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Role of the Endocannabinoid System and Medical Cannabis

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ABSTRACT

Our bodies produce complex substrates called endocannabinoids, which attach to the endocannabinoid system (ECS) receptors and impact many physiologic processes. Current research on the ECS and cannabis-based medications is accelerating in the presence of continued conflict between federal and state laws. In this article we present a summary of the latest information on the ECS, its receptors, and current research on the cannabis-based medicines and their potential to treat various disease pathologies and medical conditions. Our study includes the latest information on the continued legal ramifications nurse practitioners face in treating patients with these medications.

Keywords: cannabis, endocannabinoid receptor, endocannabinoid system

INTRODUCTION

Cannabis has been highly valued and used by many cultures throughout history for its medicinal, euphoria, and relaxation-enhancing properties. This usage dates back over 3,000 years with the report of anxiety relief with *bhang* (cannabis consumed as food) in ancient India.[1] In 2008, archeologists discovered cannabis in 2,500-year-old tombs in eastern China. Genetic testing of this ancient marijuana led researchers to believe it was used for treating illness but also for its psychotropic effects and spiritual purposes as well.[2]

It was not until much later that cannabis was introduced into the United States. In 1619, King James I ordered the Jamestown colonists to grow cannabis plants for hemp export. The hemp fibers were used to manufacture ropes, paper, and fabric.[3] In the 1850s, medicinal preparations became available in American pharmacies. Over the next 3 decades, recreational use of cannabis flourished in oriental-style hashish establishments.[4] It was during this time that cannabis was labeled as both a poison and narcotic.

In 1906, the Pure Drug and Food Act was passed requiring that certain drugs, including cannabis, be accurately labeled, and states began to restrict the sale of cannabis.[5] In 1937, the Marijuana Tax Act was passed, which made it illegal to possess or transfer cannabis. In 1970, the Supreme Court determined that the Marijuana Tax Act was unconstitutional. It was during this time Congress passed the Controlled Substance Act and listed cannabis as a Schedule I drug.[6]

Cannabis possesses over 100 different cannabinoids and has been found to modulate analgesia and anti-inflammatory pathways and provide neuroprotection, among other functions.[7] In the 20th century, Δ9-tetrahydrocannabinol (THC) was identified as a primary bioactive component of cannabis; this led to the discovery and cloning of endogenous cannabinoid receptors. It was also found that the body could produce naturally occurring substances, called endocannabinoids, which could mimic THC activity. Endocannabinoids, their receptors, and the associated mediating enzymes for synthesis and degradation comprise the endocannabinoid system (ECS).[8]

In the US there are 3 categories of cannabinoid medicines: single molecule drugs; cannabis-based liquid extracts; and phytocannabinoid botanicals.[7] Single molecule drugs are semisynthetic or synthetic prescription drugs. The US Food and Drug Administration (FDA) has approved 2 of these, nabilone and dronabinol.[7] The second category of

cannabis-based liquid extracts includes the botanical drug naximols, which is produced by the UK-based GW Pharmaceuticals Co. This drug is currently undergoing FDA Phase III trials. They are looking at whether there is a significant difference between naximols and placebo in reducing pain in patients with advanced cancer.[9]

The last category of cannabinoid medicines is phytocannabinoid botanicals, which includes the Schedule I plant *Cannabis sativa*.[7] These are dense cannabis extracts usually available in capsule or pill form. Other methods of delivery may include sublingual sprays, transdermal patches, suppositories, and topical ointments. An example of this category is a Schedule III drug called Idrasil, which is used to help alleviate pain and improve appetite.[10]

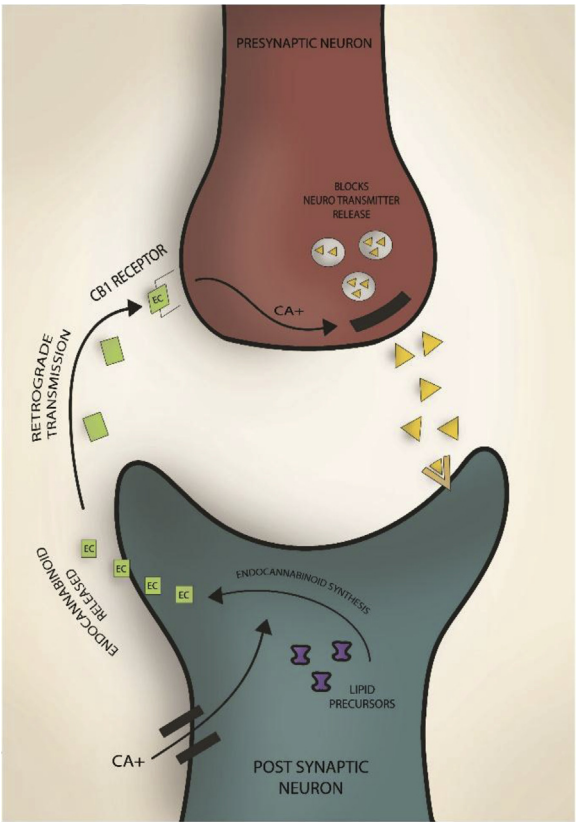
With the discovery of the ECS, scientists and researchers have been petitioning to remove the cannabis Schedule I drug restrictions so medical research can more easily be done. Current research is addressing the effects of exogenous cannabinoids in treating symptoms of epilepsy, human immunodeficiency virus neuropathy, chemotherapy-induced nausea, anorexia, multiple sclerosis spasticity, chronic and neuropathic pain, glaucoma intraocular pressures, and asthma-associated dyspnea.[7] The FDA has recently given approval for a study on the effect of medical cannabis in treating military veterans with posttraumatic stress disorder (PTSD).[11]

Currently, 25 states have passed laws permitting limited use of medicinal cannabis for specific medical conditions.[12] Patients receive state authorizations to procure and self-administer medicinal cannabis under in-state medical supervision. Yet, many health-care providers feel uncomfortable providing care to these patients. Besides geographic considerations, there continues to be a sociopolitical environment in which state laws are in direct conflict with federal laws, with potential serious legal consequences to both provider and patient.[12] Our aim in this study was to provide current information about the ECS and the research being done on medications that directly impact the ECS to reduce or alleviate disease-associated symptoms. Additional background information is provided on current cannabis plant medical research and the sociopolitical factors that continue to impact both the nurse practitioner and patient in the decision to treat with cannabinoid medications.

ECS

As a basic review, the ECS is comprised of endocannabinoids (eCBs), their receptors, and the associated mediating enzymes for synthesis and degradation. It is a unique and complex system with the eCBs acting as the only known retrograde synaptic neurotransmitters (see Figure).[13] There are 5 known eCBs produced by the body: anandamide (AEA); 2-archidonoylglyceral (2-AG); 2-archidonoylglyceral ether (noladin ether); *O*-archidonoyl ethanolamine (virodhamine); and *N*-arachidonoyl dopamine.[13] AEA and 2-AG are the 2 most commonly recognized and studied eCBs ligands and are endogenous arachidonate-based lipids.[14] AEA was discovered in 1992 and helped to provide a basic understanding of

Figure. Retrograde endocannbinoid signaling (figure is property of the authors).



ECS-neuromodulating function. AEA's effects occur in both the central nervous system (CNS) and the peripheral nervous system. There is less information on noladin ether, virodhamine, and *N*-arachidonoyl dopamine and their roles in the regulation of the ECS.[15] It is important to note eCBs are normally at low levels when body homeostasis is balanced. They only begin to be synthesized in large quantities when stimulated. This activation can occur as a response to painful stimuli, bacterial and/or viral infections, stress response, or inflammation.[16]

Although cannabis plant cannabinoids directly target cannabinoid type 1 receptors (CB1Rs) on the presynaptic neuron, AEA and 2-AG are produced, on demand, from lipid precursors found in the postsynaptic neuron and released into the synaptic space (see Figure). When depolarization of the postsynaptic neuron occurs, the naturally influxed calcium is thought to activate the enzyme transacyclase. It is suggested this enzyme catalyzes the first step in the biosynthesis of eCBs by converting phosphatidylethanolamine, a phospholipid, into *N*-acyl-phosphatidlethanolamine. The eCBs then travel retrograde to the CB1 receptors on the presynaptic neuron. The bound eCBs initiate a series of biochemical reactions, which lead to a decrease in inhibitory neurotransmitters (see Figure). This leads to the direct result of increased activity of the postsynaptic neuron. The AEA is then rapidly inactivated by fatty acid amide hydrolase and the 2-AG is broken down by monoacylglycerol lipase.[17]

The primary purpose of the ECS is to provide homeostasis for many metabolic functions, such as neurotransmitter, inflammation, and energy modulation. The ECS is located throughout the entire body and is comprised of specific cannabinoid receptors.

CANNABINOID RECEPTORS

The cannabinoid receptors are G-protein–coupled receptors that are activated by 3 major groups of ligands: endocannabinoids produced by the body; cannabinoids produced from the cannabis plant; and synthetic cannabinoids. The 2 principle subtypes of cannabinoid receptors are CB1Rs and cannabinoid type 2 receptors (CB2Rs).[18]

CB1Rs reside heavily within the CNS and are well known for their neurologic effects when activated. In addition to their presence within the brain, CB1Rs are also found within digestive organs, including the pancreas, liver, small intestines, and large intestines. They have also been found within muscle fibers and adipocyte cells.[16] Although CB1Rs are scattered throughout the body, their role and function within the CNS may hold the most potential.

CB1Rs found within the hippocampus and limbic system play a significant role in the regulation of emotions. When the hippocampus receptors are activated, cannabis users often describe experiencing a blissful euphoria.[16] Clinical data suggests eCBs and CB1Rs may modulate anxiety and depression. Augmentation of eCB signaling has been found to decrease depression and anxiety symptoms, whereas, if the CB1Rs are blocked, increased symptoms will occur.[19] There are also CB1Rs located in the basal ganglia and hypothalamus, which, when stimulated, help regulate appetite and gastric motility. These gastric effects led to the development of dronabinol, a medication used to treat cancer-related anorexia and nausea symptoms.[16]

CB2Rs are found in many areas in the body and, unlike CB1Rs, have almost no psychoactive effects when stimulated. Most are found along the spinal column or in the bone marrow, whereas only a few receptors are found within the brain.[16] Although both CB1Rs and CB2Rs have been found in inflammation leukocyte mediators, CB2Rs are predominant in leukocytes and appear to be the key mediators of cannabinoid regulation of the immune and inflammatory systems. When the CB2Rs are blocked, there is inhibition of splenocyte production and in-vivo cell death. When macrophage CB2Rs are stimulated, they inhibit proliferation and the release of pro-inflammatory factors, and decrease phagocytosis.[20] For example, in the presence of ischemia, cardiomyocytes are subject to inflammation and eventually cell death. In this state, CB2Rs are agonized as part of the body's natural response. When researchers antagonized CB2Rs during hypoxia, both inflammation and macrophage digestion were minimized.[21]

CB1Rs and CB2Rs play a role in modulating pain pathways and helping to provide analgesia. In cancer pain pathway research, cannabinoids act as analgesics in patients with neuropathic pain and are anti-hyperalagesic. They have been shown to decrease painful stimuli from sensory neurons in many animal models. There are also indications cannabinoids may potentiate the analgesic properties of morphine and help prevent drug tolerance.[22]

In neuropathic pain, cannabinoids act on peripheral and central nerve CB1Rs and keratinocyte CB2Rs. The peripheral nociceptor CB1Rs help mediate and block painful stimuli to the sensory neurons. CB2Rs located on the immune cells and keratinocytes stimulate β-endorphin release and decrease pain stimuli through μ-opioid receptors.[22]

CANNABINOIDS

The cannabis plant contains over 400 naturally occurring chemicals and approximately 100 cannabinoids.[23] *Cannabis* is the root word and the scientific plant genus from which all other names derive. There are 3 subspecies of cannabis, including cannabis *sativa*, cannabis *indica*, and cannabis *ruderalis*. Cannabis sativa is the most widely cultivated plant in the US and abroad for both commercial and pharmaceutical use.[24]

The cannabis plant can be broken down into 4 major parts, the stems, seeds, flowers or buds, and leaves. Hemp is obtained from the stems and is used to manufacture clothing, rope, paper, protein supplements, beauty products, and oils. There is no abuse potential or medicinal benefit from hemp or hemp products.[24]

Female flowers produce recreational and medicinal drugs, edible seeds, and essential oils.[24] Dried leaves and flowers are smoked for their euphoric and relaxation-enhancing properties.[24] Cannabidiol (CBD) and THC are the most commonly researched cannabinoids. In 1940, CBD was extracted from the cannabis plant and was found to have no psychotropic effects.[25] In 1964, THC, the primary psychotropic cannabinoid, was discovered and ECS research gained momentum.[14]

CBD targets CB2Rs with an agonizing effect. Because CBD has very little impact on CB1Rs, the psychoactive side effects are minimized. Colorado researchers manipulated cannabis plant genetics to remove THC in an attempt to develop pediatric epilepsy medical cannabis. The cannabis was found to be ineffective. It was discovered the cannabinoids work better together and produce a synergistic effect, leading to improved clinical outcomes.[26]

This finding led to the development of the specialized medical cannabis, Charlotte's Web, which is an example of medical cannabis high in CBD and low in THC (< 0.3%).[26] This unique formula maintains better seizure control with minimal psychoactive side effects. There is limited scientific research on the mechanism of action for seizure control, but it is theorized seizures affect the ECS and produce an increased expression of CB1R protein in the hippocampus. The CB1R agonistic activity inhibits adenyl cyclase, which causes increased potassium efflux and helps stabilize the potassium channels. It also decreases calcium influx in certain calcium channels, which inhibits neuronal hyperexcitability and seizure activity.[27]

Since 2014, GW Pharmaceuticals has been testing another medical cannabis drug, Epidiolex, which has a 99% CBD concentration and < 10% THC content. It is being used to treat Dravet's syndrome, a rare form of epilepsy. In March 2016, the company reported Phase III clinical trials of Epidiolex, which showed some promising results. A nearly 40% decrease in monthly convulsive seizures was observed in study participants.[28] The study was performed on children between 6 and 10 years old who had previously been on multiple anticonvulsants that had failed to adequately control their seizures. The company's goal is to have the first cannabis-based drug approved by the FDA for seizure control in children with epilepsy.[28]

MEDICAL CANNABIS RESEARCH

Besides research on the use of cannabinoids as anticonvulsant agents, many other ECS research studies are being done. Animal model research suggests the ECS may have an important role in the creation, maintenance, and expenditure of energy.[16] Another study linked CB1Rs to the health and maintenance of kidneys.[29] The study revealed that kidney fibrosis, which often occurs in kidney disease and diabetes, was worse in the presence of CB1R activation in

kidney tissues. In mice, when CB1Rs were blocked, there was a significant decrease in kidney fibrosis and renal scarring.[29] Some researchers believe medical conditions, such as weight loss and diabetes, may someday be controlled through CB1R manipulation.[16]

According to a recent clinical review, compelling evidence suggests medical cannabis may show promise in the areas of chronic pain and spasticity associated with multiple sclerosis. Both of these conditions would call for THC as the primary effector.[23]

Recent research has examined the role of CB1Rs and cannabinoids in the treatment of PTSD in the veteran population. There are known elevated numbers of brain CB1Rs associated with PTSD.[30] Currently, a $2,156,000 grant research project, Marijuana for Symptoms of PTSD in US Veterans, is being carried out.[31]

Other research is examining the effects of THC on the treatment of memory loss and Alzheimer's disease. Animal model research has demonstrated THC competitively inhibits the enzyme acetylcholinesterase and decreases amyloid β-peptide aggregation, a key marker of Alzheimer's disease.[32]

Cannabinoids and their receptors are also being studied for their roles in cancer tumor growth. Animal tumor models suggest eCBs may inhibit neoangiogenesis and tumor cell migration. These actions may be receptor-independent based on the type of tumor or tissue cell and the cannabinoid or eCB expressed.[33]

For these and further studies to take place cannabis needs to be legally grown, harvested, and supplied to research institutions here in the US. Over the years, researchers have struggled to gain access to medical cannabis to complete their studies. Medical cannabis has been used for research and clinical trials in animals, but human studies have been restricted by cannabis' Schedule I drug listing under federal law and the stigma cannabis continues to have among the general population. This has severely limited the availability of research-grown cannabis. Since the 1960s, the federal government has only approved the University of Mississippi's School of Pharmacy to grow cannabis. In 2013, the University had about 34 pounds of medical cannabis available for researchers. Currently, there are over 12 acres and an indoor nursery, which together provide about 1,400 pounds of cannabis grown solely for medical research and scientific studies.[26] With the significant increase in cannabis research, the Drug Enforcement Administration was again petitioned to change cannabis from a Schedule I to a Schedule II drug classification. This petition was denied on July 19, 2016, citing cannabis has "no currently accepted medical use" in patient treatment. It was cited that the drug chemistries are not standardized and reproducible and there is lack of scientific evidence and safety studies proving drug efficacy. There was also concern about the potential for abuse of the drugs.[34]

The botanists at the University of Mississippi work closely with pharmaceutical companies and researchers to provide crops to meet their unique and specific needs for the illness they are targeting. The scientists genetically modify the cannabis plant concentrations of THC and CBD.[26] Once the cannabinoid strains are chosen and procured for medical use, drug companies must then decide on the mechanism of delivery and which biochemical form they would like to use.

HEALTH-CARE PROVIDER CONCERNS

If the fast-paced research continues in its present direction, then providers will need to decide how they wish to proceed if asked to prescribe cannabis-based drugs. There are continued numerous concerns regarding cannabis use if laws and regulations remain the same. On a daily basis, providers face certain challenges should they choose to prescribe cannabis for their patients. For example, as long as federal law defines cannabis as a Schedule I drug, then states with legalized cannabis are in direct conflict with federal law. Today, medical cannabis is legal in 25 states and the District of Columbia. Despite having state law approval, providers could be subject to prosecution according to federal laws. However, most federal law enforcement agencies have left the policing of in-state marijuana cases to state authorities, resulting in national prosecutors refraining from pursuing states and their medical providers who are currently prescribing medical cannabis.[35] Yet, this does not alleviate the risk a provider takes when prescribing

medical cannabis because the federal government could decide to take a new position on enforcement at any time.[36]

Nurse practitioners must also be concerned with state-specific regulations. In states where medical cannabis use has been legalized, there continues to be no medical practice standardization across state lines. Each state determines the medical conditions that may or may not be treated. Often these conditions include a handful of serious illnesses, which have failed to respond to conventional treatment modalities. This makes it difficult to provide continuity of care to patients who have moved from one state to another. The provider must also be aware and compliant with the state-mandated medical documentation requirements, which include the frequency of re-evaluation for the medical condition being treated. Many states also differ in who can prescribe cannabis. Some states may only allow certain specialists, such as neurologists and oncologists, to prescribe cannabis medications. Qualified providers then write a recommendation stating the patient would benefit from medical cannabis.[36] However, without FDA guidelines and the standardization of medical cannabis drugs, patients and providers are left to determine proper dosing regimens on their own.

Once patients receive their medication, struggles may persist as far as who can administer it and when it can be taken. The continued conflict between state and federal laws may put nurses and parents who administer medical cannabis at risk for legal prosecution. For example, Colorado is currently reviewing its laws on allowing students with valid prescriptions to use edible medicinal cannabis in public schools. The Colorado law states it is permissible for the school nurse or parent to administer the medicinal cannabis as long as the school district agrees. Currently, no school district has given its approval. In addition, school nurses are in conflict because they are required by federal law to report to authorities any child exposed to illegal drugs, which includes cannabis-derived preparations.[37]

These regulatory inconsistencies between state and federal law leave many nurse practitioners reluctant to offer cannabis-based medicines, even when it is justified and may the best available option for the patient. Providers also fear it puts the patient at risk because human research cannabis trials are limited and there is no standardization of medical cannabis drug regimens.

CONCLUSIONS

As a basic review, it is important for nurse practitioners to understand the functioning of the ECS and its potential to treat many disease processes. Up to now, medical cannabis research, with human subjects, has been limited by federal law and the availability of government-sanctioned research on cannabis. As the interest in cannabis medical research accelerates, and involvement of pharmaceutical companies in developing cannabis-based treatments grows, research needs to be expanded to include human subjects. This comes at a time in American culture when there is a strong movement to discuss and legalize cannabis for both medical and recreational use. Currently, 4 states have legalized cannabis for recreational use and 25 states have laws sanctioning medical applications.[38]

There continues to be both state and national debate regarding changing cannabis from a Schedule I to Schedule II drug. Although states continue to legalize medical cannabis, there is inconsistency in law and policies and direct conflict with federal laws. It is hoped that a resolution will occur in which the federal government will allow and encourage continued quality cannabis medical research to be done to determine the actual efficacy and safety of cannabis in treating human disease processes.

It is important for nurse practitioners who recommend cannabis-based drugs to keep current on the latest legal prescriptive information as the conflict between federal and state laws continues. It is hoped that, as the conflict resolves and quality cannabis research is carried out, the ECS and cannabis-based drugs will offer new treatment options for patients with serious diseases refractory to conventional treatments. JNP

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