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COMMENTARY

Cannabinoids and intestinal motility: welcome to CB_2 receptors

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Δ^9-Tetrahydrocannabinol (the active ingredient of marijuana), as well as endogenous and synthetic cannabinoids, exert many biological functions by activating two types of cannabinoid receptors, CB_1 receptors (expressed by central and peripheral neurons) and CB_2 receptors (that occur mainly in immune cells). Convincing evidence has accumulated in recent years that cannabinoids inhibit gastric and intestinal motility through activation of enteric CB_1 receptors. However, a report in this issue of *British Journal of Pharmacology* has highlighted the possibility that CB_2 receptors in the rat intestine could contribute to reducing the increase of intestinal motility induced by an endotoxic inflammation. By minimizing the adverse psychotropic effects associated with brain cannabinoid receptors, the CB_2 receptor represents a new molecular target for the treatment of motility disorders associated with intestinal inflammation.
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Abbreviations: 2-AG, 2-arachidonylglycerol; Δ^9-THC, tetrahydrocannabinol; LPS, lipopolysaccharide; NOS, nitric oxide synthase

Botanical preparations of *Cannabis sativa* (Indian hemp) have been widely used in the past to treat a variety of disorders including those affecting the digestive tract. In 1964, Δ^9-tetrahydrocannabinol (Δ^9-THC) was isolated, and was later shown to be responsible for many of the pharmacological actions of *Cannabis* preparations. The understanding of the mechanism by which marijuana exerts its pharmacological actions has seen considerable progress following the discovery in the early 1990s of specific membrane, G-protein-coupled receptors for Δ^9-THC, namely CB_1 receptors, expressed by central and peripheral nerves (including the enteric nervous system), and CB_2 receptors, which occur mainly in immune cells. The discovery of these receptors has led to the demonstration that there are endogenous agonists for these receptors. The best known are anandamide, 2-arachidonylglycerol (2-AG) (nonselective cannabinoid receptor agonists), noladin ether (CB_1 receptor agonist) and virodhamine (CB_1 receptor antagonist/CB_2 receptor agonist). When released, anandamide and 2-AG are removed from extracellular compartments by a carrier-mediated reuptake process, and once within the cell, both endocannabinoids are hydrolyzed by the enzyme fatty acid amide hydrolase (also named anandamide amidohydrolase). In addition to the two cannabinoid receptors, anandamide and 2-AG (both detected in the gut) can also activate vanilloid receptors, the molecular target for the pungent plant compound capsaicin (for a review, see De Petrocellis *et al*., 2004).

Several recent, independent investigations provide compelling evidence that cannabinoids reduce gastrointestinal motility through activation of enteric CB_1 receptors. Cannabinoid receptor agonists affect motility of isolated intestinal segments in a manner that resembles the neuromodulatory response to prejunctional μ-opioid receptor or α_2-adrenoceptor activation of cholinergic, postganglionic parasympathetic neurones. Thus, a number of cannabinoid receptor agonists (*via* CB_1 activation) have been shown to reduce or inhibit excitatory transmission, neural acetylcholine release and peristalsis efficiency in isolated intestinal segments. A functional evidence for the presence of prejunctional CB_1 in the human isolated ileum and colon, through which the cannabinoid receptor agonist WIN55,212-2 inhibited electrically evoked contractile responses, has also been demonstrated. Consistent with these *in vitro* studies, cannabinoid receptor agonists reduce gastric, small intestinal and colonic motility in rodents *in vivo*, an effect counteracted by the selective CB_1 receptor antagonist SR141716A, but not by the selective CB_2 receptor antagonist SR144528. Interestingly, a CB_1-mediated reduction of intestinal motility has been observed also in some pathophysiological states in mice, including the experimental ileus induced by intraperitoneal administration of acetic acid and the model of intestinal inflammation induced by oral croton oil (for a review, see Di Carlo & Izzo, 2003).

In this issue of the *British Journal of Pharmacology*, Mathison *et al*. (2004) provide pharmacological evidence that the CB_1-mediated reduction of gastrointestinal transit was absent in rats treated with an endotoxic inflammatory agent, being replaced by a CB_2-mediated inhibition of stimulated transit. It is reported that the selective CB_2 receptor agonist JWH-133 was without effect in control animals, but it reduced the increase in gastrointestinal transit induced by intraperitoneal administration of lipopolysaccharide (LPS). The effect of JWH-133 was dose dependent and it was prevented by the selective CB_2 receptor antagonist AM-630. Perhaps surprisingly, the selective CB_1 receptor agonist ACEA inhibited motility in control rats but it was without effect in mice treated with LPS. The authors hypothesised that the lack of effect of CB_1 receptor on LPS-stimulated gastrointestinal transit might reflect an inactivation of this receptor by this inflammatory

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stimulus. It is very unlikely that CB_2 receptors are tonically activated by endogenous cannabinoids in this model of intestinal inflammation, since the CB_2 antagonist alone was without effect in the LPS-induced increase in transit. Notably, it has been recently reported that endogenous cannabinoid anandamide exerts a protective role on cholera toxin-induced fluid accumulation *via* activation of overexpressed CB_1 receptors on enteric cholinergic nerves (Izzo *et al*., 2003).

To examine the role of putative mediators that might be involved in the inhibition of LPS-stimulated increase in gastrointestinal transit by CB_2 receptors, the authors evaluated a number of antagonists/inhibitors in the absence and presence of the CB_2 receptor agonist JWH-133. Based on these experiments, it was convincingly demonstrated that the CB_2 agonist acted *via* cyclooxygenase metabolites and independently of inducible nitric oxide synthase (NOS) and platelet-activating factor (PAF). Indeed, indomethacin completely abrogated the inhibitory effect of JWH-133, while the PAF receptor antagonist PCA 4248 or the inducible NOS inhibitor SATU did not modify JWH-133-induced motility changes. Preliminary evidence for the possible involvement of interleukin-1β or endothelial NOS was also provided. Based upon these results and the literature, it is hypothesized that cannabinoids act on CB_2 receptors expressed by inflammatory/immune and/or epithelial cells to inhibit the release of inflammatory mediators, which are known to stimulate intestinal peristalsis. Consistent with this scenario, Ihenetu and colleagues have recently reported that TNF-α-induced interleukin-8 release was inhibited by cannabinoids through activation of CB_2 receptors in human colonic epithelial cells, which are recognised to exert a major influence in the maintenance of intestinal immune homeostasis (Ihenetu *et al*., 2003).

The potential therapeutic value of such findings seems to be relevant. Activation of CB_2 receptors represents a novel mechanism for the re-establishment of normal gastrointestinal transit after an inflammatory stimulus. The strategy to use selective CB_2 receptor agonists for the treatment of hypermotility during inflammatory bowel diseases is highly promising because it is likely to be devoid of the well-known *Cannabis* unwanted effects (e.g. sedation, cognitive dysfunction, ataxia and psychotropic effects), which are due to activation of brain CB_1 receptors. Also, it will be interesting to see in future studies whether a CB_2 mechanism exists to protect the gut from the fluid hypersecretion and mucosal damage associated to endotoxic inflammation. Clearly, further exploration of the role of CB_2 receptors in the gut is likely to produce worthwhile results.

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