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Editorial

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Endocannabinoids are a new type of endogenous messenger molecules derived from polyunsaturated fatty acids that share with classic plant-derived and synthetic cannabinoids the ability to activate the so-called cannabinoid receptors. These receptors include two subtypes of GTP-binding protein-coupled receptors named CB_1 (present preferentially in the nervous tissue) and CB_2 (present preferentially in the immune system). A cannabinoid-related receptor is the vanilloid TRPV1 receptor subtype which can be activated by certain endocannabinoids and analogs. Endocannabinoids and their receptors form, together with a mechanism of inactivation that includes a membrane transporter and two degradative enzymes, the so-called "endocannabinoid signaling system". This system is active in the periphery, in particular in the immune and cardiovascular systems, but its major relevance is in the brain where it is ubiquitously distributed and plays a regulatory function in processes such as the control of movement, nociception, memory and learning, emesis, appetite, and others. Recently, the endocannabinoid signaling system has also been proposed as a component of the brain reward circuitry which is activated by different types of reinforcers, among them, the habit-forming drugs. Numerous studies have provided sufficient evidence to support this new role in brain reward and also in other neurobiological processes related to drug addiction. Part of this evidence derives from neuroanatomical studies that have demonstrated that CB_1 receptors and their endogenous ligands are moderately abundant in different brain structures implicated in drug addiction, in particular the nucleus accumbens, prefrontal cortex, ventral–tegmental area and amygdala. It has been recently suggested that CB_1 receptors may be located on mesocorticolimbic dopaminergic neurons themselves, which are the major components of the reward circuitry. The neuroanatomical data have been complemented with biochemical studies that established changes in the density of CB_1 receptors and in the levels of their endogenous ligands in drug addiction-related brain regions of animals rendered dependent to most important habit-forming drugs. Finally, pharmacological studies have demonstrated that the activation and/or the inhibition of the endocannabinoid system might influence several signs indicative of drug addiction, such as individual vulnerability, craving, degree of dependence, intensity of abstinence, or risk for relapsing, which has opened the possibility of using these substances in the treatment of different addictive states. Taken together, all this new evidence would explain two relevant observations: (i) the marked changes occurring in endocannabinoid transmission, mainly at the level of CB_1 receptors, associated with the regular use of cannabis, and (ii) the frequent pharmacological and biochemical interactions of cannabinoids with different habit-forming drugs, such as opioids, cocaine, nicotine, and alcohol.

This Special Issue is aimed at exploring in depth the recent evidence supporting a role of the endocannabinoid signaling system in addictive states. The Special Issue have been generated from the lectures presented in the Symposium "Cannabinoids: Interactions with other drugs" held in Morzine (France) in January 2004, within the 5th International Pharmacology, Biochemistry and Behavior Meeting, organized by Sandra File, the former European Editor of this journal. We wish to thank Sandra File and their coworkers for organizing and supporting this scientific event, for inviting us to contribute with a symposium on cannabinoid research, and for supporting our further proposal of extending this symposium to a Special Issue. We are also grateful to the speakers at the symposium for their interesting lectures and for their kindness to extend their participation with a timely review on the topic they covered in the symposium. These thanks must be also extended to the authors that, although they did not participate in the symposium, have contributed with a review article on a topic where they have demonstrated a relevant expertise. We want, finally, to thank the present European Editor of Pharmacology, Biochemistry and Behavior, Dai Stephens, and the Elsevier Publishing Editor in the area of Behavioral Neuroscience, Sara Purdy, and their collaborators, who accepted hosting this Special Issue and provided us with continuous support and facilities.

Within this Special Issue, the reader will find the most recent update on the endocannabinoid signaling system, on the evidence relating this system to drug addictive states, and on the interactions of cannabinoids with the most

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important drugs of abuse consumed by humans. These three major topics have been used as the headings for the three parts in which we have divided the monograph. The first part, entitled "Overview of the endocannabinoid signaling system", deals with the description of the biochemical, neuroanatomical and pharmacological bases that explain the relevance of the endocannabinoid signaling system as a new modulatory system in the brain and the periphery, with emphasis in all basic, preclinical and clinical data available on diseases in which cannabinoids have been proposed of therapeutic value. In this first part, we have included three contributions, the first one prepared by Tiziana Bisogno, Vincenzo Di Marzo and coworkers (Istituto di Chimica Biomolecolare, Italy) that specifically deals with the description, from a biochemical point of view, of those elements that form the endocannabinoid signaling system. These authors outlined with great detail the mechanisms of biosynthesis, release and inactivation of endocannabinoids, indicating the importance of these mechanisms from a pharmacological point of view. Extending this idea, Julián Romero and collaborators (Fundación Hospital Alcorcón, Spain) have centered their review in the neuroanatomical aspects of this system, in particular in the distribution and function of CB_1 and CB_2 receptors, their role in the control of neurotransmitter release, and their changes under different pathological conditions. Lastly, the article written by Christopher Fowler and his colleagues (University of Umea, Sweden) explores the pharmacological potential of the endocannabinoid signaling system by reviewing the novel compounds designed to selectively target the most important proteins of this system. These authors have paid special attention to the use of these compounds in pain and neuroprotection.

The second part of the Special Issue, under the heading "Endocannabinoid signaling system and drug addiction: General part", is devoted to make a general overview of those data supporting a role of the endocannabinoid signaling system in drug addiction. The evidence that relates the endocannabinoid signaling system to a modulatory role on dopamine transmission in the reward circuitry has been reviewed by Elliot Gardner (National Institute on Drug Abuse, USA), with special attention to the importance of this system in rewarding effects of cannabinoids and the comparison with the situation of other drugs of abuse. Extending the findings of the above review article, Zuzana Justinova, Steve Goldberg and collaborators (National Institute on Drug Abuse, USA) have reviewed the consequences of this relationship for the reinforcer potential of cannabis and cannabinoids in humans and laboratory animals. These authors describe extensively recent studies aimed to demonstrate cannabinoid self-administration in laboratory animals, a fact that remained elusive up to recent studies with specific cannabinoids, and they stress the relevance of this approach to preclinically assess novel therapeutic strategies for the treatment of cannabis abuse in humans. Sara González and coworkers (Complutense University, Spain) outline a complete picture of the states of tolerance, dependence and withdrawal to cannabinoids in laboratory animals, at the light of the new discoveries on the biochemistry and physiology of the endocannabinoid system. They present an exhaustive description on how endocannabinoids and their receptors respond to the regular use of cannabinoids, resulting in adaptative situations that might be involved in specific responses elicited by the interruption of this regular use. Extending this topic, Thomas Lundqvist (Lund University Hospital, Sweden) contributes with a timely review dealing with the comparison of cannabis with other drugs of abuse as regards to their effects on cognitive processes, such as attention, memory and executive functions. Finally, due to the importance of stress and anxiety among the responses elicited by drugs of abuse, María Paz Viveros, Sandra File and coworkers (Complutense University, Spain, and King's College, UK) have prepared an interesting review article on the effects of cannabinoids on these processes and the involvement of different brain structures and various neurobiological substrates. They conclude that the endocannabinoid signaling system might represent a novel pharmacological target for anti-anxiety therapies.

The last part of this Special Issue, under the heading "Endocannabinoid signaling system and drug addiction: Interaction with other drugs", is devoted to analyzing in detail the biochemical, pharmacological and behavioral interactions of cannabinoids with the most important habit-forming drugs. Cannabinoid and opioid interactions are covered by two review articles. One of them has been prepared by Walter Fratta and coworkers (University of Cagliari, Italy) and is centered mainly in behavioral correlates of these interactions. The authors describe in detail how the opioid system mediates some classic effects of cannabinoids and vice versa, how the endocannabinoid system may play a role in the modulation of opioid rewarding and addictive properties. These authors have paid the major emphasis in processes of dependence, tolerance, sensitization, relapse and drug vulnerability. As a perfect correlate, Daniela Parolaro and collaborators (University of Insubria, Italy) have centered their contribution in the bochemical bases of opioid–cannabinoid interactions, detailing the functional links in the mechanisms of action of both substances. The authors reviewed in detail data showing that cannabinoids may increase the release of opioid peptides and vice versa, as well as the possible interaction between both types of substances at receptor and/or postreceptor levels. Another Italian group led by Giancarlo Colombo (University of Cagliari, Italy) has reviewed the pharmacological potential of the endocannabinoid system in the treatment of alcoholism. These authors describe with great detail the potential of rimonabant, a selective CB_1 receptor antagonist, to suppress acquisition and maintenance of alcohol drinking behavior in a rat strain with congenital preference for alcohol, and how opioid receptor antagonists potentiated this effect. The Special

Issue also includes two articles dealing with nicotine–cannabinoid interactions. A more basic article aimed at reviewing the biochemical and pharmacological interactions between these two substances was prepared by Rafael Maldonado and coworkers (Pompeu i Fabra University, Spain). These authors have strongly demonstrated a role for the endocannabinoid signaling system in the mechanisms underlying the addictive potential of nicotine, in concordance with similar observations for other substances. A second article prepared by Caroline Cohen and coworkers (Sanofi-Synthelabo Recherche, France) has also reviewed the interactions of nicotine and cannabinoids but it has been prepared from the perspective of the potential clinical use of rimonabant, the Sanofi CB_1 receptor antagonist. The authors describe with great detail the neurobiology of nicotine addiction, the rationale for the searching of novel pharmacotherapies for this addiction, and the preclinical evidence supporting the bases for the clinical trial that this company presently develops to demonstrate the therapeutic potential of rimonabant to reduce tobacco consumption. Opioids, alcohol and nicotine represent possibly the three drugs which have a more close relationship with cannabinoids because of pharmacological (i.e. sharing of pharmacological properties in the case of opioids) and toxicological (i.e. combinations of alcohol or tobacco with cannabis are frequent) reasons. However, there is increasing evidence that cannabinoids may also interact with other substances, such as cocaine or ecstasy. Cocaine–cannabinoid interactions have been reviewed by Jonathon Arnold (University of Sydney, Australia) in an article that is mainly centered in the elucidation of the possible involvement of the endocannabinoid signaling system in different aspects of cocaine addiction, with a special attention to the role of CB_1 receptors in the reinstatement of cocaine self-administration in laboratory animals. The interactions between MDMA (3,4-methylenedioxymethamphetamine; ecstasy) and cannabinoids have been reviewed by Mariaelvina Sala and Daniela Braida (University of Milano, Italy). These authors have summarized all evidence obtained in humans and laboratory animals in relation with possible common pharmacological, endocrine and biochemical links between both recreational drugs, and they have also indicated that the endocannabinoid signaling system might play a role in MDMA self-administration behavior in laboratory animals, as in the case of cocaine.

These are the contents of this Special Issue that we expect may be of great interest to a broad audience and provide a comprehensive summary of the current knowledge on this new role for the endocannabinoid signaling system.

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Guest Editors, Special Issue on Cannabinoids: Interactions with other drugs.

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