British Journal of Pharmacology (2008) 154, 1163–1165
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0007–1188/08 $30.00
www.brjpharmacol.org

COMMENTARY

Therapeutic options in inflammatory bowel disease: experimental evidence of a beneficial effect of kinin B_1 receptor blockade

F Marceau[1] and D Regoli[2]

[1]*Centre de Recherche en Rhumatologie et Immunologie, Centre Hospitalier Universitaire de Québec, Québec, Canada and*
[2]*Department of Clinical and Experimental Medicine, Faculty of Medicine, University of Ferrara, Ferrara, Italy*

A surprising proportion of patients with inflammatory bowel disease (IBD) remain refractory to all classes of drugs presently in clinical use. Kinins are inflammatory mediators of potential relevance in IBD, because at least the kinin B_1 receptor subtype is upregulated in human or animal intestinal inflammation and also both B_1 and B_2 receptors for kinins support inflammation and epithelial electrogenic ion transport that leads to secretory diarrhoea. In this issue of the *BJP*, Hara *et al.* report the therapeutic effect of a modern and selective nonpeptide kinin B_1 receptor antagonist, SSR240612 ((2*R*)-2-(((3*R*)-3-(1,3-benzodioxol-5-yl)-3-(((6-methoxy-2-naphthyl)sulphonyl)amino)propanoyl)amino)-3-(4-((2*R*,6*S*)-2,6-dimethylpiperidinyl)methyl)phenyl)-*N*-isopropyl-*N*-methylpropanamide hydrochloride), with benefits such as decreased neutrophil influx and improved macroscopic tissue scoring. The results were corroborated using kinin B_1 receptor gene-knockout mice. Further, kinin B_1 receptor upregulation in this inflammatory model is partially dependent on TNF-α, a recognized target for IBD pharmacotherapy. More work is warranted to evaluate the value of the kinin B_1 receptor antagonists as a novel anti-inflammatory therapeutic option for IBD.
British Journal of Pharmacology (2008) **154,** 1163–1165; doi:10.1038/bjp.2008.233; published online 9 June 2008

Keywords: kinin B_1 receptor; bradykinin B_2 receptor; inflammatory bowel disease

Abbreviations: IBD, inflammatory bowel disease; SSR240612, (2*R*)-2-(((3*R*)-3-(1,3-benzodioxol-5-yl)-3-(((6-methoxy-2-naphthyl)sulphonyl)amino)propanoyl)amino)-3-(4-((2*R*,6*S*)-2,6-dimethylpiperidinyl)methyl)phenyl)-*N*-isopropyl-*N*-methylpropanamide hydrochloride; TNF-α, tumour necrosis factor-α

Approximately 1.4 million persons in the United States of America and 2.2 million individuals in Europe suffer from inflammatory bowel disease (IBD, ulcerative proctitis/colitis, Crohn's disease; Loftus, 2004). IBD remains a therapeutic challenge because a surprisingly large proportion of patients do not benefit from available treatments, including corticosteroids, immunosuppressive drugs, 5-aminosalicylate and its derivatives, and recent biotechnological proteins (Katz, 2007). The objectives of IBD pharmacotherapy may be more or less comprehensive and include symptomatic relief, induction of clinical remission, inhibition of nutritional deficit and growth retardation in affected children, healing and prevention of fistulas and the prevention of long-term complications such as colon carcinoma.

The kallikrein–kinin system consists of circulating kininogens, the proteolytic enzymes kallikreins, kinins (bradykinin-related peptides, which are produced through the cleavage of kininogens by kallikreins) and two G-protein-coupled receptors termed kinin B_1 and bradykinin B_2 receptors, which mediate the biological effects of kinins (Leeb-Lundberg *et al.*, 2005; Alexander *et al.*, 2008). Endogenous kinins exhibit a double pharmacological personality: they are vasodilators that may be recruited in stressful situations, such as renal ischemia (Kakoki *et al.*, 2007), and, usually via bradykinin B_2 receptors constitutively expressed in endothelial cells, release nitric oxide and other negative regulators of vascular smooth muscle tone and platelet function. ACE is a major kinin-destroying enzyme and protection of endogenous kinins may account for some part of the beneficial effects of ACE inhibitors (Leeb-Lundberg *et al.*, 2005). However, kinins also reproduce all four cardinal signs of inflammation when injected into tissues and thus qualify as mediators of inflammation. In that context, the kinin B_1 receptor is

Correspondence: Professor Dr F Marceau, Centre de Recherche, Centre Hospitalier Universitaire de Québec, Room T1-49, 2705 Laurier Boulevard, Québec City, Québec, Canada G1V 4G2.
E-mail: francois.marceau@crchul.ulaval.ca
Received 7 May 2008; revised 12 May 2008; accepted 13 May 2008; published online 9 June 2008

usually absent from healthy tissues, but is inducible following tissue injury under the action of cytokines and other agents, such as bacterial lipopolysaccharide (Leeb-Lundberg *et al*., 2005).

Despite the intensive work to develop effective peptide and non-peptide kinin receptor antagonists in the last decades, the clinical impact of these agents is still minimal. Icatibant, a peptide antagonist of bradykinin B_2 receptors, is now a recognized therapeutic option in a rare congenital disease, hereditary angioedema, where endogenous bradykinin is clearly inflammatory (Bernstein, 2008). Medicinal chemistry efforts have been particularly targeted at producing analgesic drugs, both B_1 and B_2 kinin receptor antagonists showing activity in animals, but a clinically useful drug from these classes is yet to emerge. Kinins are potentially significant mediators of IBD: both B_1 and B_2 receptors for kinins have been immunolocalized in the epithelial cells of affected human intestinal tissue; the kinin B_1 receptor was constitutively expressed in normal colonic epithelium, possibly because the normal bacterial flora activates the innate immune system, but was upregulated by inflammation (at least at the level of the protein; Stadnicki *et al*., 2005). Further, kinin B_1 receptor expression was extended to macrophages present in granulomas (Stadnicki *et al*., 2005; Figure 1). In relation to a prominent symptom of IBD, both inducible B_1 and constitutive B_2 basolateral kinin receptors support the electrogenic ion transport in intestinal epithelium, the luminal secretion of Cl^- being accompanied with that of Na^+ and water, thus leading to secretory diarrhoea (Cuthbert, 2001). The effects of kinins were largely prostaglandin-independent in this system. As the kinin B_1 receptor is more resistant to functional desensitization than the bradykinin B_2 receptor, the participation of the former was felt to be more likely in the genesis of clinically significant diarrhoeal states (Cuthbert, 2001).

In this issue of the *BJP*, Hara *et al*. (2008) report the therapeutic action of a non-peptide and orally bio-available antagonist of the kinin B_1 receptors, SSR240612, in a mouse model of colitis. The drug treatment reduced polymorphonuclear leukocyte influx, improved the macroscopic tissue damage score and had favourable effects, both in preventing colitis induced by 2,4,6-trinitrobenzene sulphonic acid and alleviating the inflammation in established colitis. Importantly, the results were corroborated by exploiting kinin B_1 receptor gene-knockout mice that are partially refractory to this model of colitis. Hara *et al*. (2008) also studied kinin B_1 receptor upregulation in the tissue; interestingly, the radioligand-binding assay applied to colonic membranes showed the inflammation-induced upregulation of kinin B_1 receptors, but from a significant control baseline population. On the other hand, the freshly isolated control colonic smooth muscle did not contract in response to the kinin B_1 receptor agonist des-Arg^9-bradykinin, whereas the inflamed tissues were responsive. The binding assay may reveal the constitutive kinin B_1 receptors in the colonic epithelium, as in human tissues (Stadnicki *et al*., 2005), but transmural inflammation may be needed to induce the expression of these receptors in the underlying smooth muscle cells (Figure 1). Additional findings include a significant role for

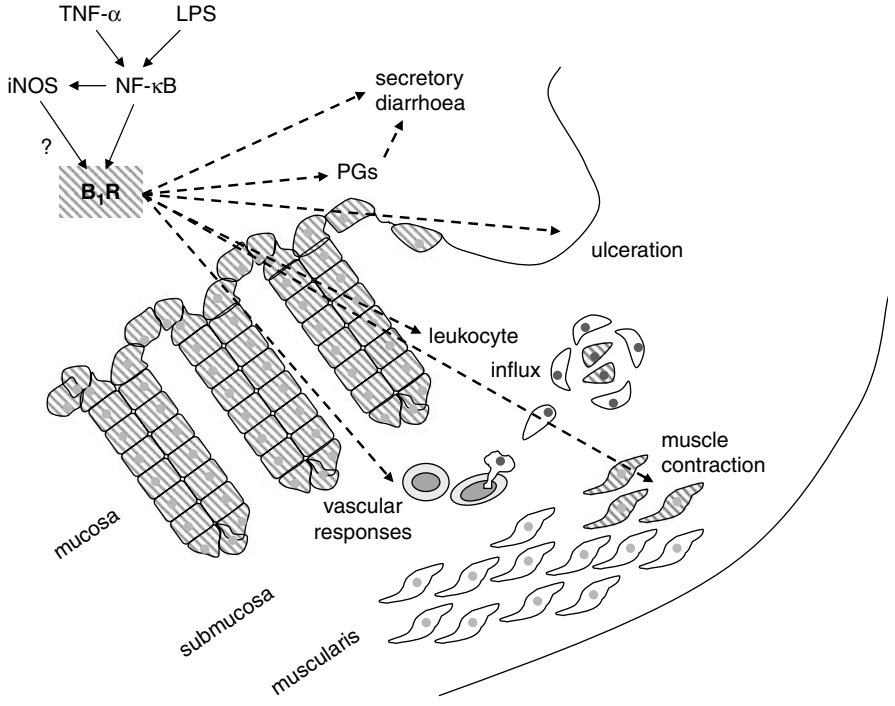

Figure 1 Schematic representation of the mechanisms of kinin B_1 receptor induction (solid arrows) and its functions (dashed arrows) in colonic inflammation, according to Hara *et al*. (2008) and other sources. The hatched surface is the symbol for kinin B_1 receptor presence in cells. B_1R, kinin B_1 receptor; iNOS, inducible NOS; LPS, lipopolysaccharide; NF-κB, nuclear factor κ-B; PGs, prostaglandins.

tumour necrosis factor-α (TNF-α) and its receptor in the expression of the kinin B_1 receptor in murine colon, as TNF-α is a recognized target for therapy in IBD (Katz, 2007). The documented therapeutic effects of anti-TNF-α agents, such as infliximab, in IBD may derive in part from the repression of kinin B_1 receptor expression. Thus, the experimental system shows robust anti-inflammatory effects of a modern and selective kinin B_1 receptor antagonist in a model of IBD (Hara *et al*., 2008). Among unresolved issues, the therapeutic place of bradykinin B_2 receptor antagonists has not been addressed, but it may be significant, as this receptor type is also upregulated in the same murine model (Hara *et al*., 2007).

In this post-Vioxx era, who will dare to develop kinin receptor antagonists as anti-inflammatory drugs in IBD? The potentially salutary effect of kinins in the peripheral circulation may discourage systemic treatments with kinin receptor antagonists (although predictable safety issues are less clear for kinin B_1 receptor antagonists). On the other hand, drug delivery to the intestine may exploit topical or galenic forms that minimize systemic distribution, as for 5-aminosalicylate and its derivatives. Further, despite the fact that almost all kinin receptor antagonists developed so far exhibit a strong selectivity for one of the two receptor subtypes, there are prototypes of drugs that block both. An example is the non-peptide Compound 1 from the studies of Ritchie *et al*. (2004), a balanced B_1 and B_2 kinin receptor antagonist. Therefore, more work is warranted to evaluate the value of the novel anti-inflammatory therapeutic option for IBD offered by the kinin receptor antagonists.

Acknowledgements

FM is supported by the Canadian Institutes of Health Research.

Conflict of interest

The authors state no conflict of interest.

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