Gut

Leading article

Some of the challenges in drug development for irritable bowel syndrome

If one accepts the concept that enhanced perception of visceral stimuli plays an important role in the pathophysiology of irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (and not everybody does![1,2]), identification of drugs which can normalise this enhanced perception should be a major effort in the search for effective IBS medications. Enhanced perception of different physiologically occurring gut stimuli can result from numerous mechanisms, including such fundamentally different but possibly interrelated processes as changes in sensory transmission (in the periphery or centrally), alterations in endogenous pain modulation, or even changes in gut directed attentional mechanisms.[3] Any of these mechanisms alone or in combination could produce some of the most prevalent clinical manifestations of visceral hypersensitivity in IBS: sensations of abdominal fullness (in the absence of excessive distension), abdominal pain (in the absence of detectable tissue injury), sigmoid tenderness during palpation or during endoscopic examination, or the sensation of incomplete rectal evacuation (in the absence of a full rectum).

Based on several studies in the rat, demonstrating that acute mucosal inflammation can produce sensitisation of primary afferents as well as dorsal horn neurones thereby resulting in acute visceral hyperalgesia,[3] the concept of targeting and testing candidate drugs for their visceroanalgesic potential has been widely accepted as a worthwhile endeavour by industry and academia alike.[4] The strategies pursued by optimists in this field are variations of the following sequence: (1) identify receptors or ion channels on visceral afferent neurones; (2) select compounds targeted at these membrane proteins; (3) evaluate candidate compounds for their ability to reduce behavioural responses of the rat or other rodents to colorectal distension (ideally in the normal colon and following some type of acute sensitisation); (4) evaluate if the compound has visceroanalgesic properties on unit activity of single afferent nerve fibres; and (5) take the compound into clinical testing. (The pessimists would say IBS is a psychosomatic disease which is not amenable to pharmacological treatment and results obtained from studies in rats cannot be extrapolated to humans.) For example, an approach as outlined above has been taken for kappa opioid agonists[5–7] and 5-HT$_3$ receptor antagonists.[8] Based on such studies, both compounds have been proposed as peripherally acting visceral analgesics which can relieve visceral hypersensitivity in IBS. Even though such a view may be attractive from a marketing standpoint, it may not be the whole story. Ironically, the first of these compounds demonstrated impressive visceroanalgesic and antihyperalgesic effects in the rat and in one study in humans, but was

ineffective in relieving IBS symptoms. For the 5-HT$_3$ receptor antagonist it was the other way around: visceroanalgesic properties of the compound in the true sense of the word were never demonstrated in the human colon,[9] even though it was highly effective in relieving key IBS symptoms.[10] All too often it is ignored that candidate compounds have peripheral *and* central effects, which may be important to explain their beneficial effects in treating IBS patients. A good example to illustrate this point are the opioids: mu opioid receptors are present on multiple peripheral and central neurones, including vagal and spinal afferents, on neurones in the superficial dorsal horn, medulla, locus coeruleus, amygdala, and anterior cingulate cortex. Following peripheral administration of a mu opioid receptor agonist, analgesia and antihyperalgesia result from the integrated effect of the compound on pain transmission, pain modulation, and modulation of attentional, emotional, and autonomic mechanisms.

The non-specific somatostatin receptor (SSTR) octreotide has also gone through some of the steps outlined above. Even though there is some anecdotal evidence and theoretical reasons to suggest that this compound (or more specific SSTR agonists) may be beneficial in the treatment of visceral pain, the mechanism(s) by which SSTR agonists might relieve clinical manifestations of IBS symptoms is not known. Based on preclinical and clinical studies, different laboratories have postulated a peripheral[11–15] or spinal[16,17] mechanism of action. In this issue of *Gut*, Su and colleagues[18] present convincing evidence that in the rat, octreotide, a non-selective SSTR agonist which interacts with the SST receptor subtypes 2, 3, and 5, does not affect pelvic nerve activation by colorectal distension, regardless of whether the colon is in a physiological or acutely inflamed state (see page 676). In contrast, and in agreement with several other preclinical and clinical studies, intrathecal administration of the compound has clear analgesic properties. Readers of this article, including investigators in the pharmaceutical industry who have selective SSTR agonists on their shelves and who are more than eager to develop an effective IBS drug, might ask two questions: do these results allow us to conclude that when octreotide was given to humans, the effect was also mediated by SSTRs in the spinal cord and not on afferent nerve terminals in the gut, or on supraspinal sites, such as the anterior cingulate cortex or the locus coeruleus? Do these studies provide any evidence to suggest that SSTR agonists may be useful in the treatment of IBS symptoms? Any

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Abbreviations used in this paper: IBS, irritable bowel syndrome; SSTR, somatostatin receptor.

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attempt to answer these questions runs into the difficulties which are so characteristic of this field of drug development.

The reported clinical studies which attempted to determine the mechanism of action underlying the visceroanalgesic effect of octreotide have raised more questions than answers. For example, investigators from Michigan interpreted their data obtained from studies using rectal balloon distension[11] and electrical stimulation of the rectum[15] to suggest an effect of subcutaneous octreotide on peripheral visceral (but not somatic) afferent pathways. An alternative interpretation of these data suggests that in both healthy controls and particularly in diarrhoea predominant IBS patients,[19] peripherally administered octreotide had no direct analgesic effect on visceral afferents as the compound increased primarily volume but not pressure thresholds in both studies. This interpretation would be similar to the conclusion reached from a careful analysis of studies evaluating the possible effects of alosetron on perception of visceral stimuli in human subjects.[9] In contrast, Plourde *et al* demonstrated that even though octreotide administered in the same way and dose as in the Michigan studies had no effect on rectal compliance, the compound selectively attenuated perceptual responses to slow rectal distension but had no effect on phasic distension.[13] The authors speculated that the compound acts on a subset of rectal afferent nerves with receptive fields in the mucosa. A third group reported that octreotide increased the threshold of colonic visceral perception in IBS patients without modifying smooth muscle tone.[12] As peripherally administered octreotide is unlikely to cross the blood-brain barrier in any significant amounts, the only conclusions from published studies are that octreotide acts on some type of afferent nerves (vagal, splanchnic, parasympathetic) innervating the colorectum, that it exerts its effect through central sites unprotected by the blood-brain barrier, or that similar to opioid agonists, it exerts an indirect central effect via activation of certain vagal afferents.

How might an agonist of somatostatin receptors attenuate the enhanced perception of visceral stimuli and thereby (hopefully) prove therapeutic for IBS symptoms? Of the five cloned SST receptors, the SST2 receptor with its two splice variants ($SST_{2A/B}$) is a plausible target for such a therapeutic compound. The distribution of these receptors in CNS regions[20] implicated in the pathophysiology of IBS, including the anterior cingulate cortex, locus coeruleus, amygdala, and superficial layers of the spinal dorsal horn,[21] makes them attractive targets for drug development. Similar to the effect of opioids, a treatment response in patients may involve multiple components, such as analgesic, anti-hyperalgesic effects, as well as effects on the attentional and emotional aspects of chronic pain and discomfort.

In summary, the study by Su and colleagues[18] in this issue of *Gut* highlights many of the difficulties that have plagued drug development in the area of functional gastrointestinal disorders. Even though clinically there is good evidence that enhanced perception of visceral events plays an important role in IBS symptom development, the site(s) and mechanism(s) of this hypersensitivity and its relationship to clinical symptoms remain incompletely understood.[22] Furthermore, it remains unknown if results obtained with colorectal distension studies in the rat can always be extrapolated to humans. For example, while this might be true for a mu opioid agonist, it may not be the case for an NK1 receptor antagonist. Finally, as the intestinal tract is innervated by three different types of extrinsic afferents and at least three types of intrinsic afferent neurones, it remains to be determined if a visceroanalgesic effect, which has been ruled out for one of these pathways (for example, for pelvic nerve afferents as in Su's study), necessarily means that the drug does not have an alternative peripheral site of action in modulating perception of visceral stimuli.

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1 Whitehead WE, Palsson OS. Is rectal pain sensitivity a biological marker for irritable bowel syndrome: Psychological influences on pain perception. *Gastroenterology* 1998;**115**:1263–71.
2 Camilleri M, Coulie B, Tack JF. Visceral hypersensitivity: facts, speculations, and challenges. *Gut* 2001;**48**:125–31.
3 Mayer EA, Gebhart GF. Basic and clinical aspects of visceral hyperalgesia. *Gastroenterology* 1994;**107**:271–93.
4 Bueno L, Fioramonti J, Delvaux M, *et al*. Mediators and pharmacology of visceral hypersensitivity: From basic to clinical investigations. *Gastroenterology* 1997;**112**:1714–43.
5 Bonaz B, Rivière PJM, Sinniger V, *et al*. Fedotozine, a kappa-opioid agonist, prevents spinal and supra-spinal Fos expression induced by a noxious visceral stimulus in the rat. *Neurogastroenterol Motil* 2000;**12**:135–47.
6 Sengupta JN, Snider A, Su X, *et al*. Effects of kappa opioids in the inflamed rat colon. *Pain* 1999;**79**:175–85.
7 Delvaux MM, Louvel D, Lagier E, *et al*. The kappa agonist fedotozine relieves hypersensitivity to colonic distension in patients with irritable bowel syndrome. *Gastroenterology* 1999;**116**:38–45.
8 Irritable bowel syndrome and the role of 5-HT. *Aliment Pharmacol Ther* 1999;**13**(suppl 2):1–82.
9 Delvaux M, Louvel D, Mamet JP, *et al*. Effect of alosetron on responses to colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 1998;**12**:849–55.
10 Camilleri M, Northcutt AR, Kong S, *et al*. Efficacy and safety of alosetron in women with irritable bowel syndrome: A randomised placebo-controlled trial. *Lancet* 2000;**355**:1035–40.
11 Hasler WL, Soudah HC, Owyang C. A somatostatin analogue inhibits afferent pathways mediating perception of rectal distention. *Gastroenterology* 1993;**104**:1390–7.
12 Bradette M, Delvaux M, Staumont G, *et al*. Octreotide increases thesholds of colonic visceral perception in IBS patients without modifying muscle tone. *Dig Dis Sci* 1994;**39**:1171–8.
13 Plourde V, Lembo T, Shui Z, *et al*. Effects of the somatostatin analogue octreotide on rectal afferent nerves in humans. *Am J Physiol* 1993;**265**: G742–51.
14 Heppelmann B, Pawlak M. Inhibitory effect of somatostatin on the mechanosensitivity of articular afferents in normal and inflamed knee joints of the rat. *Pain* 1997;**73**:377–82.
15 Chey WD, Beydoun A, Roberts DJ, *et al*. Octreotide reduces perception of rectal electrical stimulation by spinal afferent pathway inhibition. *Am J Physiol* 1995;**269**:G821–6.
16 Penn RD, Paice JA, Kroin JS. Octreotide: a potent new non-opiate analgesic for intrathecal infusion. *Pain* 1992;**49**:13–19.
17 Paice JA, Penn RD, Kroin JS. Intrathecal octreotide for relief of intractable nonmalignant pain: 5-year experience with two cases. *Neurosurgery* 1996;**38**:203–7.
18 Su W, Burton MB, Gebhart GF. Effects of octreotide on responses to colorectal distension in the rat. *Gut* 2001;**48**:676–82.
19 Hasler WL, Soudah HC, Owyang C. Somatostatin analog inhibits afferent response to rectal distension in diarrhea-predominant irritable bowel patients. *J Pharmacol Exp Ther* 1994;**268**:1206–11.
20 Schindler M, Humphrey PP, Emson PC. Somatostatin receptors in the central nervous system. *Progr Neurobiol* 1996;**50**:9–47.
21 Mayer EA. Emerging disease model for functional gastrointestinal disorders. *Am J Med* 1999;**107**:12–19S.
22 Naliboff BD, Chang L, Munakata J, *et al*. Towards an integrative model of irritable bowel syndrome. In: Mayer EA, Saper CB, eds. *The Biological Basis for Mind Body Interactions*. Amsterdam: Elsevier Science, 2000:413–23.