British Journal of Pharmacology

DOI:10.1111/j.1476-5381.2012.02238.x
www.brjpharmacol.org

Themed Section: Cannabinoids 2012

EDITORIAL

2012 cannabinoid themed section

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Linked Articles
This article is part of a themed section on Cannabinoids. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2012.167.issue-8

In this section, BJP brings together a group of reviews and original articles focussing on cannabinoids. One of the reviews deals with GPR18, an orphan GPCR which has recently attracted interest from workers in the cannabinoid area (McHugh, 2012). This interest stems from observations that GPR18 has overlapping pharmacology with the conventional cannabinoid receptors, CB_1 and CB_2 (Alexander, 2012; McHugh *et al.*, 2012). In particular, Δ^9-tetrahydrocannabinol, the major psychoactive component from the *Cannabis* plant, which is an agonist at CB_1 and CB_2 cannabinoid receptors, has also been shown to be a full agonist at GPR18 (McHugh *et al.*, 2012). The best evidence for the endogenous ligand for GPR18 points towards N-arachidonoylglycine (Kohno *et al.*, 2006; McHugh *et al.*, 2010; 2012), which is a close analogue of the original endogenous cannabinoid receptor agonist, anandamide. In this issue, Doug McHugh reviews the evidence for GPR18 expression in microglia and considers the physiological impact of this expression. Doug was the recipient of the J. Michael Walker Memorial Award of the International Cannabinoid Research Society at their annual meeting outside Chicago in 2011, for his studies on GPR18 in the laboratories of Heather Bradshaw in Bloomington, Indiana.

The second review in this Themed Section focusses on an old favourite, the CB_1 cannabinoid receptor. This review, however, addresses a distinct aspect of the CB_1 cannabinoid receptor; the dynamics of its transcription (Laprairie *et al.*, 2012). One of the underlying messages of this review, from the labs of Mel Kelly and Eileen Denovan-Wright from Halifax, Nova Scotia, highlights the need to consider changes in CB_1 cannabinoid receptor expression with distinct developmental stage and in response to pathological stimuli. This will influence the interpretation of behavioural studies (for example) and refine the thinking about potential therapeutic efficacy.

The original articles in this Themed Section bridge a number of topics within the cannabinoid research area. Chicca *et al.* (2011) present an investigation of a plant-derived compound, distinct from Δ^9-tetrahydrocannabinol, which has been reported to activate directly CB_1 and CB_2 cannabinoid receptors (da Silva *et al.*, 2011). The studies presented from the lab of Jürg Gertsch in Bern suggest that the action of β-amyrin is through inhibition of hydrolysis of the major endogenous cannabinoid receptor agonist, 2-arachidonoylglycerol. The implications of this finding include the possibility of novel chemical entities based on the orally active triterpene to exploit the cannabinoid system therapeutically.

Woodhams *et al.* (2012) look at a synthetic inhibitor of 2-arachidonoylglycerol hydrolysis, JZL184 (Long *et al.*, 2009). This compound has been reasonably well characterized in the mouse, with an anti-nociceptive profile. This collaboration between the Nottingham labs of Vicky Chapman, Andy Bennett, Dave Barrett and myself looked at the effects of JZL184 in the rat spinal system. Although administration of this agent had a marked effect on spinal recordings evoked by inflammatory stimulation in the rat hindpaw, there was no concomitant evidence for changes in 2-arachidonoylglycerol accumulation or monoacylgycerol hydrolase activity in the spinal cord. The report suggests that highly localized changes in endocannabinoid levels may be profoundly effective in regulating patho/physiological responses.

Moreno-Sanz *et al.* (2012) also report an investigation of endocannabinoid hydrolases. This particular report from the lab of Daniele Piomelli looks at URB937, a peripherally restricted inhibitor of fatty acid amide hydrolase. In their studies using both male and female rodents, the authors note that this compound effectively reduces pain behaviours in female animal models of inflammatory and visceral pain, as previously identified in males. In studying the disposition of this drug, they conclude that a major influence is the activity of the ATP-binding cassette transporter, ABCG2, which is one of three 'multidrug resistant' ABC transporters (Kerr *et al.*, 2011), which greatly influence the tissue accumulation of many pharmaceutical agents.

Hill *et al.* (2012) investigate a natural product, cannabidivarin, a less well-known metabolite from the *Cannabis* plant. Using *in vitro* and *in vivo* models of seizures, Gary Stephens, Christine Williams and Ben Whalley from Reading, collaborating with colleagues from Otsuka and GW Pharmaceuticals, observe a profile consistent with an anticonvulsant action. Although this compound lacked observable effects on motor function *in vivo*, it appeared effective in combination with the

clinically effective anticonvulsants valproate or phenobarbital against pilocarpine-induced seizures.

De Petrocellis *et al*. (2012) investigate what some have termed the ionotropic cannabinoid receptor, TRPV1, and in particular, whether the linoleic acid metabolite 9-hydroxyoctadienoic acid is an effective agonist at TRPV1 (Patwardhan *et al*., 2010) in comparison with the endocannabinoid/endovanilloid anandamide. Luciano De Petrocellis, Vincenzo Di Marzo and colleagues, from Naples, in collaboration with Kasia Starowicz from Krakow, compare TRPV1, TRPV2, TRPA1 and TRPM8 gating of calcium in heterologous expression, using a variety of oxygenated lipids. They conclude that 9-HODE is markedly less active than anandamide and appears not to be a good candidate as an endovanilloid.

A pan-Italian contribution from Daniela Parolaro, Tiziana Rubino and co-workers from Insubria/Milan, in collaboration with colleagues from Naples and Cagliari, investigates a model of schizophrenia using the prepulse inhibition (PPI) paradigm (Zamberletti *et al*., 2012). Post-weaning social isolation results in a PPI deficit reminiscent of one of the symptoms of schizophrenia in man. Using a selective CB_1 cannabinoid receptor inverse agonist/antagonist, in chronic administration, normalized PPI responses in these animals, as well as correcting alterations in 2-arachidonoylglycerol content and dopamine and glutamate receptor levels. They conclude that further investigation is warranted into the exploitation of CB_1 cannabinoid receptor inverse agonists/antagonists as potential antipsychotics.

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