Cannabinoids and the Brain

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Editor

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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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