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COMMENTARY

CB_2 cannabinoid receptors: new vistas

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Over the years CB_2 cannabinoid receptors have received much less attention than CB_1 receptors, the latter mediating most of the psychoactive effects of cannabis. Primarily this was due to difficulties in assigning a physiological function to CB_2 receptors. In recent years this situation has changed, and CB_2 receptors have been implicated in processes as diverse as analgesia, hepatic fibrosis, bone growth, and atherosclerosis. This special issue of the *British Journal of Pharmacology* addresses these and other topics in CB_2 receptor research by compiling a series of reviews and primary research papers stemming from a meeting '*$CB2_2$ cannabinoid receptors: New vistas*' that was held in Banff, Canada, from May 31 to June 3, 2007.
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Abbreviation: CB, cannabinoid

The meeting '*CB_2 cannabinoid receptors: new vistas*' was held in Banff, Canada, from 31 May to 3 June 2007 and was organized by a team led by Keith Sharkey of the University of Calgary. The motivation for this meeting was the growing appreciation that cannabinoid 2 (CB_2) receptors appear to be involved in many biological processes, several of which may be potential therapeutic targets. However, the very diversity of systems involving CB_2 receptors has limited the interactions between scientists studying CB_2 receptor-mediated responses. This meeting was designed to bring together scientists studying CB_2 receptors from diverse perspectives, including those interested in the chemistry of CB_2 ligands, the role of CB_2 receptors in normal biological processes and the involvement of CB_2 receptors in pathological processes.

To meet this goal, the meeting was comprised of six sessions: 'Structural and molecular determinants of CB_2 receptors and CB_2 receptor signaling', 'CB_2 receptors in osteoporosis', 'CB_2 receptors and immune modulation', 'CB_2 receptors and the modulation of pain', 'Talks from submitted abstracts' and 'The role of CB_2 receptors in reproductive, cardiovascular, liver, and gastrointestinal systems'. In addition, there were more than two dozen poster presentations. This themed issue of the *British Journal of Pharmacology* is comprised of contributed reviews from many of the speakers at the meeting as well as several original research papers involving aspects of CB_2 receptor biology.

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The CB_2 receptor was the second cannabinoid receptor cloned, the first being CB_1. As their names might suggest, CB_1 and CB_2 are closely related. As such there is considerable overlap in the specificity of CB_1 and CB_2 ligands, an issue accentuated by the lipophilicity of most of these ligands. A theme that emerged from several of the talks was that great care must be taken in assigning a biological response to being CB_2 receptor-mediated. Many of the ligands that are thought to be 'CB_2 receptor-specific' have varying degrees of activity at other receptors, and this must be considered in interpreting experimental responses. Some of the highlights that emerged from the meeting were as follows:

(1) The need for more specific CB_2 receptor agonists and, to a lesser degree, antagonists.
(2) To unequivocally establish the role of the CB_2 receptor in a process, it is prudent to use both pharmacological and mouse genetic tools.
(3) Agonist trafficking at the CB_2 receptor must be considered when interpreting the results from different agonists (for example, AM1241 ((2-iodo-5-nitrophenyl)-[1-(1-methylpiperidin-2-ylmethyl)-1*H*-indol-3-yl]-methanone), 2AG (2-arachidonoyl glycerol) and JWH133, (6aR, 10aR)-3-(1,1-Dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran.
(4) There are significant differences in ligand efficacy between rodent and human CB_2 receptors. This has important implications for drug development.

In this special issue, various potential therapeutic targets of CB_2 receptors are explored and reviewed by experts in this field. Emerging targets for ligands directed to the CB_2 receptor include pain (Hohmann and Guindon, 2008; McDougall *et al.*, 2008; Rimmerman *et al.*, 2008), (neuro)

inflammation (Romero *et al*., 2008), hepatic fibrosis (Loterszajn *et al*., 2008), gastrointestinal motility and inflammation (Sharkey *et al*., 2008), atherosclerosis (Mach and Montecucco, 2008), immune function (Cabral *et al*., 2008; Dittel, 2008; Stella and Miller, 2008) demyelinating disease (Arevalo-Martin *et al*., 2008), ischaemia (Pacher and Hasko, 2008; Pacher *et al*., 2008), bone disease (Bab and Zimmer, 2008) and disorders of reproduction (Maccarrone, 2008). Although the toolbox of ligands directed towards the CB_2 receptor is rapidly expanding, the pharmacology of these ligands is complex (Fox *et al*., 2008; Huffman and Poso, 2008; Lunn *et al*., 2008; Meyer and Yao, 2008; Pertwee, 2008).

This special issue highlights the diverse physiological role of the CB_2 receptor and its involvement in the pathophysiology of a variety of disease states. Clearly, more research is required to illuminate further the nature of CB_2 receptor agonist and antagonist action in these various conditions. The development of conditional CB_2 receptor knockout mice (Buckley, 2008) and of ligands with greater selectivity will serve to further clarify the role of the CB_2 receptor in the many physiological and pathophysiological processes in which it appears to be implicated.

Conflict of interest

The authors state no conflict of interest.

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