

**DO YOUR HOMEWORK**

In order to advise clients about the use of cannabis as medicine, veterinarians must understand how the endocannabinoid system functions and affects the central nervous system.

INTEGRATIVE MEDICINE

The Endocannabinoid System and Phytocannabinoids

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In recent years, attention toward the use of cannabis in veterinary medicine has been unprecedented. Even new pharmaceutical innovations rarely evoke the level of interest being seen with cannabis. From a veterinarian's perspective, incorporating cannabis into practice necessitates learning about a system of neurotransmitters and receptors of which many of us heretofore were completely unaware.

To use and/or advise clients about the use of cannabis as medicine, veterinarians must understand how the endocannabinoid system functions and how compounds in cannabis (phytocannabinoids) exert physiologic effects through accessing endogenous pathways. This article serves as an introduction to those topics.

THE ENDOCANNABINOID SYSTEM

The endocannabinoid system (ECS) (**FIGURE 1**) was discovered in the 1970s by Israeli researcher Raphael Mechoulam. What Dr. Mechoulam discovered was a previously unknown system of neurotransmitters and receptors that profoundly affected our understanding of how the human body functions.

Endocannabinoids are chemical compounds that are naturally produced within the body and bind to the

same receptors as compounds naturally produced by cannabis. The ECS is a biological system composed of neurotransmitters (the endocannabinoids) that bind to cannabinoid receptors that are expressed throughout the central and peripheral nervous systems.

The major function of the ECS is neuromodulation, and its effects often lead to alteration of the physiologic function and behavior of body tissues. The ECS is widely found throughout the animal kingdom; all complex animals have an ECS, as do many of the most primitive animals such as nematodes.¹ The ECS comprises receptors, neurotransmitters, and degradation enzymes.

Receptors

Endocannabinoid receptors are present on neurons throughout the central nervous system (CNS), peripheral nerves, immune cells, and in many tissues throughout the body. The variety of ECS receptors include G-protein (GPR)-coupled receptors, ligand-gated ion channels, and nuclear receptors.² The most common receptors are the GPR-coupled receptors cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2).



CB1 Receptors

CB1 is the most abundant protein-bound receptor in the CNS; it is also found in a variety of other tissues, including fat cells, liver cells, musculoskeletal tissues, the gastrointestinal tract, cardiovascular tissues, peripheral nerves, immune cells, and the reproductive tract. The ubiquitousness of CB1 throughout the body provides insight into how vital the ECS is to the body's functions. CB1 exerts inhibitory action on a wide variety of neurotransmission systems (e.g., dopaminergic, glutamergic, and serotonergic) as well as on the neurotransmitters γ -aminobutyric acid, noradrenalin, and acetylcholine.³ As a result, CB1 receptors affect mood, cognition, pain and inflammation, appetite, and nausea. In addition, CB1 receptors are responsible for the psychoactive effects of Δ -9-tetrahydrocannabinol (THC), the active ingredient in marijuana.

CB2 Receptors

CB2 receptors are found predominantly in the immune system as well as in tissues and organs throughout the body. They are frequently expressed on T and B lymphocytes and macrophages as well as on cells of the spleen, liver, kidneys, and skin. CB2 receptors function,

not surprisingly, in immune modulation and mediation of inflammation. Research also indicates that they play a role in maintaining bone density.^{4,5}

Other Receptors

Although CB1 and CB2 receptors are the most studied, numerous other receptors interact with endogenous cannabinoids (endocannabinoids) and, by association, exogenous cannabinoids (phytocannabinoids). Some of these receptors (and their functions) include GPR18 (G-protein-coupled receptor 18 [immune, anti-inflammatory, and blood pressure effects]), GPR15 (pancreatic insulin release), and GPR119 (energy intake regulation). Ligand-gated ion channels—such as transient receptor potential vanilloid type 1, serotonin, and glycine receptors—interact with the ECS to provide analgesia. Nuclear receptors, such as peroxisome proliferator-activated receptors alpha and gamma, provide CNS neuroprotection.⁶

Neurotransmitters

ECS neurotransmitters, or endocannabinoids, are generated on demand rather than being stored within cells. "Demand" is sometimes a function of physiologic

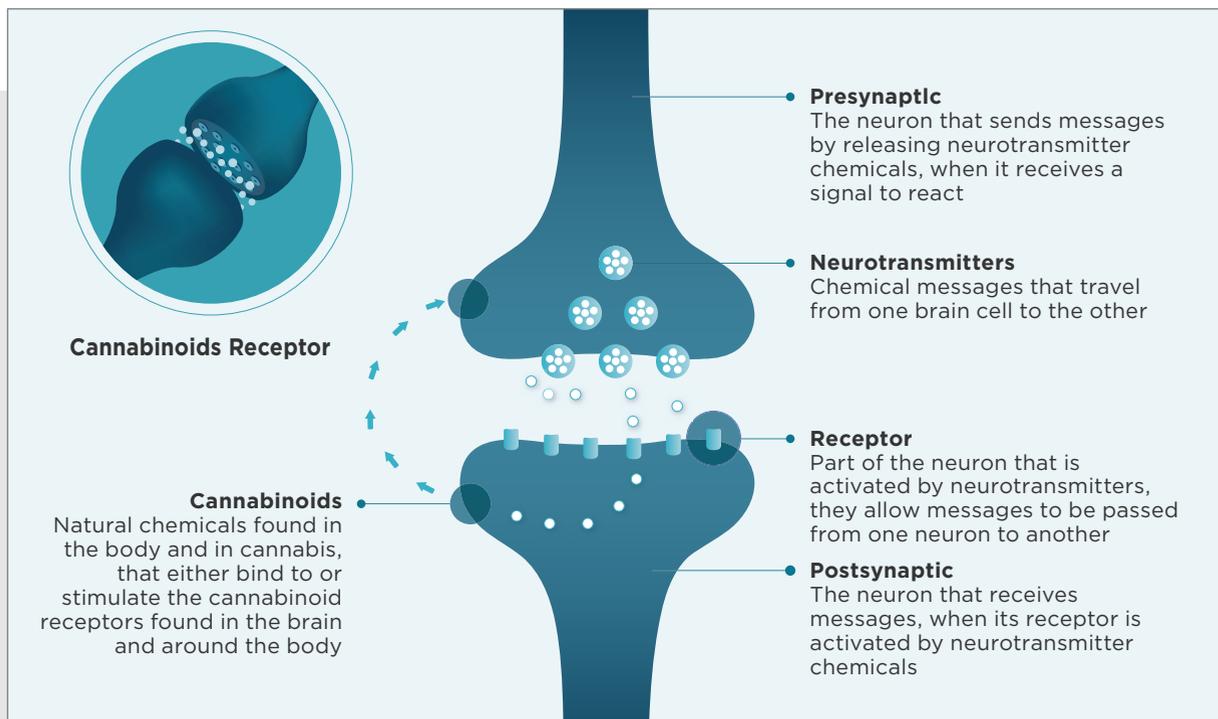


FIGURE 1. Retrograde neurotransmission of endocannabinoids regulates the anterograde transmission of a variety of neurotransmitters.

stress (e.g. pain, injury, inflammation, illness). Endocannabinoids are also generated as a part of normal physiologic function to help maintain homeostasis. Two endocannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (FIGURE 2), interact with CB1, CB2, and the other receptors. AEA and 2-AG function on the cell surface and within the interior, depending on receptor location. AEA is the primary endogenous ligand for CB1 and is a highly selective partial agonist for CB1. 2-AG is the primary endogenous ligand for CB2 and is a moderate-affinity full agonist for CB2 as well as CB1.⁷⁻⁹

Degradation Enzymes

Just as the endocannabinoids are synthesized on demand, they are degraded when no longer needed. The 2 major degradation enzymes are fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Although FAAH enzymatically degrades AEA, MAGL hydrolyzes 2-AG.¹⁰ Fatty acid-binding proteins mediate the transport of AEA to FAAH. AEA and 2-AG are also metabolized through the cyclooxygenase-2 pathway.

PHYTOCANNABINOIDS

Phytocannabinoids are plant-based compounds that act on endocannabinoid receptors in the body. Around 100 phytocannabinoids have been isolated from cannabis, and these compounds have varying affinity for endocannabinoid receptors. Some of these compounds have profound physiologic effects and are the subject of intense medical research.^{11,12}

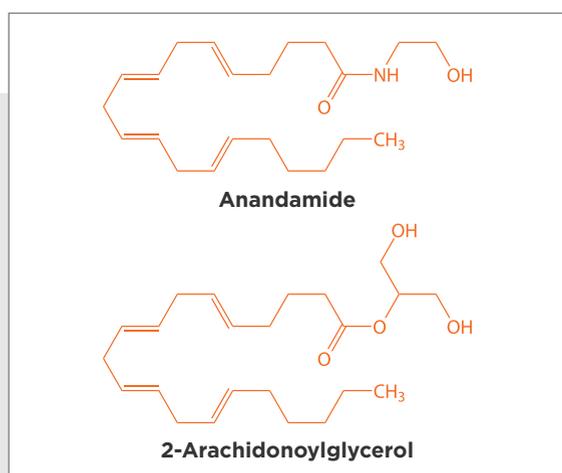


FIGURE 2. Molecular structure of anandamide and 2-arachidonoylglycerol (2-AG).

THC

One of the most well-known and well-studied phytocannabinoids is THC, which is a partial agonist of CB1 and CB2 receptors and is phytomimetic for AEA. THC's binding affinity for CB1 receptors is responsible for its psychoactive properties.

Many medical benefits of THC in humans and animals have been hypothesized, although few have received enough study to be definitively proven. THC has been shown to be effective against chronic pain, specifically neuropathic pain. Preclinical research has shown THC to also be possibly effective against nausea and vomiting, cancer, controlling intraocular pressure in glaucoma, and limiting insulin sensitivity.¹³ Clinical reports from both human and veterinary medicine suggest that THC has a broader range of medical application than is currently recognized. However, the lack of more extensive research related to medicines containing THC results largely from legal restrictions.

One of the most misunderstood aspects of THC in veterinary medicine is its safety profile. THC does not cause respiratory depression at any dose and thus, unlike opioids, will not lead to apnea. In addition, cannabis in dogs has no known 50% lethal dose. THC doses of 3,000 mg/kg given to dogs did not lead to death from THC toxicity.¹⁴ This is not to say, however, that no harm can come to animals from THC. Static ataxia (standing rigidly, rocking back and forth as if trying to move but cannot) is pathognomonic for THC toxicity in dogs and, in many cases, requires medical intervention. In extreme cases of THC toxicity, animals have died from aspiration pneumonia and secondary sepsis. Static ataxia and THC-associated deaths, however, are exclusively the result of accidental ingestion of high-dose products intended for humans or from inappropriate administration of cannabis "medicine" to animals without proper medical guidance. Animals suspected of ingesting potentially toxic doses of THC should receive immediate medical intervention that includes decontamination and supportive care as clinically indicated.

Cannabidiol

The other cannabinoid receiving a great deal of attention in discussions about cannabis as medicine is cannabidiol (CBD). Unlike THC, CBD is a CB1 and CB2 antagonist, although its binding affinity for each receptor is relatively low to moderate. In addition to its effects on CB1 and CB2, CBD has other modulatory



effects on the ECS. CBD binds fatty acid-binding proteins, which slows/limits FAAH degradation of AEA and thus may promote greater AEA activity.

Research into the physiologic effects of CBD has been less legally restricted than that of THC, and multiple veterinary-specific studies have been published in recent years. Those studies have shown CBD to be generally safe in dogs and cats, although alkaline phosphatase was elevated in some animals.^{15,16} CBD at 2 mg/kg q12h was also proven to be effective in the treatment of osteoarthritis in dogs and at 2.5 mg/kg q12h had a positive effect on seizure frequency in dogs with epilepsy.^{17,18} Other potential applications being evaluated include treatment of cancer, inflammation, anxiety, and reduction of insulin resistance.¹⁹

Other Phytocannabinoids

In addition to THC and CBD, many other phytocannabinoids show promise as medicine. Although a detailed discussion of these cannabinoids is beyond the scope of this article, the reader should be aware that phytocannabinoids such as the cannabinoid acids (e.g., tetrahydrocannabinolic acid, cannabidiolic acid, cannabigerolic acid) and other cannabinoids (e.g., tetrahydrocannabivarin, cannabichromene, cannabigerol, cannabinol) are also commonly encountered in cannabis extracts, and according to preclinical and in vitro studies seem to have significant medical benefits. Compounds of an entirely different class, called terpenes, have benefits as well and, in some cases, may act synergistically with cannabinoids through what is known as the entourage effect. Research is ongoing to evaluate anti-inflammatory, anti-neoplastic, anti-epileptic, and other activities that may make them as useful as THC and CBD for the future of cannabinoid medicine.

DRUG INTERACTIONS

Given the widespread availability of CBD and its popularity with pet owners, potential interactions with co-administered pharmaceuticals is a logical topic of concern. Ingested CBD is metabolized in the liver by cytochrome P450 (CYP450) and it is also a competitive inhibitor of CYP450.²⁰ In addition, CBD decreases expression of P-glycoprotein.²¹ Theoretically, CBD could affect the performance of certain pharmaceuticals that are metabolized by CYP450 or P-glycoprotein. As such, consideration is warranted when co-administering CBD with pharmaceuticals metabolized through

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similar pathways. Depending on the mechanism of action and metabolism of the drug in question, co-administration with CBD could lead to increased drug levels and resultant toxicity or decreased levels and resultant lack of efficacy. However, the extent to which these herb/drug interactions are truly a clinical concern is unclear. In a recent study, phenobarbital or potassium bromide levels remained unchanged when CBD at 2.5 mg/kg q12h was given to epileptic dogs.¹⁸ As administration of medical cannabis to humans and animals concurrently receiving pharmaceuticals becomes more widespread, the question of interactions between CBD (or other cannabinoids) and pharmaceuticals is sure to continue to receive attention.

THE FUTURE OF CANNABIS USE IN VETERINARY PRACTICE

The intense interest of the medical community and public in medical uses of cannabis is unprecedented for a plant-based medicine. The combination of this degree of attention and the progression of state (and possibly federal) laws to allow physicians and veterinarians to integrate cannabis into their treatment plans will serve to further the drive for clinical research. Although there is clearly still a great deal to learn about this complex plant and its interactions with the ECS, cannabis has apparent clinical applications in veterinary medicine. Although at present only osteoarthritis and epileptic seizures have been evaluated and shown to be positively affected by administration of cannabis, many clinicians and pet owners have seen broader positive effects. Anecdotal reports of cannabis effectiveness for reducing anxiety, signs of gastrointestinal disease, pain (beyond that of osteoarthritis), and for palliative care for cancer patients are commonplace.

To ensure safety and effectiveness of cannabis use in animals, the challenge for pet owners and veterinarians

is to become educated with regard to the ECS and cannabis administration. Approved continuing education lectures and courses are available for veterinarians who are interested in the use of cannabis for animals. Legal challenges, however, continue to plague the veterinary profession. They make it difficult for veterinarians to

have meaningful discussions with clients about cannabis use, which puts an undue burden on clients who are often turned away by their veterinarian and forced to seek medical advice about cannabis from the Internet, pet stores, or cannabis dispensaries.

Regardless of individual opinions within the veterinary profession, medical cannabis for animals is here to stay. Medical and/or recreational cannabis is legal in 30-plus states and hemp-based CBD products are marketed for pets nationally. Although almost everyone is in favor of more research, we cannot sit on the sidelines until we have it. Veterinarians need to be at the center of the conversation about safe and effective medical cannabis for our patients rather than abdicating the responsibility to untrained people who are trying to sell a product. Only by educating ourselves and vocally supporting our need as medical professionals to provide guidance to clients will the veterinary profession be able to address client concerns and keep our patients safe. **TVP**

Gary Richter

Dr. Richter is a graduate of the University of Florida College of Veterinary Medicine and is certified in acupuncture, chiropractic, and Western herbology. His book on integrative medicine, *The Ultimate Pet Health Guide*, was released in 2017. In addition to full-time practice, Dr. Richter is a vocal advocate for the safe use of medical cannabis for animals. He is also the current president of the American College of Veterinary Botanical Medicine and co-president and a founding member of the Veterinary Cannabis Society, a nonprofit society dedicated to education and advocacy in support of the use of medical cannabis in veterinary patients.



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