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Themed Issue: Cannabinoids in Biology and Medicine, Part I

EDITORIAL

Themed issue on cannabinoids in biology and medicine

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Current cannabinoid research is based on a number of major discoveries made by Professor Raphael Mechoulam. In the mid-1960s, he, together with Professor Yechiel Gaoni, identified in the plant *Cannabis sativa*, the psychoactive component of marijuana and hashish, Δ^9-tetrahydrocannabinol (THC), determined its chemical structure (Gaoni and Mechoulam, 1964; Mechoulam and Gaoni, 1967) and synthesized it (Mechoulam *et al.*, 1967). The pertussis toxin-sensitive inhibition of adenylate cyclase activity by THC and related synthetic cannabimimetic compounds, such as desacetyllevonantradol (Howlett, 1985), led a couple of decades later to the cloning of the first cannabinoid receptor (CB_1) in neural cell lines and several regions of the brain (Matsuda *et al.*, 1990). Reasoning that this receptor is targeted by an endogenous component(s), Professor Mechoulam made his second major breakthrough, the discovery of ligands for this receptor, arachidonyl ethanolamide (anandamide) (Devane *et al.*, 1992) and 2-arachidonyglycerol (Mechoulam *et al.*, 1995), thus establishing the presence of the endocannabinoid system. These discoveries were followed by cloning of another, predominantly peripheral cannabinoid receptor (CB_2) (Munro *et al.*, 1993) and the endocannabinoid metabolizing enzymes diacylglycerol lipases, NAPE-selective phospholipase D, monoacylglycerol lipase and fatty acid amide hydrolase (Ligresti *et al.*, 2005; McKinney and Cravatt, 2005).

Professor Mechoulam's discoveries have led to a wealth of basic, translational and clinical studies. It is now well established that endocannabinoids regulate a handful of central and peripheral pathophysiologic functions. Furthermore, cannabinoid ligands and enzyme inhibitors of the endocannabinoid degrading enzymes hold great promise for treating several pathological conditions. In fact, a cannabinoid medicine consisting of THC and another phytocannabinoid, cannabidiol (CBD), has made its way to the clinic as a treatment of spasticity due to multiple sclerosis and for cancer and neuropathic pain. Academically, the field of cannabinoid research generates a huge number of articles, with a current annual rate higher than 10 000. A substantial number of these articles have been published in journals of the highest impact factor.

The present *BJP* Themed Issues bring together reviews summarizing an international workshop, entitled 'Cannabinoids in Biology and Medicine', convened in Jerusalem in October 2010 to celebrate Professor Mechoulam's 80th birthday and acknowledge his past and ongoing contributions to the field of cannabinoid research. These reviews describe a range of topics in the cannabinoid arena. A couple of them focus on the mode of receptor activation by cannabinoid ligands. One of them addresses the issue of endocannabinoid tone versus constitutive activity of cannabinoid receptors, concluding that receptor activation in the absence of agonist ligands is rather unlikely (Howlett *et al.*, 2011). The other article explores the pharmacological activity and therapeutic potential of phytoterpenoids (Russo, 2011).

Being historically based on the psychoactivity of marijuana and hashish, cannabinoid research has had its main focus on pathophysiology of the central nervous system. Indeed, almost half of the present reviews deal with topics related to the role of cannabinoids in brain disorders. The potential therapeutic role of CB_1 and CB_2 ligands in neurodegenerative and neuroinflammatory disorders is covered, as well as possible mechanisms associated with the activation of CB_1 and CB_2 in these instances (Fernández-Ruiz *et al.*, 2011; Maccarrone *et al.*, 2011). The neuroprotective effect of cannabinoid ligands is discussed versus their potential neurotoxicity (Sarne *et al.*, 2011). The neuroprotective activity of the endocannabinoid system, especially after traumatic brain injury, is further addressed in view of the involvement of both CB_1 and CB_2 receptors in this condition (Shohami *et al.*, 2011). Mechanisms involved in the anti-nausea effects of anandamide and the non-psychoactive phytocannabinoid, CBD, are highlighted based on recent findings pointing towards activation of the serotonergic system by CBD (Parker *et al.*, 2011).

Extensive research has been carried out, especially in the past decade, on the peripheral functions of the endocannabinoid system. This Themed Issue underlines the role of CB_1 and endocannabinoids in pathophysiology of the metabolic syndrome, with a special emphasis on the potential therapeutic role of peripherally selective CB_1 antagonists (Kunos and Tam, 2011). A related article broadens this spectrum by further discussing the prospects of treating chronic liver disease with CB_1 antagonists and CB_2 agonists (Mallat *et al.*, 2011). The skeletal cannabinoid system is portrayed as part of the larger family of fatty acid amides, recently implicated in the regulation of skeletal remodelling and bone mass (Bab *et al.*, 2011).

Another review examines how activation of the endocannabinoid system impacts breast, prostate and bone malignancies in *in vitro* and *in vivo* models, including the therapeutic potential of cannabinoids for cancer, as identified in clinical trials (Guindon and Hohmann, 2011). Last but not least, a summary of 18 clinical trials assessing the analgesic effects of different phytocannabinoid preparations in instances of chronic non-cancer pain is reviewed. The important message is that cannabinoids are safe and modestly effective, particularly in neuropathic pain (Lynch and Campbell, 2011).

In addition to these review articles, the two Themed Issues hold 26 exciting research articles on the molecular, cellular, tissue and whole animal aspects of cannabinoid activities. Several of them report novel interactions of the endocannabinoid system with other biological processes. These papers illustrate the rapidly expanding cannabinoid research field that encompasses a broad spectrum of physiological and pathophysiological mechanisms in diverse cell types. Hopefully, these Themed Issues deepen and expand our knowledge and understanding of the biological actions of cannabinoids and their medical significance.

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Conflict of interest

The author states no conflict of interest.

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