

Preface: Cannabinoids as New Tools for the Treatment of Neurological Disorders

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This special issue that the editorial board of Molecular Neurobiology has kindly accepted to host has been prepared from the lectures presented in an International Symposium on “Cannabinoids: new tools for the treatment of neurological disorders” held in Madrid, Spain, in March 2006, organized by the “Fundación Ramón Areces”. Since 1998, this was the third time that this Spanish foundation includes an international event on different aspects of the physiology and pathophysiology of the cannabinoid system in its yearly scientific program. We want to thank all members responsible for this foundation, in particular, Professor Julio Rodríguez Villanueva, for his continuous support to the progress in the research of these clinically promising molecules. These thanks must also be extended to Professor Nicolas Bazan, the senior editor of Molecular Neurobiology, for accepting that the symposium lectures become in review articles available for all readership of this important review journal, and of course, to all researchers that contributed with excellent lectures in the symposium which have been continued by excellent review articles for this special issue.

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In this International Symposium, we addressed the reasons for the great increase experienced by cannabinoid research during the last 10 years. There is consensus that this is directly related to the discovery of the so-called “endogenous cannabinoid system”, a new intercellular messenger system that is active at both central and peripheral levels. This goal has provided the basis to explain why cannabinoids present in *Cannabis sativa*, the so-called plant-derived cannabinoids, had already shown for a long time to have therapeutic properties, but also, it has allowed to further explore the modifications that this system undergoes in certain pathologies, and then, to determine the best pharmacological treatment in each case. The different elements that constitute this intercellular messenger system are already known. The endogenous ligands are mostly derived from arachidonic acid, and they are synthesized on demand by different enzymes widely acting in lipid metabolism. These ligands activate various membrane receptors, mainly the so-called cannabinoid CB₁ and CB₂ receptors, although the existence of other cannabinoid receptor types and the involvement of other related receptors, such as the vanilloid TRPV₁ receptors, cannot be ruled out. Cannabinoid receptors contain seven transmembrane domains typical of GTP-binding protein-coupled receptors, and their activation triggers various intracellular cascades and/or modifies the conductance for several ions. The mechanism involved in the finalization of the biological action of cannabinoids is also known and involves two processes, an uptake mechanism through the cell membrane and the action of various enzymes involved in the hydrolysis of endogenous cannabinoids. All this general information, divided in two parts, one dealing with specific biochemical aspects and another addressed to review the pharmacological compounds targeting the different proteins

of the cannabinoid system, has been the basis for the two first review articles of this special issue, the one prepared by José A. Ramos (Complutense University, Madrid, Spain) and another one written by Christopher Fowler (Umea University, Umea, Sweden), respectively.

These two general reviews are essential to understand the proposals of a potential for cannabinoid-based medicines in different neurological disorders that have been reviewed in the subsequent articles. This potential is based on results obtained in studies addressed to determine the distribution of these elements in the body, the effects caused by cannabinoid agonists and antagonists in the brain physiology and pathophysiology, and the changes observed in mice deficient in some of the key proteins of this system. These data strongly demonstrate that the cannabinoid system is active not only in the nervous system but also at the peripheral level. In the brain, the cannabinoid system plays a modulatory role, including its action as a retrograde messenger system in certain synapses, in processes such as the control of motor activity, memory and learning, appetite, emesis, nociception, and certain motivational responses. In addition, it also participates in the death/survival cellular decision, a phenomenon notably important in the nervous tissue due to the postmitotic characteristics of neuronal cells. Therefore, the modulatory function exerted by the cannabinoid system on these and other brain processes supports the idea that the modulation of the different elements of this system might have therapeutic potential for the treatment of several neurological disorders. Even, the occurrence of changes in cannabinoid activity in certain brain regions have been already demonstrated in some of these disorders, which supports that the pharmacological approach is timely. For instance, direct or indirect agonists of cannabinoid receptors produce analgesia, so they might be used in the treatment of chronic pain through effects that would be CB₁ or CB₂ receptor-mediated, as has been reviewed by Victoria Chapman (University of Nottingham, UK). They might also be useful in the treatment of inflammatory processes associated with different types of pathologies in which glial cells are key elements (reviewed by Nephi Stella, University of Washington, Seattle, USA). This includes multiple sclerosis, an autoimmune disease in which cannabinoid agonists ameliorate several symptoms typical of this disease, as has been reviewed by Roger Pertwee (University of Aberdeen, UK). Cannabinoid agonists produce apoptosis of tumoral nerve cells, in

particular, in the case of glioma cells, without affecting normal cells, an effect in which both CB₁ and CB₂ receptors seem to be involved (reviewed by Manuel Guzmán, Complutense University, Madrid, Spain). Furthermore, we already know that they are capable of providing protection, through different mechanisms (e.g., by reducing excitotoxicity, calcium influx, oxidative injury, and inflammation), of nerve cells with emphasis in neuronal cells, which has relevance for the therapy in acute neurodegenerative episodes (cerebral ischemia and trauma; reviewed by Raphael Mechoulam, Hebrew University, Jerusalem, Israel) and also in chronic disorders, including Alzheimer's disease (reviewed by Julián Romero, Fundación Hospital Alcorcón, Madrid, Spain), and Parkinson's and Huntington's diseases (reviewed by Javier Fernández-Ruiz, Complutense University, Madrid, Spain). The participation of the cannabinoid system in memory and learning supports that the management of this system may be useful in various memory-related diseases, such as the memory extinction processes needed in posttraumatic stress disorder, as has been reviewed by Beat Lutz (University of Mainz, Germany). The same happens with the presence of the cannabinoid system in limbic structures and in the anterior hypothalamus, which supports that the management of this system, in particular, the blockade of CB₁ receptors, may be useful in the treatment of compulsive phenomena related to drug addiction (e.g., alcoholism, reviewed by Giancarlo Colombo, University of Cagliari, Italy) or of feeding disorders (anorexia and obesity; reviewed by Francisco Arias, Fundación Hospital de Alcorcón, Madrid, Spain). All these review articles serve as an excellent overview of those key aspects that support a therapeutic potential of the cannabinoid system in neurological disorders. However, this special issue needed to be culminated with a last review article dealing with one of the few cannabinoid-based medicines that are presently under clinical evaluation, Sativex®, for neurological disorders, developed by the British company GW Pharmaceuticals, Salisbury, UK (reviewed by one of its research directors, Stephen Wright). This completes a series of timely and updated review articles that we expect may be of great interest to a broad audience and provide a comprehensive summary of the current knowledge, at both preclinical and clinical levels, on the cannabinoids as novel medicines for the treatment of specific symptoms and/or the disease progression in different neurological disorders.