leukotrienes). The significance of the EC–COX-2 eicosanoid pathway is under investigation.[29]

Pharmacologic Therapy

Cannabinoid receptor agonists

THC and cannabidiol (which together make up the drug Sativex) are active components of *Cannabis sativa* that bind to CB1-R and CB2-R receptors. Their bioavailability is unknown. A buccal spray is approved for use for neuropathic pain associated with multiple sclerosis in Canada only.[20, 30, 31, 32]

Dronabinol (Marinol), a synthetic THC, is a CB1-R and CB2-R receptor agonist that has been approved by the US Food and Drug Administration (FDA) for use as an antiemetic for chemotherapy and an appetite stimulant for persons with acquired immunodeficiency syndrome (AIDS). Its bioavailability is 10%.[33, 34]

Nabilone (Cesamet) is a synthetic analogue of THC; it is a CB1-R and CB2-R receptor agonist that has been FDA approved as an antiemetic in chemotherapy patients in whom all other therapy has failed. Unapproved use is employed in patients with upper motor neuron syndrome who have spasticity-related pain not controlled by conventional treatment.[20, 35]

CB1-R receptor antagonists

CB1-R receptors activate the dopaminergic reward system. Commonly abused drugs, such as nicotine, opiates, THC, and alcohol, share a common pathway, the dopaminergic surge in the nucleus accumbens. Independent studies involving humans and mice, respectively, reported an increase in smoking cessation rates, decreased alcohol intake, and a reduction in cocaine-seeking behavior with CB1-R antagonism.

Rimonabant (Acomplia or Zimulti) is a selective CB1-R receptor antagonist, SR141716, with an affinity to centrally acting CB1-R receptors. Rimonabant was sold in Europe for the treatment of obesity. It was not approved in the United States and later withdrawn because of psychiatric effects, especially depression.[36, 37, 38]

Nevertheless, the ECS is ubiquitous regulator of cellular function in both health and diseases, which offers many potential therapeutic targets. Below is a list of ECS agonist and antagonist intervention with therapeutic potential.[39]

Potential therapeutic targets for cannabinoid pharmacologic intervention are as

follows:

- Pain
- Antinausea
- Cough
- Glaucoma
- Cachexia
- Neurologic diseases: Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, multiple sclerosis, alcohol-induced neuroinflammation/neurodegeneration, traumatic brain injury, stroke, seizures
- Autoimmune diseases: Autoimmune uveitis, systemic sclerosis, inflammatory bowel disease
- Infection: HIV-1 brain infection
- Psychiatric disorders: Anxiety-related disorders, impulsivity, bipolar disorder, personality disorders, attention-deficit/hyperactivity disorder, substance abuse and addictive disorders, anorexia nervosa
- Cardiovascular: Atherosclerosis
- Gastrointestinal: Gut motility disorders, inflammatory bowel syndrome, chronic liver diseases, alcoholic liver disease
- Diabetic nephropathy
- Osteoporosis
- Cancer: Breast, prostate, skin, pancreatic, colon, and lymphatic, among others

Conclusion

In summary, the ECS is a unique and ubiquitous cell-signaling system that is just beginning to be understood. The biochemistry of EC synthesis, metabolism, and bioactivity has been difficult to study in the past. Newer techniques such as genetically modified animals, pharmacologic probes, and molecular biology promise to reveal some of these mysteries in the future. The greater promise is that with this understanding, the ECS will yield an important therapeutic target for future pharmacologic therapy.

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