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Endocannabinoids in the retina: From marijuana to neuroprotection

Stephen Yazulla*

Department of Neurobiology and Behavior, Stony Brook University, Stony Brook, NY 11794-5230, United States

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A B S T R A C T

The active component of the marijuana plant *Cannabis sativa*, Δ^9-tetrahydrocannabinol (THC), produces numerous beneficial effects, including analgesia, appetite stimulation and nausea reduction, in addition to its psychotropic effects. THC mimics the action of endogenous fatty acid derivatives, referred to as endocannabinoids. The effects of THC and the endocannabinoids are mediated largely by metabotropic receptors that are distributed throughout the nervous and peripheral organ systems. There is great interest in endocannabinoids for their role in neuroplasticity as well as for therapeutic use in numerous conditions, including pain, stroke, cancer, obesity, osteoporosis, fertility, neurodegenerative diseases, multiple sclerosis, glaucoma and inflammatory diseases, among others. However, there has been relatively far less research on this topic in the eye and retina compared with the brain and other organ systems. The purpose of this review is to introduce the "cannabinergic" field to the retinal community. All of the fundamental works on cannabinoids have been performed in non-retinal preparations, necessitating extensive dependence on this literature for background. Happily, the retinal cannabinoid system has much in common with other regions of the central nervous system. For example, there is general agreement that cannabinoids suppress dopamine release and presynaptically reduce transmitter release from cones and bipolar cells. How these effects relate to light and dark adaptations, receptive field formation, temporal properties of ganglion cells or visual perception are unknown. The presence of multiple endocannabinoids, degradative enzymes with their bioactive metabolites, and receptors provides a broad spectrum of opportunities for basic research and to identify targets for therapeutic application to retinal diseases.

Contents

* Tel.: +1 631 632 9877; fax: +1 631 632 6661.
E-mail address: stephen.yazulla@stonybrook.edu

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1. Introduction

Marijuana, pot, hashish, reefer, clip, roach, bong and munchies are words that need no introduction or definition for most people. Depending on one's age, they may conjure up images of Vietnam-era hippies, coffee houses, the New Orleans jazz scene, student dorm life, "Harold and Kumar", and so on. For many others, these words evoke images of a gateway drug and serious drug addition. Marijuana has been cultivated for thousands of years for manufacturing and recreational use. Its negative image as a dangerous drug of abuse has hampered research on the mechanisms by which marijuana exerts its physiological and psychotropic effects. A certain "giggle" factor accompanies the introduction to a general audience of any speaker who studies the biology or pharmacology of marijuana. Chuckles devolve into laughter when I mention that, on two occasions, my studies were carried out in the laboratory of Maarten Kamermans, in Amsterdam. Such a reaction has not and does not occur with a researcher who studies the opiates or dopamine transporters. No one glibly questions as to whether samples of morphine or heroin were injected or cocaine snorted during experiments on pain or drug addition. The fact is that the effects of marijuana can be detected in virtually every organ system in the body. We now know that the active component of marijuana, Δ^9-tetrahydrocannabinol (THC), acts on specific receptors that are distributed throughout the body. These receptors, of course, respond to endogenous ligands. Given the global distribution of this system, there has been extensive research effort into its fundamental properties, and interest from pharmaceutical companies for potential therapeutic use of drugs that modulate these receptors. Progress in this field has exploded in the last 10 years. Understanding how marijuana exerts its numerous physiological and psychological effects has advanced greatly since the identification of an endogenous system that is activated by, and mimics many of the effects of marijuana. There is a huge literature, growing by the day, investigating this endogenous system in neural and non-neural tissues. This review will focus on the retina and include, to some extent, other ocular tissues. All of the fundamental work on the characterization and function of the components of this endogenous system has been done in non-retinal preparations. As a result, the background for interpretation of the retinal data must necessarily come from these other studies. Numerous excellent reviews have appeared in the last several years that treat the history, biochemistry, pharmacology and therapeutic potential of this system (for example, Piomelli, 2003; Lambert and Fowler, 2005; Hohmann and Suplita, 2006; Pertwee, 2006; Kogan and Mechoulam, 2007). A comprehensive treatment of all these topics was published by CRC press (Onaivi et al., 2006). In addition, for an entertaining and informative introduction to this topic, I recommend the highly readable book "The Science of Marijuana" by Iversen (2000). Also, two older reviews that appeared in Science (Weil et al., 1968; Hollister, 1971) are of particular interest because they were written during the height of the Vietnam War and long before the discovery of the endocannabinoid system. They point out the difficulty of obtaining and interpreting psychophysical data on the effects of smoking marijuana, due largely to problems in adequate controls for concealing the placebo and effects of the drug on attention.

The marijuana plant *Cannabis sativa* has been cultivated as hemp for thousands of years in the Middle East, India and Europe for food and to make rope and fabric. Hemp seeds contain an excellent balance of amino acids, omega-3 and omega-6 fatty acids. With the increased awareness of the importance of dietary omega-3 fatty acids for the control of cholesterol and overall cardiac health benefits, food products containing hemp seed are becoming more available; these seeds do not contain any appreciable THC. "Canvas" is derived from "cannabis", appearing in English usage in the 13th century. Jamestown, the first settlement in the United States, had a law in 1619 requiring farmers to grow hemp. By 1850 there were over 8000 *Cannabis* plantations in the United States. In antiquity, *Cannabis* also was used therapeutically to relieve pain, reduce inflammation and as a sedative. Its psychotropic effects, though known, were less important in ancient China, Rome and Greece but not so in 15th century Iraq and Egypt. Napoleon returned to France from Egypt with *Cannabis* seeds in 1799, and therein began its widespread use in Europe as an intoxicant. In the latter half of the 19th century, *Cannabis* was freely available and used extensively to treat migraine headaches and ulcers. The word "marijuana" or "marihuana" came from ballads sung by Pancho Villa and his men in the 1890s, giving *Cannabis* its current popular name and English translation "MaryJane". By the 1930s, the therapeutic use of marijuana was being replaced by more effective drugs to relieve pain and nausea. Also, its long reputation as a drug that corrupted morals and stilted personal initiative grew. For historical context, recall that the U.S. was still in the Prohibition era (1919–1933) and the effects of the Stock Market crash of 1929 were yet to be fully felt. Pulp fiction of the 1930s and the hilariously inept propaganda film "Reefer Madness" of 1936 portrayed users of marijuana as hopelessly depraved and driven to homicidal madness. The U.S. Congress (1937) passed the Marijuana Tax Act that made it so expensive and difficult to get marijuana that it was effectively banned. The coup de grace came in 1970 when marijuana was classified as a Class 1 drug, on a par with heroin, LSD and methamphetamine, as lacking any medicinal value with highest addictive properties. The controversy over the biomedical use of smoking marijuana to relieve pain, nausea and appetite stimulation continues today with court battles between State and Federal Laws.

2. Marijuana and the endocannabinoids

The active component of the marijuana plant *C. sativa* was first identified as Δ^9-tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1964; Mechoulam and Gaoni, 1967). THC, also known as dronabinol,