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Editor

Cannabinoids and the Brain

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Editorial

Did you know that if you take aspirin or some other type of painkillers, you simply upregulate your endocannabinoid system against your endovanilloid system? If it happens to be a completely new piece of information to you, then this book is for you! Seriously speaking, the first part of the book you are holding in your hands is an exhaustive source of scientific reviews on the molecular biology, pharmacology, anatomy, and physiology of the endocannabinoid and related lipid mediator systems. The second part of the book, however, covers the involvement of these signaling systems in metabolic, neurological, and psychiatric disorders, and gives an overview on clinical trials and on recent advances in cannabinoid-based medicine. Therefore, the target audience for this book are (a) physicians, especially endocrinologists, neurologists, psychiatrists, and neuroscientists who want to update their knowledge about metabolism, basic brain physiology, molecular biology, and pathology and about novel therapeutic opportunities; (b) graduate and undergraduate students who also wish to broaden their knowledge about endocrinology, neuroscience, neurology, and psychiatry, or may need orientation to determine their future scientific goals; (c) politicians and health care employers who hesitate whether marijuana or cannabinoid-based medications should be legalized; and last but not least, (d) journalists who can help the scientists to convey their message to a larger audience. All the authors of the present volume are world's leading neuroscientists and physicians, who are also regarded to be pioneers in the cannabinoid research area. Here I would like to gratefully thank them for all their altruistic contributions, and for sparing their precious time on this work.

The very first idea of writing this book occurred to me in 2005 when I had an interesting conversation with a neurologist professor from the USA, after his exciting lecture about the impact of adenosine receptors on epilepsy. I asked him whether he would be interested in the role of cannabinoid receptors also besides adenosine receptors. I noticed a faint note of indignation in his answer when he said: "No, I do not treat drug addicts, but epilepsy patients." He was apparently unaware of those facts which are extensively reviewed in this book, especially the CB_1 receptor that is believed to have the highest density among metabotropic receptors in the nervous tissue, and, together with its endogenous agonists, they represent a unique signaling system, which seems to be a goldmine of therapeutic targets against many neuropsychiatric disorders. The reaction of the professor may be

excusable, since the body's own cannabinoid system as well as the body's opioid system or the nicotinic receptors were discovered in the quest to find the specific targets for drugs of abuse, such as marijuana, morphine, heroin, and tobacco's nicotine. Importantly, the last 16 years of constant research has discovered a much broader role for endocannabinoids than for the opioid or nicotinic acetylcholine signaling. Nevertheless, this role does not seem to receive sufficient recognition by those who otherwise should find it important in their professional activity. At present, I have the growing belief that the endocannabinoid system and related systems of lipid mediators, such as eicosanoids and endovanilloids, constitute a major modulator/messenger supersystem, which is at least as important as the monoaminergic, purinergic, and cholinergic systems. Furthermore, these modulator systems work hand in hand, and thus they cannot be viewed as solitary therapeutic targets. The borders between classical pharmacological areas are likely to be forgotten. Therefore we, the authors, consider ourselves extremely fortunate to make this book happen and to disseminate challenging up-to-date reviews on the role of cannabinoids in the brain.

Now I would like to take the opportunity of addressing a few challenging ideas to the cannabinoid research area. There are some minor and major problems cannabinoid researchers normally encounter, which could be easily alleviated. For instance, it seems to be ironic and even ridiculous to some extent that permission is required for using certain cannabinoid research tools, such as Δ^9-THC and its potent derivative HU-210. More importantly, their experimental usage is further hindered by other rules in certain places. I will never forget the incident when the police appeared in my lab, inquiring how I had used Δ^9-THC and for what purpose. Absurdly enough, at that point of time, I still had not received the shipment of the compound from the pharmaceutical company due to permission issues. It is no more than pure hypocrisy, knowing that there are several other even more selective, potent, and efficacious cannabinoid ligands available, causing even more expressed effects than Δ^9-THC in animals. It is understandable that Δ^9-THC requires permission, it being the major constituent of marijuana. Nonetheless, the price of Δ^9-THC and HU-210 appears to be so high, especially considering the remarkably little buyable amounts, that selling these products for research purposes without permission would not represent a gross criminal risk.

Normalization of chemical names would also be desirable. For instance, researchers may face a considerable challenge to find all the articles of the popular nonselective potent cannabinoid agonist WIN55212-2 in searchable databases, since the ligand is variously termed WIN-55,212-2, WIN 55212-2, WIN 55,212-2, WIN-2 or R-(+)-WIN55212, R-WIN55212, R-WIN 55212, R-WIN 55,212, etc. with all possible permutations. The same is true for other compounds, such as the popular CB_1 receptor antagonist AM251. It is frequently used as AM 251, and a search for the terms AM and 251 in a database may result in a lot of additional unrelated articles. Thus, combining two or more ligands in one search is definitely a vain idea. The problem could be solved with only a slight common effort to standardize chemical names. It is also unfortunate that several old-fashioned journals still force the authors to use the long cumbersome chemical names of cannabinoid

compounds even in the abstract of the article, for example, R(+)-[2,3-Dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolo[1,2,3-de]-1,4-benzoxazinyl]-(1-naphthalenyl) methanone mesylate or [N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-carboxamidehydrochloride]. Deciphering this long chemical name or similar ones would represent an enormous challenge to almost every researcher in the field. Even a chemist would spend several hours to realize that these terms mean WIN55212-2 and SR141716A (Rimonabant, Acomplia™). Apparently, the reason for these unnecessary complications is again the limited knowledge about the cannabinoid field (including the lack of information about the most common chemical tools used in cannabinoid pharmacology) in the general scientific community.

My other growing concern arises from the rapidly increasing number of publications (in 2006 and 2007, it was ~100 articles per month; see Fig. 2 in Chap. 1). Thus it seems difficult to keep up to date with the physiology, pharmacology, molecular biology, and pathology of cannabinoids. Recently, it has become easier to publish "unorthodox" research findings, as most of them proved to be valid, since they resulted from complex interactions between the endocannabinoid system and other signaling systems, and between new ligands, new receptors, and other targets. Although many laboratories are making an enormous effort to rule out the underlying mechanisms of these unorthodox findings, concomitantly, the same unusual pharmacological or physiological actions are recurrently rediscovered and reported occasionally by new research groups. To be more explicit, I would mention here the pharmacology of cholinergic, purinergic, GABAergic, or glutamatergic signaling, in which commonly accepted ligands, such as methyllicaconitine, nicotine, ATP, PPADS, CGS21680, CNQX, AP5, bicuculline, etc. with well-established maximal selective nanomolar or micromolar concentrations can be found. These concentrations are never to be exceeded because it is common knowledge that it would question the reliability of conclusions about the observations. In contrast, ligands of low nanomolar or picomolar affinity are often used in the micromolar range in the cannabinoid research field. There are research reports in which SR141716A and WIN55212-2 were used even at 10–100 μM in vitro and the authors claimed that the observed effects were CB_1 receptor mediated. Chapter 9 in this book thus tries to establish a bottom line for the pharmacology of cannabinoid research, listing common "side effects" and unorthodox mechanisms that can be easily misinterpreted as actions at novel receptors.

Another chapter also tackles the question of inverse agonism. Several antagonists of the cannabinoid receptors are known as inverse agonists (such as SR141716A and AM251; see Chap. 7). Nonetheless, recent data shed new light on this question by indicating an apparent lack of inverse agonism in the absence of endocannabinoids (which are otherwise generally present in most experimental preparations); in other words, these antagonists would not cause an effect opposite to the agonists. This is topped by reports on novel CB_1 receptor-selective neutral/silent antagonists. Thus, it might be worth solving this problem; otherwise one may eventually conclude that a neutral antagonist inhibits the binding of only the synthetic agonists at the CB_1 receptor, but not that of the endogenous agonists.

As a concluding remark, I would like to express again my gratitude to the contributing authors and to Joseph Burns from Springer-Verlag for recognizing the compelling need for the present volume and for giving me the opportunity to make this work happen. We (the authors) apologize for not discussing many significant publications in the present volume; it is entirely unintentional and completely due to space limitations. Nevertheless, the book the reader may hold right now in his hands has made a serious attempt to give a comprehensive overview of all the essential literature concerning the endocannabinoid and related systems in the nervous tissue.

Coimbra, June 2007 Attila Köfalvi

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Part I
Molecular Biology, Pharmacology, Anatomy, and Physiology of the Endocannabinoid and Related Lipidergic Signaling Systems in the Brain

Chapter 1
An Historical Introduction to the Endocannabinoid and Endovanilloid Systems

Istvan Nagy, John P.M. White, Cleoper C. Paule, and Attila Köfalvi

Abstract Cannabis and chili pepper have been used for medical, gastronomical and recreational purposes for at least 8,000 years. Nevertheless, it was discovered only eight years ago that the cloned neuronal targets of their active principles, delta^9-tetrahydrocannabinol (Δ^9-THC) and capsaicin are related to each other, as they all can be activated by some arachidonic acid-derivative endogenous ligands. Here, we will summarize the history of man's relationship with cannabis and capsaicin, and we will detail the most important scientific keystones in the evolution of cannabinoid and vanilloid research, featuring the list of cannabinoid and capsaicin effects, the discovery of endogenous ligands and the cloning of receptors, namely, the CB_1 and the CB_2 cannabinoid receptor as well as the $TRPV_1$ vanilloid receptor, where the endogenous and the plant-derived substances act upon. This chapter serves, therefore, as an introduction to *Cannabinoids and the Brain*, the book which will extensively describe the neuronal and, to some extent, the peripheral cannabinoid and vanilloid systems in molecular, pharmacological, physiological, pathological and neuropsychiatric viewpoints.

Introduction

The History of Cannabis

The Asiatic plant *cannabis* or *hemp* (*Cannabis sativa/indica = useful/Indian Cannabis*) has been used for more than 8,000 years due to its medical and psychotropic effects. It is most likely that the original Sumerian word "kunibu" developed into the forms "kan(n)ab(is)" and "hanaba", then "hennep" and finally, hemp. The plant cannabis belongs to the family *Cannabaceae* and the order *Urticales*. Its leaves and flowering tops are used to produce marijuana and hashish (also known as charas, bhang, ganja, dagga, grass, pot). Seeds of cannabis were found in 8,000 years old Chinese food remains. Interestingly, the first written note about the medical use of cannabis was also discovered in China, which dates back to 2727 B.C. The Atharvaveda, the sacred text of Hinduism, also mentions the use of cannabis for medical purposes in India between 1200 and 800 B.C. The psychotropic properties

A. Köfalvi (ed.), *Cannabinoids and the Brain.*

of cannabis were first described in a Chinese medical book around 100 B.C. It is believed that *Cannabis sativa* was first introduced in Europe by the Scythians, as recorded by Herodotus in 430 B.C. In 100 A.D., Dioskurides inferred that cannabis was a Roman medical plant, whereas Galen highlighted its psychotropic action in 170 A.D. The medieval Europe was first informed about the popularity of cannabis in Asia by Marco Polo. Later cannabis was used mainly as a medicine in England. Even Queen Victoria was prescribed cannabis by her doctor in 1890. Consequently, cannabis was declared harmless and legalized in 1901. However, in 1925, the Geneva Convention included cannabis and hashish in the list of dangerous and illicit drugs. In the USA, cannabis was also used for medical purposes from 1840, but the Mexican Revolution in 1910 changed the general opinion about cannabis. It became a symbol of terrible sins. Until 1931, 29 states prohibited the use of marijuana, and from 1937, the Federal Law proclaimed marijuana as an illicit drug. Still, it regained its popularity when both president Kennedy and president Johnson suggested that cannabis should be legalized. Presumably, due to these propositions, 200–250 million cannabis users were reported by the UN worldwide till 1970. In the last 40 years, the debate on the safety and legal status of cannabis-based medical treatments is becoming increasingly intense at both political and scientific levels (see for example Wall et al., 2001; Hayry, 2004; Comeau, 2006). Although clinical trials with cannabinoid ligands are allowed in many countries, the general use of marijuana to treat the pain and eating problems of cancer patients as well as to reduce intraocular pressure in glaucoma is still not legalized. The main issue is that the concentration of beneficial constituents in the smoke of cannabis cannot be controlled, and furthermore, conservative politics can hardly agree with the medical use of an illicit drug. Nonetheless, we should mention that morphine, codeine, lidocaine and procaine, which are all illicit drug-derivatives, are commonly used in medicine. Moreover, nicotine is regarded as one of the most addictive drugs, yet its use is perfectly legal. All the same, we have to acknowledge certain concerns, as chronic marijuana consumption (ca. ≥50 times) can induce schizophrenia in susceptible persons (see Chap. 22).

The History of Capsaicin

Chili peppers (*Capsicum frutescens var. longum*) are members of the nightshade family (*Solanaceae*), and have been domesticated since about 7500 B.C. in the Americas (Perry et al., 2007). Christopher Columbus was one of the first Europeans who found chili peppers and subsequently transferred a certain amount to the Old World. He accidentally named them “peppers” because of their similarity in taste with the black peppers of the *Piper* genus. This pungent taste is due to capsaicin, a neurotoxin derived from the chili pepper plant. Capsaicin has been extensively used for centuries both as a herbal remedy and a food product prized in the cuisine of many societies. Capsaicin is also responsible for the reduced sensitivity of the mouth to high temperatures and painful mechanical stimuli which results from regular chili pepper consumption. The fact that capsaicin also relieves

the spontaneous pain associated with inflammation prompted healers in many different cultures to employ hot peppers to treat painful conditions of varying aetiologies over the centuries. Thus, Native Americans rubbed their gums with hot peppers as a cure for tooth ache, while Europeans used an alcoholic extract prepared from chilies for a similar purpose (Szallasi and Blumberg, 1999). Capsaicin is still commonly used for treating painful conditions as an "over-the-counter" remedy in the form of capsaicin-containing ointments.

The Discovery of the Endocannabinoid and Endovanilloid Systems

The Endocannabinoid System

Although Eastern cultures have been using marijuana as medicine for centuries, Western cultures started to recognize the therapeutic potential of marijuana only recently. For instance, cannabis extract was a licensed medicine and sold under the name of "Tincture of Cannabis" in the UK (Gill et al., 1970). The first observed medicinal benefits encompassed anesthetic, airway opening, antihypertensive, eye pressure reducing (in glaucoma) as well as antiemetic actions, but for decades, the underlying physiological and molecular mechanisms were unknown. The first isolated plant-derived (phyto-) cannabinoid was cannabinol, found in the red oil extract of hemp more than a century ago, and in the 1930s, its chemical structure was elucidated (Pertwee, 2006). Although tetrahydrocannabinols (THCs) and cannabidiols were discovered and isolated from hemp extracts in the following years, the structure and stereochemistry of the naturally occurring (–)-cannabidiol (Mechoulam and Shvo, 1963) and (–)-trans-Δ^9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive constituent of marijuana and hashish (Gaoni and Mechoulam, 1964) were unraveled in the decade when hippies also became interested in cannabis preparations. The major phytocannabinoid structure was identified as a tricyclic ring constituted from a phenol ring, having a 5-carbon alkyl chain meta to the hydroxyl, a central pyran ring, and a mono-unsaturated cyclohexyl ring (Fig. 1; Howlett et al., 2004). Raphael Mechoulam and his laboratory pioneered the discovery and synthesis of numerous novel phytocannabinoids, which enumerate at least 66 distinctive ones hitherto (Mechoulam and Hanus, 2000; Pertwee, 2006). In parallel with their discovery, hemp constituents were tested for psychotropic and motor effects in man and in animal models, mostly in mice, rats, rabbits, and dogs. THCs proved to be the most effective among all phytocannabinoids, whereas among THCs, Δ^9-THC seems to be responsible for the vast majority of effects such as motor disturbances and catalepsy, corneal areflexia (in rabbits), scratching, euphoria and dysphoria, anxiety, drowsiness, altered time and audiovisual perceptions, panic attacks and impaired memory (Haagen-Smit et al., 1940; Loewe, 1946; Paton and Pertwee, 1973; Howlett et al., 2004). The following years then proved that the more psychotropic a cannabinoid substance is

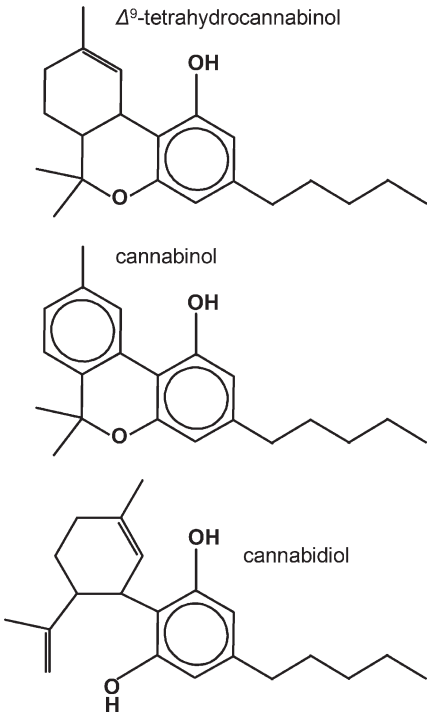

Fig. 1 The most important constituents of *Cannabis sativa* L., namely Δ^9-tetrahydrocannabinol ((–)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol; Δ^9-THC), cannabinol (6,6,9-trimethyl-3-pentyl-6H-benzo[c]chromen-1-ol) and cannabidiol (2-((1S,6S)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)-5-pentylbenzene-1,3-diol)

the greater motor disturbances it causes. Furthermore, among phytocannabinoids, Δ^9-THC is the most potent and effective psychomotor compound. The underlying mechanisms for these effects were mostly believed to result from "non-specific" interactions between the lipophilic Δ^9-THC and the cell membranes, changing the fluidity and structure of the latter, therefore affecting most cell types (Lawrence and Gill, 1975; Hillard et al., 1985). Nonetheless, a nearly identical molecule, Δ^8-THC, was much less potent and efficacious than Δ^9-THC, and most other phytocannabinoids were devoid of effect, which all weakened the hypothesis of changing membrane fluidity. The next important cornerstone was the discovery that Δ^9-THC inhibits cAMP accumulation (Howlett and Fleming, 1984), and the recognition of specific cannabinoid binding sites in the brain (Devane et al., 1988). These two findings from Allyn Howlett's laboratory predicted that the discovery of atleast one cannabinoid receptor was imminent. And indeed, in 1990, both the rat and the human CB_1 receptors were characterized (Gérard et al., 1990, 1991; Matsuda et al., 1990), and the first study on its distribution found the receptor at an unexpectedly high density in the brain (Herkenham et al., 1991). Right at the moment when we write

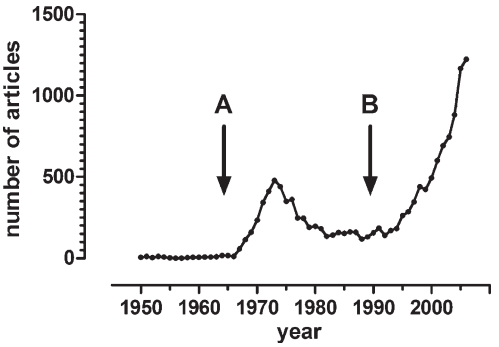

Fig. 2 The yearly number of research and review articles on the cannabinoid field from 1950. The *two arrows* indicate the onset of the two booms: (**a**) Gaoni and Mechoulam (1964) report the structure of Δ^9-THC; (**b**) Gérard and colleagues (1990) and Matsuda and colleagues (1990) report the cloning of the first cannabinoid receptor (the CB_1 receptor) from human and rat (See text for further explanations.)

these lines, there are 14,000 articles published in relation to cannabinoids. The first one – listed by PubMed – is from 1909. As Fig. 2 demonstrates, the first "boom" of cannabinoid research occurred after 1964, the year when Gaoni and Mechoulam reported the structure of Δ^9-THC. The second boom – which is related to the discovery of the CB_1 receptor – resulted in a continuously increasing number of publications in the last 15 years, and in 2006 and in the first five months of 2007, it reached a peak of 100 publications per month. Thus, recognizing the significance of cannabinoid research very early, Di Mahadeen and Rik Musty founded the International Cannabinoid Research Society in 1991 (http://www.cannabinoidsociety.org for further information). Soon, another cannabinoid receptor, the CB_2 receptor was discovered, but its expression was found to be restricted mainly to immune tissues (Munro et al., 1993). Importantly, both cannabinoid receptors are G protein-coupled seven-transmembrane-domain receptors of the rhodopsin type (see Chaps. 5 and 6). In the meantime, the first endogenous cannabinoid ligand, arachidonoylethanolamine or anandamide, was found in porcine brain (Devane et al., 1992), which was followed by 2-arachidonoylglycerol (2-AG) described by two independent laboratories in the same year (Mechoulam et al., 1995; Sugiura et al., 1995; see Chap. 2). As one can notice from their name, both ligands are arachidonic acid derivatives, and interestingly, one of them, namely anandamide, is capable of activating the $TRPV_1$ receptor as well (Zygmunt et al., 1999; and see below). Later in this book, we will mention some new cannabinoid receptors and endocannabinoid candidates (Chaps. 4 and 9). However, hitherto these four molecules received the biggest attention. The last 20 years provided a major boost to the renaissance of the synthesis of novel cannabinoid ligands as well, and further readings can be found in recent reviews (Mechoulam and Hanus, 2000; Howlett et al., 2004; Pertwee, 2006; see Chap. 7). However, we should highlight 1994 when the first selective CB_1 receptor antagonist, SR141716A or Rimonabant, was reported (Rinaldi-Carmona et al., 1994) and, has been marketed in 2006 in Europe under the name Acomplia™ as a promising alternative medicine