Mixed Signals: Cannabinoid System Offers New Therapeutic Possibilities As Well As Challenges

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For an instance of good coming from the seemingly evil, consider the cannabis plant. Although treasured by many for its medicinal properties, this herb is officially reviled for being the source of hashish and marijuana, two popular drugs of abuse. Nevertheless, it is the study of this plant that has led to the discovery of the cannabinoid system, a signaling mechanism present in many cell and tissue types in the body, affecting a vast range of processes from brain development and cardiovascular function to immune response, bone growth, pain, hunger, mood, movement, and memory. Recent advances in understanding this system are now translating into novel drugs and therapies for pain, cancer, stroke, and many other disorders. "The dopaminergic and serotonergic systems were discovered in the '30s, but it has taken us much longer to discover this system, which is perhaps just as important," says Israeli biochemist Raphael Mechoulam, Ph.D., widely considered the founder of modern cannabinoid research. "It offers a treasure trove of new medical possibilities waiting to be unearthed."

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Opium and coca yielded their chemical secrets in the 19th and early 20th century, but it wasn't until the 1960s that Mechoulam's team at the Weizmann Institute in Rehovot (with Yehiel Gaoni, Ph.D.) and later at the Hebrew University in Jerusalem turned the spotlight on cannabis. A big challenge was obtaining any form of this illegal plant for research. To tackle this issue, Mechoulam sought the help of the Tel Aviv police, who obligingly handed over to him 5 kg of top-quality smuggled Lebanese hashish. Later, it turned out that Mechoulam had broken several drug laws in procuring an illegal substance without approval from Israel's Ministry of Health. In another country, such an act might have ended in imprisonment and disgrace; however, this story has a happy ending. Thanks to his status as a respected researcher, all Mechoulam had to do was apologize, and, since then, for the past 40 years, the Ministry has been providing him all the hashish he needs for his research. Thus it was that in the mid 1960s, Mechoulam's lab isolated a "toxic red oil" as the main psychoactive ingredient in cannabis and identified it as Δ^1-tetrahydrocannabinol (or Δ^1-THC, later renamed Δ^9-THC). Several other cannabis constituents, which Mechoulam termed "cannabinoids," were soon identified. "The timing was good," recalls Mechoulam. "The 'flower generation' was getting interested in cannabis for entirely different reasons, and the US government wanted us to find out if it did anything nasty."

It would take scientists another 20–30 years to start figuring out how these newly identified compounds act in the body. "Initially, we thought they acted through membranes, just like anesthetics or solvents," says University of Aberdeen researcher Roger Pertwee, Ph.D., another cannabinoid pioneer. This belief was overturned in 1988, when researchers at the St. Louis University Medical School in Missouri found evidence of a cannabinoid receptor in the brain. Subsequently, a team at the National Institutes of Mental Health in Maryland cloned a G-coupled protein receptor in brain cells that responded to cannabinoids, and termed it CB1. Later, another cannabinoid receptor, CB2, showed up in immune cells. These startling findings suggested that mammals are in fact hard-wired to respond to cannabinoids. Further, it turned out that the cannabis plant does not have a monopoly on this type of compound; mammalian cells make them, too. In 1992, Mechoulam's group isolated a substance from brain cells that bound to cannabinoid receptors; subsequently, Pertwee's group in Aberdeen found that it acted just like THC, the psychoactive compound in cannabis. This substance was named anandamide, from "ananda," Sanskrit for joy or bliss. (Mechoulam jokes that he first looked for a Hebrew word meaning "joy" but found mostly synonyms for "sorrow.") The researchers went on to discover 2-arachidonoyl glycerol (2-AG), another important "endo"-cannabinoid in the body.

It was now obvious that the cannabinoid system has an important biological role. "Everyone realized there's a reason why we have those receptors, not just the off chance of one of our predecessors picking up some cannabis and smoking it," says Aron Lichtman, Ph.D., of the Virginia Commonwealth University in Richmond. Subsequent studies have shown that the cannabinoid system is a short-range, lipid-based signaling mechanism that helps calm nerve and immune cells and maintains homeostasis. "It plays a general physiological role in brain activity, reproduction, metabolism, cell proliferation, stem cell differentiation, and many, many other functions," says Vincenzo Di Marzo, Ph.D., a researcher at Italy's National Research Council. In the early stages of many disorders, especially neurodegenerative ones such as stroke, Alzheimer's, or multiple sclerosis (MS), the cannabinoid system seems to play a protective role. Anandamide and 2-AG levels shoot up, activating CB1 and CB2 receptors in the affected areas; this, in turn, modulates neural and immune activity to reduce cell deaths, improve blood circulation, and reduce inflammation. In

later stages of the disease, however, the cannabinoid system may itself go astray and make things worse. "It has a dual nature, just like the immune system," says Di Marzo.

Exploiting the cannabinoid system for new therapies has proved challenging. First, while CB1 activation can help in many disorders—such as nausea and vomiting caused by anticancer agents, cancer pain, and lack of appetite—it is also responsible for cannabis' psychoactive effects; i.e., its "high." However much some patients may enjoy it, cannabinoid-induced euphoria is frowned upon by the medical community. Second, since cannabinoid receptors have such diverse roles, targeting them directly can cause unwanted effects. Administering THC, which activates CB1, can cause dizziness, palpitations, and other problems. Conversely, the antiobesity drug rimonabant, which works by *blocking* CB1, seems to increase the risk of anxiety, depression, and suicide by negating the receptor's protective role. Finally, the cannabinoid system's dual nature—either ameliorating or aggravating a disorder—means that targeting it could have paradoxical effects. "For instance, at a low dose, a cannabinoid will do X, and at a high dose, it will do the opposite of X," says Beat Lutz, Ph.D., of the University Medical Center Mainz in Germany. "Depending on the dose, it can increase or decrease appetite, promote or reduce anxiety, induce or prevent convulsions."

Second-generation strategies may help avoid some of the problems caused by external CB1 agonists such as THC. Compounds that reduce metabolic degradation of endocannabinoids or modulate cannabinoid activation via allosteric sites may give better results. "Instead of giving THC and flooding the entire system, we get a more selective effect," says Pertwee, whose team recently discovered allosteric sites on the CB1 receptor. Psychoactive effects can be minimized by keeping the drug outside the brain; for instance, by delivering it as a local injection or skin patch. Alternatively, one could target CB2 alone, which may help with myocardial or hepatic ischemia/reperfusion injury, chronic inflammatory pain, gastrointestinal inflammation, and liver disorders. Nonpsychoactive cannabis components such as cannabidiol (CBD), a powerful antioxidant that doesn't bind to either CB1 or CB2, are also relatively safe. Cannabinoids also work well as low-dose add-ons to other therapies such as opiate painkillers and cancer drugs. For instance, although THC and CBD by themselves have only weak antitumor effects, they dramatically boost the efficacy of classic cancer drugs such as temozolomide, says Manuel Guzmán, Ph.D., of the Complutense University in Spain. "Cannabinoids are extremely good synergizers," he says.

Combining THC with CBD seems to give better results than THC alone. This principle underlies Sativex, one of the most commercially promising medicines to emerge from cannabinoid research. Made by UK-based GW Pharmaceuticals and delivered as an oro-mucosal spray, the formulation contains equal parts of the two compounds along with other cannabis components. This drug is now approved in the UK, New Zealand, and Spain (with 6 other EU countries to follow) as add-on treatment for symptom improvement in patients with spasticity in MS and in Canada for the relief of neuropathic pain in MS and as an adjunctive analgesic treatment for cancer patients. "Clinical trial data demonstrate that Sativex is able to positively affect a wide variety of clinical symptoms," says the company's senior medical advisor Ethan Russo, MD. "And it is able to do this without an attendant 'high.'"

Medical marijuana advocates are not impressed. "From the patient's point of view, Sativex is an inferior product," says Rick Doblin, Ph.D., of the Multidisciplinary Association for Psychedelic Studies in Santa Cruz, California. Doblin argues that swallowing or spraying isolated cannabinoids—unlike smoking cannabis—doesn't provide all the medicinal benefits of the whole plant, nor does it act as quickly or make it as easy for the patient to self-adjust the dose for optimal effect. UCSF cancer specialist Donald Abrams, M.D., agrees. "In cannabis, there are about 70 other cannabinoids, terpenoids, and flavonoids that help synergize, boost, and regulate the effect of THC," he says. "Using just one or two active ingredients from the plant is not ideal." In a 2007 study, Abrams found that smoked cannabis relieves HIV-associated chronic neuropathic pain. The drug has also shown some benefits for anorexia, nausea, and vomiting in patients undergoing cancer chemotherapy. "As a cancer doctor, here I have this one drug that I can recommend my patients for all their symptoms," says Abrams. "Instead of writing them five prescriptions for expensive drugs, I write them just one that they can actually grow themselves."

Some researchers disagree. "When someone is in pain, we don't give them opium to smoke—instead, we take its active ingredient and give it through the best route of administration," says Lichtman, who has developed a specialized inhaler for delivering THC in metered doses. Popular support for medical marijuana remains high, however. A poll conducted by ABC News and The Washington Post last year showed that 8 out of 10 Americans supported legalizing marijuana for medical use, and nearly half want the drug to be made legal. Federal agencies remain strongly opposed to medical marijuana, but several US states have passed laws allowing its limited use. Cannabis' legal fate is hard to predict. What is undeniable is that this plant has been the key to one of the biggest neurochemical discoveries of recent times. "The endocannabinoid system plays a role in so many tissues and organs and is involved in such a variety of disorders" says Di Marzo. "Irrespective of whether any useful therapies emerge from it, it's one of most important signaling systems ever discovered."

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