Cannabis and Hearing Care: History, Legalization, and Biochemistry

By Dennis Colucci, AuD, MA, FAAA

Editor's note: This is part one of a two-part series. Part two will be published in the August issue.

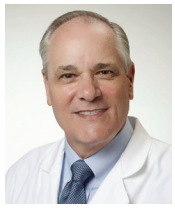
The legalization of medical and recreational cannabis has placed a spotlight on the role of cannabinoids in society and health care. People of all ages are experimenting due to the novelty of the products, anecdotal claims, history of use, online information, and available research. Claims of pain relief, anxiety reduction, improved sleep, neuroprotection, autoimmune support, and skin cures are flooding the marketplace, as well as multiple online reports suggesting that cannabis reduces the symptoms or even cures several diseases.

The need for research in this area has produced a wealth of new information. Currently, nearly 20,000 "cannabis" citations are listed in PubMed, with 6,800 published in the last five years. Hundreds of new cannabis projects are also listed on ResearchGate, ranging from Alzheimer's disease to schizophrenia. Although cannabis is a hot topic, very few studies have investigated the effects of cannabinoids on hearing loss, hyperacusis, tinnitus, or balance disorders, despite the fact that the endocannabinoid system is a part of the central and peripheral nervous systems and directly influences the neurons down to the inner ear.

Notably, there is a lack of long-term, double-blind, large population studies on the full effects of cannabis. Numerous studies from some of the world's most prestigious universities have shown very promising results, but most are not sanctioned by the FDA and only a few products have been approved. Not all studies are conclusive and some had conflicting findings primarily due to lack of control groups in the research design, inadequate sample size and/or, study duration, and poor control over the products used or dosing regimens. This two-part article explores the history, regulations, and biochemistry of cannabis, particularly on its application to hearing care.

FDA VS. STATE REGULATIONS

Due to lack of evidence showing efficacy and safety, the FDA regulation of cannabis and cannabis-derived products will require adherence to new drug policies, including proper procedures for applying for a new drug status and FDA approval.[1] States are looking at cannabis much differently because of widespread and long-term use patterns that show acceptance, reported benefits, and market demands. Some risks accompany the use of these products, especially for pregnant women, infants, children, adolescence, and classes of patients with psychopathologies that need to be addressed.



Dr. Colucci is a clinical and forensic audiologist in private practice in Laguna Hills, CA.

HISTORY OF MARIJUANA AND HEMP

Most ancient civilizations grew cannabis for fiber and seed production, as well as for religious or medicinal use starting in Asia at around 2700 B.C.[2] Cannabis in the United States started when industrial hemp was cultivated to make food and textiles, such as paper, sails, clothing, and rope. In fact, farmers were required to grow hemp as part of the annual crops. In the early 1800s, Sir. William Brooke O'Shaughnessy found that cannabis extracts helped reduce the pain and vomiting associated with cholera. By the late 1800s, U.S. doctors and pharmacists were prescribing cannabis extracts for nausea and stomach problems.[2]

Recreational use of cannabis in the country was not widely available until the Mexican Revolution in 1910 when marijuana (not industrial hemp) cultivated in Mexico was introduced for smoking. In view of the psychoactive properties of the marijuana plant (tetrahydrocannabinoid or THC) and public sentiment, cannabis was criminalized by the U.S. government in 1937.

In was not until 1964 that researchers isolated and described THC. Later, the biochemical receptors responsible for the psychoactive effects of THC were identified on the surface of neurons, followed by the establishment of the existence of the endocannabinoid system (ECS) within the central and peripheral nervous systems.

About the same time as the ECS was discovered, drug use became more common but not widely accepted. Eventually, former U.S. President Richard Nixon made drug abuse public enemy number one. In 1973, he signed the Drug Enforcement Act (DEA) as part of his War on Drugs.[3] This made all cannabis products (hemp and marijuana) illegal, essentially curtailing research into the potential benefits. It was not until the 1990s that the benefits of cannabis started to be explored.

In 1996, the Compassionate Use Act was passed in California for patients with chronic illness, changing the status of cannabis. In 2018, the Farm Bill was passed allowing hemp cultivation and extraction of cannabidiol (CBD) under specific regulation. Hemp was rescheduled from a Schedule I to a Schedule V drug, a category of drugs described as having a low affinity for addiction (similar designation as cough medicine with codeine).[4,5] Medicinal use and further exploration of hemp and marijuana products have led to an avalanche of

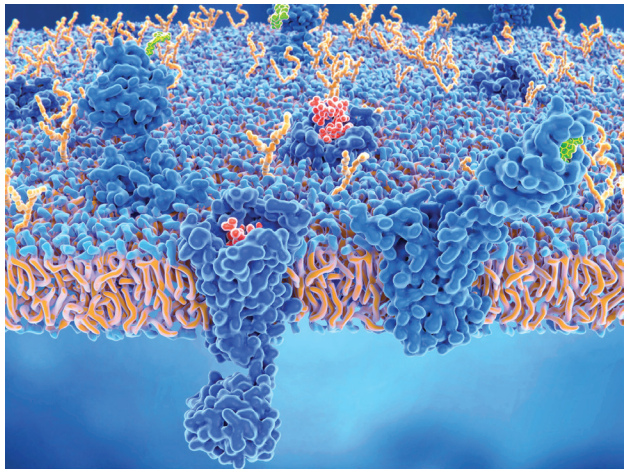


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Figure 1. Brain Cell Receptors with Ligands Embedded. Activation by injury of two brain cell receptors: delta-opioid and cannabinoid receptor. Ligands (pink and green molecules) bind to the receptor, changing the shape and delivering biochemical instructions inside the cell.

interest and legalization in some form in 33 U.S. states.[6] It appears the rigors of ownership has not dissuaded entrepreneurs from developing an entire industry scheduled to be worth $146.4 billion by 2025.[7]

Audiologists encounter patients who may ask about cannabis for hearing loss, tinnitus, hyperacusis, or balance problems. At present, there is a lack of research and, therefore, insufficient evidence to qualify the efficacy of cannabinoids for these conditions. In the future, cannabis research targeting the auditory nervous system may prove to be a new direction in auditory neuroscience. Nonetheless, knowing how the endocannabinoid system works and the associated risks can help audiologists understand some of the benefit claims of cannabis as well as screen for patients who may be misusing or abusing the drug.[8]

BIOCHEMISTRY OF CANNABINOIDS

Specific biochemical reactions are responsible for directly and indirectly altering, modulating, inhibiting, activating, or influencing important functions such as pain regulation, mood, appetite, addiction, anxiety, inflammation, and neuroprotection. Cells communicate using a system of receptors and signaling or messenger molecules (ligands). Among the nearly 1,000 types of receptors, some have an affinity for cannabinoid ligands whether produced in the body (endocannabinoids) or introduced as THC, CBD, or other phytocannabinoids through ingestion, smoking, or skin application.

Receptors are divided into two basic groups: those that interface at the cell surface and those that interface within the cell. The electron microscopy illustration in Figure 1 shows two activated receptors embedded in the nerve cell membrane with ligand binding on the receptor surface in a lock and key scenario. This demonstrates how the receptor can alter its shape and mobility when activated.

Receptors and ligands are paired to act as an agonist or produce excitability or act as an antagonist or inverse-agonist to regulate or inhibit receptor activities. An agonist could activate a receptor and turn on a gene expression such as neurite outgrowth in neurogenesis. An antagonist would suppress an action, such as the binding of a ligand to a receptor, that creates no action but blocks the agonist. For example, this action takes place when naloxone (antagonist) is used to bind with opioid receptors to block the heroin (agonist) ligand in an overdose.[9] Within a cell, a complex pathway begins with a single crucial event: the binding of a signaling molecule to its receiving receptor, which is designed to restore homeostasis. Signaling molecules include hormones such as estrogen, scents such as lavender, or an enzymes, such as those released during a tissue damage signaling injury.

HUMAN ENDOCANNABINOID SYSTEM

Cannabinoids regulate a variety of functions in both plants and animals. In plants, cannabinoids are found inside plant resins known to deter both insects and herbivores. In humans, endocannabinoids regulate physiological and psychological responses to internal and external forces to maintain homeostasis, coupling both mind and body. Endocannabinoids are introduced on-demand when any system is out of balance. For example, nerve cell firing can be manipulated by introducing of cannabinoid molecules that bind to the Cannabinoid 1 (CB1) receptor through a feedback loop. This occurs when there is injury and over-activity. Acccording to Martin A. Lee, co-founder and director of Project CBD:

> "Cannabinoid receptors function as subtle sensing devices, tiny vibrating scanners perpetually primed to pick up biochemical cues that flow through fluids surrounding each cell. The mechanism, known as presynaptic inhibition, occurs when a postsynaptic neuron releases endocannabinoids in retrograde transmission, which then bind to cannabinoid receptors on the presynaptic terminal."[10]

In Figure 2, the release of endocannabinoids (open polygons) from the postsynaptic terminal are transported via fluids to the presynaptic cell receptor (CB1), setting into motion cell instructions inhibiting neurotransmitter production. Because the

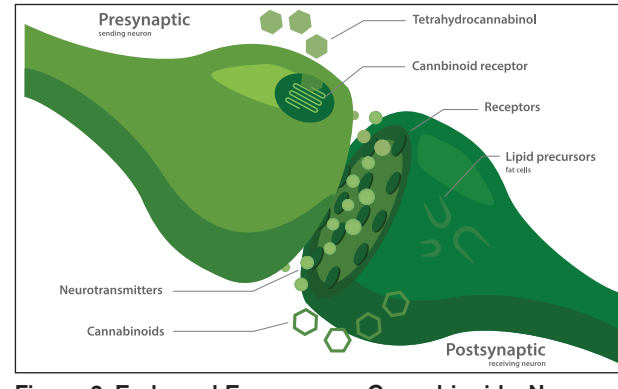

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Figure 2. Endo and Exogeneous Cannabinoids. Neuron firing from presynaptic cell to postsynaptic cell with two methods of cannabinoid delivery to the presynaptic CB1 receptor. Endocannabinoids: open polygons; THC: solid green polygons.

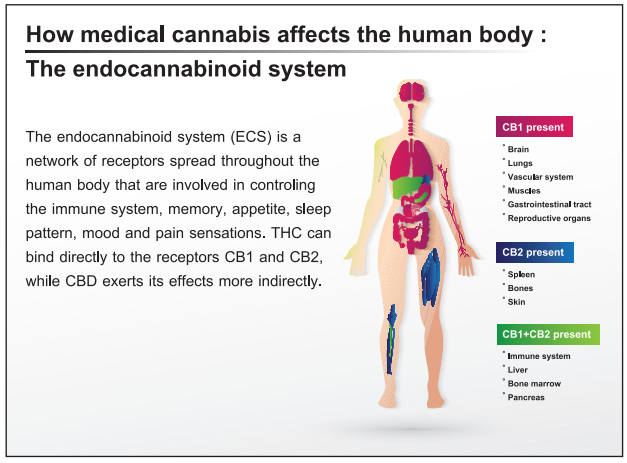

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Figure 3. The Endocannabinoid System. Suggested distribution of the endocannabinoid system within the central nervous system and peripheral organs.

cannabinoids are created in the postsynaptic cell, the action is retrograde. When THC (solid green polygons) is added to the blood stream, the CB1 receptor in the presynaptic neuron receives the molecule directly. Both endogenous and exogenous cannabinoids create changes in cellular function, including gene expression, setting off intracellular signaling molecules and turning down the release of excessive neurotransmitters causing excitotoxicity and cell death.[10] Unlike CB1 receptors, CB2 receptors are outside of the CNS and can instruct the cell to release inflammatory mediators to reduce pain or control potential destructive actions by the immune system.[11] These and other cannabinoid G-Protein receptors are coupled to important biochemical functions that protect and build cells.

The primary cannabinoid receptors for cannabigerol (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinol (CBN), and delta-9-tetrahydrocannabinol (THC) are Cannabinoid Receptors 1 (CB1) and 2 (CB2).[12] However, a number of other receptors and targets are activated by cannabinoids that have direct and indirect influence on cellular activity.[2]

CB1 receptors are primarily in the central nervous system (Fig. 3), but also in the lungs, liver, gastrointestinal tract, and kidneys. In the brain, CB1 receptors are highly expressed in the hypothalamic areas that are involved in feeding behavior. Cannabinoid 2 receptors are primarily found on immune cells effecting neuroinflammation, atherosclerosis, and bone remodeling.[11]

In view of the ability of ECS to engage disease and interact within the CNS and other organs, the use of cannabis in healthcare is a trend that is just starting to take shape. The second part of this article in the August issue will discuss how cannabis may be used to treat various diseases, hearing and tinnitus cannabis research, and consumption patterns and issues.

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