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Visceral analgesics: drugs with a great potential in functional disorders?⋆

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Abstract

Irritable bowel syndrome remains an incompletely understood, common syndrome with significant unmet medical needs. In IBS patients, abdominal pain is a primary factor related to quality of life impairment, symptom severity and health care utilization, and chronic visceral hyperalgesia has been identified as an important aspect of IBS pathophysiology. However, the development of therapies aimed at reducing this hyperalgesia (visceral analgesics) has been only partially successful despite preclinical evidence supporting the potential usefulness of several preclinical compounds aimed at peripheral as well as central targets.

Introduction

Abdominal pain and discomfort in the absence of detectable organic disease are the hallmark of functional GI disorders (FGIDs). When such symptoms are referred to the lower abdomen and are associated with altered bowel habits, they make up the symptom complex of irritable bowel syndrome (IBS). Efforts during the past decade to develop highly effective drugs to treat patients with IBS have largely been disappointing. Although several novel treatments aimed at normalizing bowel movements have been developed recently, the overall effect of such therapies on patients' well being and quality of life is relatively small, with an effect size over placebo generally not above 15%.

An alternative approach in the drug development efforts for FGID has targeted the abdominal pain component of the syndrome. Visceral hypersensitivity, determined experimentally in patients (as increased perceptual ratings of controlled visceral distension) and in animal models (as pseudo affective reflex responses), has been considered as a reliable marker of the disease [1••]. Even though there is only a modest correlation between experimentally determined colorectal sensitivity in rodent models and perceptual sensitivity to rectal distension in human subjects, and between the latter and IBS symptoms [2], the traditional approach to the

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development of new visceral analgesics has used a translational strategy to take candidate compounds from rodent models to human sensitivity testing. Candidate compounds are either molecules which had been developed for other targets (e.g. motility modulators such as tegaserod or alosetron; or centrally acting drugs such as serotonin-specific reuptake inhibitors [SSRIs]), or molecules specifically developed to target membrane receptors or ion channels on visceral afferent pathways which play a role in visceral mechanotransduction and which may be upregulated in models of visceral hyperalgesia. Ideally, candidate drugs should have no analgesic effects (e.g. not affect normal afferent sensitivity) but only antihyperalgesic effects (e.g. normalize enhanced visceral sensitivity). One major challenge in the development of visceral analgesics for IBS therapy is the fact that three major questions remain unanswered: Firstly, is the primary abnormality that leads to the observed enhanced perception of visceral signals, first, increased peripheral encoding and transduction of stimuli, second, central pain amplification or third, both? Secondly, are drugs specifically targeted at peripheral afferent mechanisms (analgesics or antihyperalgesics) relevant for effective IBS therapy? Thirdly, are drugs aimed at reducing central pain amplification relevant for IBS therapy?

Drugs and treatments in clinical development

Serotonin receptor modulators—The serotonin (5-HT) signaling system is widely distributed within the brain–gut axis and with potential effects on visceral afferent pathways and central pain modulation mechanisms [3••]. Several agents targeting various 5-HT receptors have been developed as modulatory agents of gut functions, including viscerosensory functions, though the precise roles of the various 5-HT-related mechanisms in IBS pathophysiology remain to be established.

5-HT$_3$-receptor antagonists: 5-HT$_3$Rs are expressed on subsets of neurons intrinsic to the enteric nervous system including intrinsic primary afferent neurons (IPANs), as well as on extrinsic primary afferents (EPANs; both spinal and vagal afferents). Several 5-HT3Rs antagonists have been developed for the treatment of diarrhea-predominant IBS (IBS-D), and unequivocal evidence for their clinical effectiveness in treating several IBS symptoms, including diarrhea and abdominal pain has been reported (reviewed in Ref. [4]). The mechanism(s) by which abdominal pain and discomfort are reduced remains to be determined, but are unlikely due to a peripheral visceral analgesic effect as originally suggested. They may involve attenuating effects on central targets in the brain and spinal cord [5], while peripheral receptors on vagal afferents may actually mediate pronociceptive effects. Owing to rare but potentially serious side effects (ischemic colitis and severe constipation), the first such drug approved for use in female IBS patients with diarrhea (alosetron) is only available within a restricted access program. Two newer compounds, a selective 5-HT3R antagonist (DPP-733) and a combined norepinephrine (NE) reuptake inhibitor and 5-HT3R antagonist (NARI) have been evaluated in small clinical trials in IBS and preliminary results have been presented in abstract form [6,7]. Efforts aimed at understanding the mechanisms underlying the side effects of ischemic colitis and severe constipation, and the role of several receptor subtypes located on different intestinal and neuronal cells have only been partially successful.

5-HT$_4$R agonists—Although there is extensive clinical and preclinical evidence that serotonin [8], via 5-HT4Rs, plays a pivotal role in the modulation of gastrointestinal motor function, a possible role of 5-HT4Rs in the modulation of visceral afferent function remains controversial. Some preclinical [8] and clinical evidence [9] suggest that the partial 5-HT4R agonist tegaserod may exert a modulatory effect on visceral afferent pathways. It remains to be determined if these effects are mediated by 5-HT4 receptors or other 5-HT receptor subtypes, such as the 5-HT2 receptors. The marketing of tegaserod, the first commercially available 5-HT4 receptor agonist, was suspended in March 2007, when an analysis of the data from clinical trials identified a significant increase in the number of cardiovascular ischemic events

(myocardial infarction, stroke, and unstable angina) in patients taking the drug [10]. The possible visceral analgesic effect of more specific and more potent, full agonists of the 5-HT4R receptors as well as mixed 5-HT4R agonist and 5-HT3R antagonist activities have not been reported.

Probiotics—Beneficial effects of probiotics on gastrointestinal functions have been proposed based on their ability to modulate pathogenic bacteria adherence, enhance barrier function of the epithelium, alter mucosal response to stress as well as from their immunomodulatory properties. Evidence for possible antihyperalgesic effect of probiotics has been reported in several animal models. For example, the administration of *Escherichia coli* Nissle 1917 (EcN) was found to reduce TNBS (2,4,4-trinitrobenzenesulfonic acid) colitis associated with visceral hyperalgesia in rats [11], while *Lactobacillus paracasei* reduced the visceral hyperalgesia associated with antibiotic-induced inflammation in healthy mice [12]. A modulatory role of *L. paracasei* on the synthesis of neuro-peptides involved in nociception was suggested in this effect. Similarly, *L. paracasei* was found to reduce visceral hyperalgesia in response to restraint stress in rats [13]. Interestingly, oral administration of *Lactobacillus acidophilus* produced both visceral analgesic and antihyperalgesic effects in rats, and these behavioral changes were associated with the increased expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells, suggesting a mechanism of action different from anti-inflammatory properties [14•]. At the clinical level, whereas increasing data have emerged on the potential beneficial role of probiotics in IBS [15•,16–18], inadequate reporting of trial methodology and the assessment of poorly defined composite endpoint generally used in these studies, which includes nonpainful discomfort such as bloating, makes it difficult to reach definitive conclusions on true visceroanalgesic effects of probiotics in human patients.

Adrenoceptor (AR) modulators—Similar to 5-HT receptors, αARs are widely distributed within the brain–gut axis and have the potential to modulate sensitivity of visceral afferents, spinal cord transmission, and central pain modulation [19]. There is evidence of sympathetic nervous system dysfunction in a subgroup of patients with IBS [20]. Converging evidence suggest a role for abnormal noradrenergic signaling involving αARs in patients with chronic functional pain, including IBS.

Alpha$_2$-adrenoceptor agonists: The α_2ARs agonist clonidine reduced the perception of colonic or rectal balloon distension in healthy volunteers. As this effect was associated with colonic and rectal wall relaxation, no direct visceroanalgesic effect was demonstrated [21]. In an exploratory RCT of clonidine in IBS-D patients, clonidine was associated with satisfactory symptoms relief compared to placebo [22]. No data on more selective agonists for treatment in IBS have been reported till date.

Beta$_3$-adrenoceptor agonists: Beta$_3$-adrenoceptors (β_3-AR) have been under investigation as novel targets for functional gastrointestinal disorders in which abdominal discomfort and pain are key features. In a rat model of visceral pain induced by intracolonic mustard oil, the β_3-AR agonist elicited somatostatin-dependent visceral analgesia [23]. In addition, in view of several older reports on the visceroanalgesic effect of the somatostatin analog octreotide in human subjects [24] and the preliminary results about a favorable effect on IBS symptoms [25], this class of drug holds promise for IBS therapy.

CRF$_1$R antagonists—Extensive preclinical evidence supports an important role of the brain CRF-CRF$_1$R signaling system in mediating the endocrine, autonomic, behavioral, and pain modulatory responses to stress, suggesting that these receptors might be an ideal target in the context of functional bowel disorders [26]. Specifically, consistent antihyperalgesic effects of CRF$_1$R antagonism on stress-induced visceral hyperalgesia has been demonstrated in different

stress models in rats [27–30]. In humans, a recent study from Sagami *et al*. reported an inhibitory effect of intravenous injection of the CRF-receptor antagonist α-helical CRF9–41 on abdominal pain and anxiety scores in a model of colonic distension and electrical stimulation of the rectal mucosa in IBS-D patients [31]. As this compound is not thought to cross the blood–brain barrier, the findings suggest the possibility that antagonism of peripheral CRF_1R may have therapeutic effects in IBS patients. Additional evidence for a peripheral role of CRF in IBS comes from a recent study in which peripheral administration of a CRF antagonist, α-helical CRH9–41 (αhCRF) in IBS patients improved decreased alpha power spectra and increased beta power spectra of electroencephalogram (EEG) in response to colonic distension, compared with controls [32]. By contrast, a recent preliminary report on a clinical trial in female IBS-D patients with the selective CRF_1R antagonist Bms-562086 did not show any significant effects on IBS symptoms (GI transit and bowel habits) [33]. It remains to be determined if the strong preclinical evidence supporting the usefulness of CRF_1R antagonists in reversing stress-induced visceral hyperalgesia in rodents will translate into therapeutic efficacy in IBS patients, reducing symptoms of abdominal pain and discomfort.

Kappa opioid receptor agonists—Fedotozine is a κ opioid receptor (KOR) preferring agonist for which a peripheral antinociceptive mechanism of action had been proposed based on several studies in rodent models [34]. However, a series of elegant studies from G. Gebhart's laboratory demonstrated that the apparent visceroanalgesic effect of these compounds was mediated by a combination of inhibition of Na channels on primary afferents together with central effects on MOR and KORs [35]. Even though a small number of phase IIa studies in IBS patients suggested a possible visceral analgesic effect [36], the majority of human studies, including two well-designed phase IIb studies were negative and further development of this compound was discontinued. Asimadoline, a different KOR agonist, failed to reduce the severity of abdominal pain in IBS patients with on-demand dosing schedule [37]. However, in a recent large (596 patients), randomized, placebo-controlled, 12-week, dose-ranging (0.15, 0.5, or 1.0 mg tablets, b.i.d.) study [38], asimadoline (0.5 mg) produced significant improvement on total number of months with adequate relief of IBS pain or discomfort (46.7% versus 20.0%), pain scores (week 12: −1.6 versus −0.7), and pain free days (42.9% versus 18.0%), in IBS-D patients with at least average moderate pain. Despite the encouraging recent clinical data, several questions remain: First, is the beneficial effect of asimadoline mediated by an effect on peripheral KOR on visceral afferents, or does it involve effects on other peripheral targets, such as Na channels? Second, is there a central component to the drug's effectiveness and is it mediated by central opioid receptors? Third, what is the therapeutic window, between antagonism of peripheral KOR and the development of side effects mediated by central KOR, in particular dysphoria and diuresis.

Antidepressants—Preclinical and clinical evidence supports the effectiveness of tricyclic antidepressants (TCAs) in neuropathic pain [39]. In addition, the effect of SSRIs and particularly norepinephrine (NE)–serotonin (5-HT) reuptake inhibitor (NSRI) on enhancing the effectiveness of endogenous pain inhibition systems has been suggested. Despite the attractive rationale for using these centrally acting drugs in IBS patients, strong supportive evidence from well-designed clinical trials in IBS patients is currently not available. This is in contrast to the well-documented clinical effectiveness of both TCAs and NSRIs in the treatment of other chronic pain conditions [40•].

Low-dose tricyclic antidepressants: TCAs, although not FDA approved for IBS, are frequently used to treat IBS and while several randomized, placebo-controlled trials have supported the use of low-dose TCAs in the treatment of IBS patients [41], a systematic review of TCA trials for IBS failed to observe a beneficial effect of TCA on global IBS symptoms or abdominal pain, mainly because of insufficient statistical power (although they were effective

against depressive and anxiety symptoms) [42]. In a large randomized 12-week placebo-controlled trial including 431 female adult patients, it was found that desipramine (150 mg/day) was not superior to placebo in the intention-to-treat analysis (probably linked to a high dropout rate due to side effects) [43]. It is unclear whether TCAs, in particular at doses greater than 50 mg qd act by influencing mood or anxiety or through an analgesic effect. It is also unclear whether their efficacy in IBS is owing to their effect not only on reuptake inhibition but also on their postsynaptic receptors. Chronic intake of low-dose amitriptyline has been shown to alter CNS processing of visceral sensory information during stressful conditions [44].

Selective and nonselective monoamine uptake inhibitors: SSRIs may have beneficial effect in IBS patients through central effects by reducing both anxiety and pain, yet, their efficacy for IBS remains to be confirmed. Both animal and human studies have indicated an analgesic effect of SSRIs in chronic pain conditions and it has been suggested that the improvement seen in IBS trials (only few randomized controlled trials) mainly relates to increase in overall well being and improvement of extra-intestinal symptoms rather than specific gut-related dysfunctions [45]. In a wide randomized, multicenter, controlled study comparing the effect of paroxetine, with psychotherapy and routine treatment care, the severity and frequency of abdominal pain improved in both the paroxetine and psychotherapy groups; but showed no statistically significant improvement when compared with routine treatment of care [46]. Newer monoamine reuptake inhibitors, such as the 5-HT and NE reuptake inhibitors (SNRIs) duloxetine and venlafaxine have been proposed as more effective treatments for chronic pain conditions associated with depression, and while they have been evaluated in patients with painful diabetic neuropathy [47] and fibromyalgia [48], their effect in IBS remain to be evaluated.

In summary, although a visceral analgesic effect of antidepressants has been demonstrated in animal models [49] supportive evidence from well-designed clinical trials in IBS patients is currently not available.

Pregabalin—Pregabalin (Lyrica), is a second-generation α2δ ligand that is approved for the treatment of neuropathic pain and epilepsy. Although its mechanism of action for pain relief remains unclear, it is believed to bind potently to the two auxiliary proteins associated with voltage-gated calcium channels, reducing depolarization-induced calcium influx at the nerve terminals, and consequently reducing the release of several excitatory neurotransmitters [50]. In animal models, pregabalin has been shown to be effective at reducing TNBS or LPS (lipopolysaccharide)-induced visceral hyperalgesia [51,52]. In a recent randomized, double-blind, placebo-controlled clinical trial in IBS patients, three weeks of oral treatment with pregabalin normalized the perception threshold for rectal distension in patients with rectal hypersensitivity [53]. A concomitant increase in rectal compliance was thought to be unrelated to the reduction in sensitivity.

Drugs in preclinical development

TRP channel antagonists—The transient receptor potential (TRP) family of ion channels are molecular sensory transducers involved in a wide range of processes including osmoregulation and sensing of thermal, chemical, and mechanical stimuli. [54•] The TRP family comprises five main members (TRPA, TRPC, TRPM, TRPP, and TRPV) among which TRP vanilloid TRPV1 and TRPV4 are involved in the encoding of chemical and mechanical stimuli on visceral afferents, and thus have attracted interest as possible new targets in the development of drugs for visceral pain.

TRPV1: Considerable preclinical evidence supports the potential role of TRPV1 in visceral hyperalgesia. First, TRPV1 is expressed on primary afferent fibers (as well as on epithelial cells lining the esophagus and the urinary bladder) and can become sensitized by proalgesic and inflammatory mediators. Second, there is evidence for an upregulation of the TRVP1 in animal models of postinflammatory visceral hyperalgesia as well as human GI syndromes characterized by enhanced visceral sensitivity, including idiopathic rectal hypersensitivity and fecal urgency (reviewed in [55•]). An upregulation of TRPV1 immunoreactivity has also been described in several visceral conditions where pain is a prominent symptom: on colonic biopsies of patients with active Crohn's disease [56], on esophageal biopsies of patients with gastroesophageal reflux disease [57], on bladder biopsies of patients with interstitial cystitis [58] and on rectosigmoid biopsies of IBS patients [59]. In the latter study, the IBS patients also exhibited increased CD3+ cells as well as increased mast cells number in the mucosa, and showed evidence for a correlation between TRPV1 expression and IBS pain severity rating on a visual analog scale [59]. In this study, the role of prior infectious gastroenteritis and the possible role of altered mucosal immune activation as a potential trigger in the upregulation of TRPV1 have been suggested. Despite the potential of agents targeting TRPV1 for the treatment of visceral hyperalgesia states, the incomplete understanding of the role of TRPV1 in mucosal homeostatis, including thermosensing and protection of the GI mucosa constitutes a challenge to a safe therapeutic effect.

TRPV4: TRPV4 has been implicated in mechanosensation and pain and has been shown to play an important role in somatic pain [60]. In a recent study, TRPV4 was localized on colonic sensory afferents (in both mice and humans) where they are thought to be specifically involved in the transmission of nociceptive visceral stimuli. In tissue obtained from patients with active colitis, they observed that serosal blood vessels were more densely innervated by TRPV4-positive fibers [61]. In a different report, the role of TRPV4 in visceral nociception was confirmed by the observations in a mouse model, where intracolonic administration of a TRPV4 agonist was able to induce visceral hyperalgesia, and this effect was blocked by intervertebral knockdown of TRPV4 expression by siRNA. Similar siRNA treatment reduced basal visceral nociception and decreased visceral hypersensitivity induced by a PAR2 agonist [62]. Viewed together with a previous report suggesting a key role of PAR2 in IBS-related pain symptoms [63], these data suggest a potential role of TRPV4 in increased abdominal pain in IBS patients. Till date, there are no reports about TRPV4 expression in patients with visceral pain, or about the potential effectiveness of TRPV4 antagonists in such patients.

PAR: Protease-activated receptor type 2 (PAR2) is a member of the G-protein-coupled seven transmembrane-domain PAR receptors family that can be activated by trypsin and mast cell tryptase. The role of PAR2 activation in inflammation and its involvement in visceral nociceptive responses has been established in various animal models [64]. Elevated colonic luminal serine protease activity has been observed in IBS-D patients [63]. The involvement of proteases and PAR2 activation in the generation of pain symptoms has been suggested by the observation that mice injected with mediators released from colonic biopsies of patients with IBS exhibit enhanced nociceptive responses to colorectal distension whereas transgenic mice without PAR2 failed to show such visceral hyperalgesia [63].

CRF_2R agonists—CRF has been shown to have receptor-based bimodal effects on multiple physiological responses, such as gastrointestinal motility and stress. Similarly, a divergent role of the CRF receptor subtypes has been suggested in the modulation of visceral pain. While the CRF1 receptor is involved in a pronociceptive effect of CRF, the CRF_2 receptor can exert antinociceptive effects at both the peripheral and spinal level [65]. Additional evidence supporting an antinociceptive effect of CRF_2R was provided by M. Mulugeta *et al*. showing that the activation of CRF_2R blunted visceral pain and inhibited sensitization to colorectal

distension in awake rats. These effects were completely blocked by a selective CRF_2-receptor antagonist [66].

Compounds with potential visceral analgesic effects

Preliminary reports indicate that Na(v) channels [67] or acid-sensing ion channels (ASICS) [68] may be involved in visceral pain transduction, though their implication in the physiopathology of visceral hypersensitivity remains to be studied.

Conclusions

Despite the well-documented phenomenon of visceral hypersensitivity (enhanced perception of visceral signals) in IBS patients, the clinical results with drugs presumed to have visceral analgesic effects have largely been disappointing. One reason for the discrepant results between preclinical and clinical evaluations may be due to the fact that although many of these compounds are effective in reducing nociceptive reflex responses in rodents, this effectiveness may not necessarily translate into normalizing an abnormal human perception of visceral signals, which is influenced by many other factors besides visceral afferent input to the brain (discussed in [2]). A better characterization of normal as well as abnormal visceral pain perception (e.g. central pain amplification) and underlying mechanisms (sensory, cognitive, and emotional) in human patients is required before more effective drug development is possible.

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