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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).