



Editorial

The endocannabinoid system: From biology to therapy

Emerging literature reveals that endocannabinoids are currently intensively investigated by scientists as they play important roles in human health. It is becoming clear that an underlying mechanism for most human diseases is shared by the endocannabinoid system. Therefore, there is high potential to develop new therapeutic tools from research on the endocannabinoid system, particularly for those disorders for which no satisfactory treatment exists to date.

The biology of the endocannabinoid system is based on cannabinoid receptors and their ligands, pathways of synthesis and degradation, signaling, and physiological effects. The auto-protective role of endocannabinoids has been widely documented in several pathological conditions: thermal, neuropathic and inflammatory pain, multiple sclerosis, cancer, intestinal disorders, post-traumatic stress or phobias or anxiety, excitotoxicity and traumatic brain injury, hemorrhagic, septic or cardiogenic shock, hypertension, atherosclerosis, and others [1]. This auto-protection is likely mediated by an increase in the release of endocannabinoids onto their receptors and/or by the density or coupling efficiency of these receptors. Further exploitation of basic research and new *in vivo* studies are required to trigger preclinical research and clinical trials in several diseases.

However, an imbalance between basic biological studies on the complexity of the system and preclinical evaluations of drugs targeting it emerges from the available literature. This prompted us to organize—in collaboration with the European Life Scientist Organization (ELSO), in the frame of the annual ELSO meeting “Frontiers of cellular, developmental and molecular biology” (30 August 2008, Nice, France)—a specific subgroup meeting on “Endocannabinoid biology”. The aim of this meeting was to spread and establish the ‘endocannabinoid biology’ topic in an important basic science conference, providing an intimate forum with leading scientists in the field discussing the latest advances, problems, and the work needed to be done in the next future to collate basic research studies with preclinical and clinical evaluations, normally supported by pharmaceutical companies. The proceedings of the meeting have been the starting point for this Special Issue of *Pharmacological Research*, which contains a number of updated reviews from leading scientists in this field. The objective is of acquainting the reader with the topic of the endocannabinoid system ‘from biology to therapy’. This Special Issue follows another recent one, i.e. “The endocannabinoid system and psychopathology”, published in *Pharmacological Research* edited by Prof. Filippo Drago, which has attracted attention on the central actions of endocannabinoids [2 and references therein].

The scope of included reviews featured in this Special Issue is, obviously, not to cover the whole area of ‘endocannabinoid biology’, but to touch on some of the major topics in this field. This Issue is introduced by an accurate overview of the endocannabinoid signaling system, its involvement in a number of pathological conditions, and the currently available tools for pharmacological studies and therapeutic intervention, providing an overview of the topics discussed in the subsequent reviews [3]. After the discoveries of cannabinoid receptors and their endogenous mediators, cannabinoid research was first developed in two major directions: neurobehavioral properties of cannabinoids and the impact of cannabinoids on the immune system. Pandey et al. review the role of endocannabinoids in the regulation of the immune response and the potential to treat inflammatory disorders, due to their immunosuppressive properties [4]. It is well known that the endocannabinoid system plays a physiologic role in the central regulation of food intake, body weight, and substrate metabolism (glucose and lipid). The subsequent section of the Issue sets the stage for the presentation of key preclinical and clinical findings, which suggest that the endocannabinoid system modulates energy homeostasis, hepatic and adipose tissue lipogenesis, dyslipidemia, insulin resistance, and glucose homeostasis [5]. Alteration of the endocannabinoid system has been reported to be implicated in the pathogenesis of several cardiovascular diseases, ranging from hypertension, atherosclerosis, myocardial infarction, to hemorrhagic or septic shock, heart failure and cardiovascular complications of liver cirrhosis [6]. Batkai and Pacher focus on the recent knowledge of the involvement of CB1 receptors and endocannabinoids in the regulation of cardiac function in cirrhotic cardiomyopathy and in doxorubicin-induced heart failure, opening new possibilities for therapeutic intervention [7]. Since the end of 1990s, endocannabinoid-related agents have been reported to affect multiple signaling pathways and biological processes involved in the development of cancer, displaying an interesting anti-proliferative, pro-apoptotic, anti-angiogenic, and anti-metastatic activity both *in vitro* and *in vivo*, in several types of tumors. Therefore, agonists of cannabinoid receptors could represent novel tumor-selective tools to treat cancer, in addition to their already exploited use as palliative drugs to treat chemotherapy-induced nausea, pain, and anorexia/weight loss in cancer patients [8]. This topic has been here analyzed and updated in light of most recent knowledge of the role of the endocannabinoid system in cancer biology and the potentiality of its modulation in cancer therapy [9]. In particular, since endocannabinoids up-regulation exerts a protective action during inflammatory conditions and compelling

data indicate a functional link between chronic inflammation and colon cancer, Izzo and Camilleri propose that pharmacological elevation of endocannabinoid levels may be a promising strategy to counteract intestinal inflammation and, hence, colon cancer [10]. Among the physiological processes and pathological conditions modulated by the endocannabinoid system, its involvement in reproduction and fertility appears to be very interesting. Lewis and Maccarrone focus on the multifaceted process of male reproduction, highlighting the FAAH enzyme as a potential new target for infertility treatment [11].

Finally, after the analysis of endocannabinoid system biology, its physiological homeostasis, its perturbation in several pathological conditions, and, in turn, the wide range of opportunities to target this system in the clinical setting, we have to take into account the health effects of cannabinoid abuse for recreational purpose. The contribution of Realini et al., exploiting animal models of cannabis consumption, provides evidence that further multidisciplinary studies, combining behavioral, neurochemical, and genetic approaches, are required to establish the real risk for impaired emotional and cognitive performance and for reproductive function, especially during adolescence [12]. The message that can be derived from this Issue is paradigmatic: together with the development of cannabinoid agonists and strategies aimed at enhancing the endocannabinoid tone to contrast several pathologies, the development of selective CB1 receptor antagonists unable to pass the blood–brain barrier (and avoid psychotropic side-effects) is increasingly needed in order to treat pathologies ranging from hepatic fibrosis, chronic inflammatory conditions to diabetes, atherosclerosis, and cancer [13].

In turn, the eight reviews in this Issue address many state-of-the-art aspects of endocannabinoid system biology. They summarize current knowledge of this field, cover data from molecular and cell biology to clinical therapy, and suggest the pathway to follow to advance the field. This Issue also highlights the need for increased interdisciplinary collaborations.

In summary, I hope the readers will find the reviews collected in this Special Issue interesting and stimulating and I would like to thank the contributors for their participation.

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Prof. Maurizio Bifulco*
*Department of Pharmaceutical Sciences, University of
 Salerno, Via Ponte Don Melillo,
 84084 Fisciano (SA), Italy*

*Tel.: +39 089969742; fax: +39 089969602.
 E-mail address: maubiful@unisa.it

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