Review article: modulation of the brain–gut axis as a therapeutic approach in gastrointestinal disease

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SUMMARY

Background
The importance of bi-directional brain–gut interactions in gastrointestinal illness is increasingly being recognized, most prominently in the area of functional gastrointestinal disorders. Numerous current and emerging therapies aimed at normalizing brain–gut interactions are a focus of interest, particularly for irritable bowel syndrome and functional dyspepsia.

Methods
A literature search was completed for preclinical and clinical studies related to central modulation of gastrointestinal functions and published in English between 1980 and 2006.

Results
Existing data, while sparse, support the use of different classes of antidepressant drugs, including tricyclics, and selective and non-selective serotonin reuptake inhibitors in irritable bowel syndrome. Serotonin receptor agonists and antagonists with peripheral and possibly central effects are effective in treating specific subtypes of irritable bowel syndrome. Based largely on theoretical and preclinical evidence, several novel compounds that selectively target receptors at multiple levels within the brain–gut axis such as neurokinin, somatostatin and corticotropin-releasing factor receptor antagonists are promising.

Conclusions
This review discusses the rationale for modulation of the brain–gut axis in the treatment of functional gastrointestinal disorders and highlights the most promising current and future therapeutic strategies.

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INTRODUCTION

Bi-directional brain–gut interactions play an important role in the regulation of many vital functions in health and disease. In health, brain–gut interactions play a crucial role in the regulation of digestive processes (including appetite and food intake), in the modulation of the gut-associated immune system, and in the coordination of the overall physical and emotional state of the organism with activity in the gastrointestinal (GI) tract. In disease, altered brain–gut interactions are likely to underlie the symptom generation in functional GI disorders (FGIDs), and may be involved in the modulation of immune activity in irritable bowel syndrome (IBS), and in the pathophysiology of various eating disorders. In this current review article, we will focus on evolving pharmacological strategies aimed at various targets within the brain–gut axis, which may yield novel therapies for IBS and related FGIDs. Even though the gut itself is one component of the brain–gut axis, the review will not deal with targets restricted to peripheral mechanisms in the gut and the reader is referred to other recent reviews.

While research over the past few years has provided significant advances in the understanding of IBS pathophysiology, the precise mechanisms underlying the symptom generation remains incompletely understood. However, the various aspects of IBS symptomatology can best be viewed as a dysregulation in the complex interplay between events occurring in the gut lumen, the mucosa, the enteric nervous system (ENS) and the central nervous system (CNS) leading to alterations in sensation, motility and immune function. A schematic of the afferent component of the brain–gut axis is shown in Figure 1.

Rationale for modulation of brain–gut interactions

Over the past decade, a remarkable convergence of research strategies pursued by different specialties (in particular pain, psychiatry, psychology and stress neurobiology) in understanding the interface among the stress, pain and emotion has occurred. Rather than viewing each of these areas as mutually exclusive targets of research, the overlap of CNS circuits and neurotransmitter systems involved in the regulation and modulation of these processes is fundamentally changing the perspective of national funding agencies and of the pharmaceutical industry. The fact that drugs acting at the brain–gut axis make up an important aspect of every recent review published on the pharmacologic treatment of IBS indicates the firm support of the field for this treatment approach.

Afferent signals arising from the lumen of the gut are transmitted via various visceral afferent pathways (enteric, spinal and vagal) to the CNS. Homeostatic reflexes, which generate appropriate gut responses to...
physiological as well as pathological visceral stimuli, occur at the level of the ENS, the spinal cord and the pontomedullary nuclei and limbic regions. Vagal visceral afferent inputs may also play an important role in such diverse functions as modulation of emotion, pain, satiety and immune response. Whereas the reflex circuits within the ENS, in principle, can regulate and synchronize all basic GI functions (motility, secretion and blood flow), co-ordination of gut functions with the overall homeostatic state of the organism requires continuous communication between the CNS and the GI tract. As shown in Fig. 1 descending cortico-limbic influences can set the gain and responsiveness of these reflexes or impose distinct patterns of motor responses on lower circuits. These descending influences can be triggered by cognitive or emotional influences or in response to environmental demands and can override local reflex function during sleep, in the context of environmental stressors, or during strong emotions such as fear and anger.

While the great majority of homeostatic afferent inputs from the gut (as well as other viscera) to the CNS is not consciously perceived, there are both peripheral and central adaptive mechanisms that can result in the enhanced perception of visceral stimuli. For example, acute tissue irritation and injury are typically associated with the sensitization of peripheral afferents, spinal circuits and spino-bulbo-spinal circuits, which may result in a transient or prolonged up-regulation of afferent sensitivity, as demonstrated in preclinical models. Similarly, various stressors have been shown to regulate the visceral pain responses in animal models, and chronic life stressors have been associated with symptom severity in FGIDs. There are multiple mechanisms within the brain–gut axis, which can tonically or phasically up-or down-regulate the sensitivity within visceral afferent pathways and the responsiveness of homeostatic reflexes. It is important to realize that only some of these mechanisms have a direct effect on the conscious perception of visceral pain and discomfort in humans.

CURRENTLY AVAILABLE DRUGS AIMED AT THE BRAIN–GUT AXIS

Sedatives and anxiolytics

The rationale for the use of anxiolytic drugs for the treatment of FGIDs likely stems from the clinical observation that the majority of patients also show evidence of comorbid psychological symptoms, particularly anxiety. More recently, disease models of IBS include the overlap of brain circuits involved in emotion regulation, autonomic responses and pain modulation as prominent features. Up to 40% of treatment-seeking IBS patients suffer from anxiety disorders, and the majority of patients score higher than control subjects on anxiety questionnaires, without meeting the full DSM IV criteria for an anxiety disorder. Surprisingly, despite the strong theoretical, preclinical and empirical rationale for the use of sedatives or anxiolytics, there are no well-designed clinical trials of this class of compounds in treating FGID symptoms. For decades, one of the most common treatment strategies for IBS patients has been the combination of so-called antispasmodics with long-acting benzodiazepines (such as Librax) or barbiturates (such as Butibel or Donnatal). Despite the widespread use of such therapies, there has never been supportive evidence from high-quality clinical trials. Limited clinical and anecdotal evidence suggests a possible beneficial effect for benzodiazepines in IBS patients with anxiety disorders. However, concerns about side effects of sedation and potential for addiction have discouraged further investigation of benzodiazepines.

Buspirone is a partial serotonin 1A (5-HT1A) receptor agonist used for anxiety disorders. Despite the well-known anxiolytic properties of buspirone, recent interest in this class of compounds has focused on their potential peripheral effects on GI motility. In a rat model, buspirone abolished the stimulatory effects of psychological stress and corticotropin-releasing factor (CRF) on caecal motility through 5-HT1A receptors. A preliminary report of a crossover study of buspirone in patients with functional dyspepsia suggested a reduction in dyspepsia symptoms. When studied for its potential use for bowel symptoms, acute dosing of buspirone did not significantly alter colonic compliance, tone or visceral perception relative to placebo in healthy control subjects.

In summary, considerable theoretical, preclinical, epidemiological and clinical evidence suggests that drugs aimed at central anxiety circuits may be beneficial in treating patients with functional GI symptoms. However, there is currently no convincing clinical trial evidence to support the efficacy of these drugs. Additionally, the side effect profile of benzodiazepines argues against the use of this class of compounds for chronic treatment.
Antidepressants

Multiple central and peripheral mechanisms have been suggested as mediators of the beneficial effect of different classes of antidepressant drugs on IBS symptoms. Proposed central mechanisms include the treatment of comorbid depression, sleep restoration, analgesia or antihyperalgesia, while proposed peripheral mechanisms include anticholinergic effects, normalization of GI transit, fundic relaxation and peripheral antineuropathic effects. A detailed review of relevant studies and a suggested paradigm for their use has recently been reported.14

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) are prescribed for a number of pain-related disorders, including neuropathic pain, migraine and fibromyalgia,38–40 as well as FGIDs. With regard to their beneficial effects on clinical pain, a primary beneficial effect on neuropathic pain has been implicated.18 However, a variety of other effects of these compounds may be important for their therapeutic benefit in FGIDs. For example, TCAs have been shown to slow orocaecal transit and have been shown to alter the duration, but not frequency, of the phase III contractions of the migrating motor complex.41 Studies of TCAs on visceral perception as measured by barostat-controlled rectal balloon inflation have been inconclusive.42–44 Amitriptyline has been shown to alter the activation of limbic brain regions in response to an auditory stressor combined with rectal balloon inflation suggesting a possible benefit for TCAs in stress-related perception of GI symptoms.

Most published studies have shown that TCAs improve the symptoms in FGID patients; however, the quality and design of these trials has been variable.44–48 Of the three recent meta-analyses that have evaluated the possible beneficial effects of TCAs on functional GI symptoms, two concluded that such treatments were beneficial,49, 50 while one concluded that they were not superior to placebo, for the treatment of IBS.51 Jackson et al.49 evaluated 90 studies published between 1966 and 1988, and selected 11 for further analysis. Based on this review, the authors reported a significant improvement in global GI symptoms [odds ratio (OR) 4; 95% CI 2–8] as well as improvement in standardized pain scores compared with placebo, with a number needed to treat (NNT) of 3.2.49 Lesbros-Pantoflickova et al.50 found nine evaluable studies performed from 1978 to 1998, out of 51. A significant effect of antidepressants in IBS was found for overall improvement, with an OR of 2 (CI 1–3) when the analysis was restricted to higher quality studies. Finally, Brandt et al.51 reviewed six studies evaluating the effect of TCAs on IBS symptoms published during 1978 and 1987, and concluded that all were of poor quality and that TCAs were not superior to placebo for global GI symptom improvement. Unfortunately, these meta-analyses are hindered by inclusion of studies with poor study design, including the inadequate sample sizes, differences in the functional disorders included, use of different drugs and doses, and choice of outcome measures.

In the largest randomized placebo-controlled trial to date, including 431 female IBS and functional dyspepsia patients followed for 12 weeks of therapy, Drossman et al.52 evaluated the efficacy of a full dose of desipramine (150 mg/day). The study demonstrated that treatment with desipramine was superior to placebo only in the per-protocol analysis (responder rate 73% vs. 49%, NNT = 5), but not the intention-to-treat analyses. This is likely due to the increased side effect profile of TCAs at a full dose (i.e. dry mouth, drowsiness, constipation and weight gain) leading to non-compliance and a high drop out rate. However, in clinical practice, TCAs are typically used at much lower and individually titrated doses (as low as 10 mg/day) and may be better tolerated with sufficient beneficial effect. In the Drossman study, the beneficial effect of desipramine was seen primarily in diarrhoea-predominant patients with moderate IBS symptom severity, with a history of abuse, but without depression.

Tricyclic antidepressants have been shown to decrease the sensitivity to somatic pain and to improve sleep, thus they might also be particularly beneficial for FGID patients with associated extra-intestinal symptoms.42, 53 TCAs should not be used primarily to treat psychiatric symptoms in FGID patients, as the selective serotonin reuptake inhibitors (SSRIs) have a lower side effect profile and greater therapeutic window at effective doses.

Serotonin reuptake inhibitors

It has long been hypothesized that SSRIs may have beneficial effects in IBS patients mainly by treating comorbid depression and anxiety. However, prelimin-
ary results from several recent clinical trials suggest a possible direct effect on IBS symptoms. A recent double-blind, placebo-controlled study of the SSRI citalopram showed benefits in a number of IBS symptoms compared with placebo in a group of non-depressed patients. After 6 weeks of therapy patients treated with citalopram showed decreased abdominal pain and bloating, and increased overall well-being, although stool scores showed little change. Acute dosing with citalopram has also been shown to increase the colonic phasic motility and decrease colonic response to a meal in healthy subjects, as well as decreasing the oesophageal sensitivity to both the acid infusion and distension. The relevance of such acute effects on physiological readouts for clinical benefit from chronic treatment with these compounds is unknown.

Other SSRI studies for IBS have shown benefit, but have not well differentiated the improvement of psychological symptoms from GI symptoms. In a study by Tabas et al., 81 IBS patients were randomized to paroxetine or placebo and the paroxetine group showed the greater improvements in global well-being (63% vs. 26%, P = 0.01), but no difference in abdominal discomfort or bloating. While the global improvement scores did not appear to be due to changes in depressive symptoms, anxiety symptoms significantly improved in the paroxetine group, possibly mediating the overall improvement. Another study of paroxetine for IBS compared it to usual care, showing the improvement in the physical component of the SF-36 health-related quality-of-life score, but not in abdominal pain. Additionally, the study showed high drop out with only 43 of an initial 86 patients completing the 12 weeks of therapy. In a randomized placebo-controlled 12-week trial of low-dose fluoxetine (20 mg) in 44 constipation-predominant IBS patients, a significant decrease in the presence of discomfort, bloating, hard stool and decreased stool frequency was noted at 4 and 12 weeks. However, this study did not report a global improvement outcome measure and did not report whether the symptom change was associated with a change in psychological symptoms.

Newer monoamine reuptake inhibitors, such as the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine have been proposed as more effective treatments for chronic pain conditions associated with depression. It is assumed that the combined effect of these drugs on descending serotonergic and noradrenergic pain inhibition systems (similar to the effect of TCAs) may be responsible for their effectiveness in the treatment of chronic functional pain conditions, such as fibromyalgia, and in patients with painful diabetic neuropathy. While theoretically there may be an advantage of these newer drugs over TCAs and SSRIs for the treatment of IBS symptoms, clinical trial evidence for such a superiority is currently not available.

In summary, the theoretical rationales for using centrally acting drugs such as anxiolytics and antidepresants in the treatment of FGIDs are strong, and include the anxiolytic effect of these drugs on central mechanisms thought to play a role in IBS pathophysiology (hypervigilance, symptom related anxiety, increased stress-responsiveness), the potential antihyperalgesic effects of TCAs and SNRIs, and the therapeutic effects on mood. The use of low-dose TCAs and full-dose SSRIs in selected patients (or patient populations) appears promising, although individualized dosing and patient education are essential to avoid the side effects and to ensure compliance. The reasons for the effectiveness in subgroups of patients are incompletely understood but may be related to differences in underlying pathophysiology and possibly differences in genetic polymorphisms. The regular use of benzodiazepine anxiolytics and sedatives is discouraged due to the risk of habituation and potential for dependency. Novel compounds with anxiolytic and/or antidepressant activity such as neurokinin 1 (NK1) receptor or CRF receptor subtype 1 (CRF1) receptor antagonists are currently in development and are discussed below.

5-HT3 receptor antagonists

Serotonin has well documented effects on gut motility, secretion and sensation, likely via both the central and peripheral pathways, making it a key pharmacological target in the treatment of FGIDs. More than 80% of the organism’s serotonin is stored in enterochromaffin cells of the GI tract. Serotonin can be released from these cells in response to chemical or mechanical stimulation of the mucosa, or in response to experimental stressors. Upon stimulation of enterochromaffin cells, serotonin acts in a paracrine fashion on serotonin receptors on intrinsic and extrinsic afferent nerve terminals. 5-HT3 receptors are expressed on subsets of neurons intrinsic to the ENS (intrinsic primary afferent neurons,
IPANs) as well as on extrinsic primary afferents (EPANs; both spinal and vagal afferents). At the dorsal horn level, 5-HT3 receptors presumably located presynaptically on the central terminals of spinal afferents have been implicated as mediators of the descending facilitatory drive on spinal neurotransmission.

5-HT3 receptor antagonists were originally developed as novel anxiolytics, followed by a development phase as potential visceral analgesics. This was based on the rationale of decreasing the responsiveness of spinal afferent neurons innervating the intestine to enterically released 5-HT and/or to mechanical stimulation. In addition, antagonism of 5-HT signalling to IPANs was thought to attenuate the peristaltic and the secretomotor reflexes, thereby decreasing the intestinal motility and secretion. More recently, preclinical evidence has implicated 5-HT3 receptors located on the central terminals of primary afferent nerves as important components of spino-bulbo-spinal pain facilitation loops. Several large randomized double-blind, placebo-controlled trials have demonstrated that alosetron 1 mg b.d. for 12 weeks is effective in decreasing the stool frequency and bowel urgency, and in providing the adequate relief of abdominal pain and discomfort, as well as general global improvement of IBS symptoms and increased health-related quality-of-life, in female, and subsequently male, patients with diarrhoea-predominant IBS. Despite the unequivocal evidence for clinical effectiveness of this compound, efforts aimed at understanding the mechanism(s) of action of 5-HT3 receptor antagonists have only been partially successful. Initial studies in human subjects have demonstrated that the 5-HT3 receptor antagonist alosetron slows intestinal transit in both the IBS patients (patients with severe constipation excluded) and healthy controls. However, neither preclinical nor clinical studies have ever demonstrated a true visceral analgesic effect of the compound (reviewed in Mayer and Bradesi, 2003). In IBS patients, the apparent effect of alosetron on perception of rectal distension was related to the drug-induced changes in rectal compliance. There is both clinical and preclinical evidence to support the concept that the drug’s effect may be mediated in part by central effects. For example, IBS symptom reduction was correlated with reduction in neural activity in the amygdala complex, a brain region involved in the central modulation of gut function and pain. The most common adverse effect associated with alosetron use is constipation which affects about 25–30% of subjects. The occurrence of serious complications from constipation in 1/1000 patients (ileus, bowel obstruction, fecal impaction and perforation) or ischaemic colitis (prevalence of 0.1%) has been reported from both the clinical trials and postmarketing studies. The mechanism(s) underlying the development of ischaemic colitis remain poorly understood and the identification of factors predictive of these side effects has only been partially successful. The adverse event profile of the drug has led to restrictions to the prescription of alosetron by the FDA. Since its reintroduction to the market in November 2002, alosetron is indicated only for women with severe diarrhoea-predominant IBS who have experienced the chronic IBS symptoms for at least 6 months and for whom conventional IBS therapies have failed. Other 5-HT3 receptor antagonists (such as cilansetron), which have shown similar clinical effectiveness as well as side effect profile, are currently in development.

In summary, 5-HT3 receptor antagonists are highly effective drugs to treat multiple symptoms in male and female patients with diarrhoea-predominant IBS. However, because of rare, but potentially serious side effects, their use is currently restricted to the most severe patients who have failed other therapies. Should it become possible to predict patients with a vulnerability to develop ischaemic colitis while on drug treatment and to develop more receptor subtype specific compounds, this class of drug may yet become an important treatment strategy in the clinic.

**Somatostatin receptor agonists**

Somatostatin (SST) has been used for many years as an antisecretory agent for various types of chronic diarrhoea, including IBS, but later research has suggested a potential broader function of SST analogues in FGIDs. SST receptors are localized both in the periphery (including the GI tract) and the CNS, and SST receptor-mediated signalling is involved in pain modulation, as well as vascular, neuroendocrine, neuronal and autonomic responses. The localization of SST2 receptors on spinal afferents, superficial dorsal horn neurons and within the locus coeruleus complex is similar to those of mu opioid receptors and makes this class of receptors an attractive target for the treatment of visceral hypersensitivity. Experimental evidence in a rodent visceral pain model suggests a
central site of action, although an action on splanchnic and vagal afferent has not been ruled out. A schematic of receptor targets for SST receptor agonists is shown in Figure 2.

In humans, octreotide, a non-selective SST2, SST3 and SST5 receptor agonist, has been demonstrated to have potent visceral analgesic, as well as GI motility, effect. Several pharmacodynamic studies have shown an effect of one-time dosing of octreotide on the perception of rectal, colonic and gastric distension without affecting tone or compliance. Preliminary evidence from an 8-week controlled clinical treatment trial showed that octreotide treatment was associated with a reduction in the perception of barostat-induced rectal distension in non-constipated IBS patients. In addition, octreotide treatment was found to reduce the abdominal complaints and improve the stool consistency, suggesting an overall beneficial effect.

In summary, both the animal and clinical studies have provided consistent evidence for an analgesic and anti-hyperalgesic effect of the non-selective SST receptor agonist octreotide in preclinical and clinical visceral pain models, presumably mediated by central SST2 receptors. However, potential side effects (including the inhibition of gall-bladder emptying and endocrine effects), in addition to the difficulty to produce an orally available agent and the phenomenon of receptor desensitization with chronic therapy, have slowed the development of this class of drugs for IBS.

CANDIDATE DRUGS CURRENTLY IN DEVELOPMENT

Neurokinin receptor antagonists

The neurokinins are a family of neuropeptides including the substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) which bind with the different degrees of specificity to their respective neurokinin receptors (NKR), NK1R, NK2R and NK3R. The wide expression of SP and the distribution of NKR throughout the autonomic nervous system (including the ENS) and CNS and the general role of the neurokinin signalling system as a modulatory rather than a primary transmission system make the NKR a potentially interesting target for the pharmacological modulation of sensory and motor dysfunctions in FGIDs. Early evaluations of NK1R antagonists for the treatment of acute and chronic somatic pain have been disappointing. Similarly, studies evaluating the same class of compound for the treatment of depression have been equivocal, even though both the preclinical as well as early clinical data were highly encouraging. However, newer compounds have several advantages over the originally tested compounds, including better CNS...
penetration, optimization for the human receptor, and the reduced interference with the CP450 system. Thus, a re-evaluation of these treatment strategies for IBS is currently underway.

**NK1R antagonists**

NK1Rs are the preferred NKR subtype for SP and their role in GI motility has been extensively described in preclinical studies. In general, NK1R antagonism reduces GI motility in sensitized rodent models (inflammation and stress) but has little effect on motility under the control conditions. The NK1R antagonist TAK-637 was found to reduce SP- or stress-induced exacerbation of colonic transit and defecation in gerbils. The selective NK1R antagonists SR-140333 and MEN10930 were found to inhibit the colonic propulsive activity induced in vitro. A central/spinal site of action has been proposed based on the observations that enhanced visceral sensitivity to colonic/colorectal distension observed after a stress exposure or colonic inflammation is attenuated by intracerebroventricular or spinal injection of NK1R antagonists. A schematic summary of potential receptor targets within the brain–gut axis is shown in Figure 2.

Even though there has been an extensive clinical trial experience with the different NK1R antagonists in somatic pain, depression and chemotherapy-induced nausea, the data supporting the possible use of NK1R antagonists in the treatment of IBS symptoms are limited. The only reported double-blind, placebo-controlled, randomized study in 14 IBS patients showed that a 7-day course of the NK1R antagonist ezlopitant (CJ-11974) reduced the emotional response to rectosigmoid distension and produced a trend towards the decreased perception of rectal distension.

**NK2R antagonists.**

Extensive preclinical data from rodent models support the concept that NK2R antagonists can attenuate increased intestinal motility, secretion and visceral sensitivity by acting at the peripheral level. In addition, significant preclinical evidence supports a role for these compounds in the treatment of CNS disorders, including anxiety. In the isolated human colon circular muscle, nepadutan (MEN11420) was found to be a potent, selective, competitive and reversible antagonist of NK2R-mediated contractile and electrical events, whereas saredutan (SR-48968) was pseudo-irreversible and non-competitive. Results from a phase I clinical trial with nepadutan have demonstrated an inhibitory effect on human intestinal motor response and IBS-like symptoms induced by i.v. administration of NKA without affecting basal motility. To date, there are no published data on the effect of NK2R antagonists on visceral sensitivity or on IBS symptoms in humans.

**NK3R antagonists**

A number of preclinical studies using selective NK3R antagonists have revealed a potential role of NK3Rs in the regulation of intestinal motility and nociception in rodent models. Similar to the findings with NK1R antagonists, these effects have been seen in pathological situations (sensitized models), whereas the role of NK3Rs seems limited under normal conditions. Even though this class of compounds is also being evaluated for several CNS indications and the compounds have high CNS penetration, it has been proposed that the mechanism of action is via a direct or indirect (via IPANs) effect on C-fiber sensitivity. Talnetant (SB-223412) is a selective, orally active NK3R antagonist under the development by GlaxoSmithKline for the potential treatment of several disorders, including the urinary incontinence and IBS. Data from completed phase II clinical trials have not been published to date.

In summary, despite promising preclinical data on the effect of NKR antagonists on intestinal motility, secretion and visceral sensitivity in experimental pathological conditions, the effectiveness of these compounds in the treatment of IBS symptoms remains to be established. The distribution of NKRs on multiple targets within the brain–gut axis, including the dorsal horn of the spinal cord, brainstem regions and limbic system, and the prominent role of these signalling systems in sensitized, but not normal, states make them an attractive avenue to pursue.

**CRF receptor antagonists**

Following the discovery of new CRF-related peptides, CRF receptor subtypes and the development of selec-
tive antagonists for CRF receptor subtype 1 (CRF1) and 2 (CRF2) have provided tremendous insights into the mechanisms by which stress affects GI functions. Convergent evidence from extensive preclinical studies has established the role of the brain CRF-CRF1 receptor signalling system in mediating the endocrine, autonomic, behavioural, and visceral responses to stress, suggesting that these receptors might be an ideal target in the context of functional bowel disorders. Selective CRF1 antagonists (CP-154 526, CRA-1000, NBI-35965, or NBI-27914) injected intracerebroventricularly or peripherally were found to blunt stress-related anxiety-like behaviour, stress-induced visceral hyperalgesia, and stress-induced stimulation of colonic secretion and motility in rodents and monkeys. In addition to its central effects, CRF, via the activation of CRF1 receptors on myenteric neurons, plays an important role on colonic secretory and motor functions as well as colonic permeability. A schematic summary of targets for CRF1 receptor antagonists within the brain-gut axis is shown in Figure 2.

In humans, a recent study from Sagami et al. reported an inhibitory effect of i.v. injection of the non-CNS penetrable CRF receptor antagonist z-helical CRF9–41 on exaggerated motility induced by colonic distension and electrical stimulation of the rectal mucosa in diarrhoea-predominant IBS patients. A significant reduction of abdominal pain and anxiety scores was also reported. Unless the IBS patients participating in this study exhibited the increased permeability of the blood-brain barrier, this study suggests that antagonism of peripheral CRF1 receptors alone may have therapeutic effects in IBS patients. Even though these initial observations need to be confirmed, the extensive preclinical evidence for the crucial role of the CRF1 receptor in mediating the majority of altered behavioural, perceptual and visceral alterations implicated in IBS pathophysiology is encouraging for the development of CRF1 receptor antagonist for the treatment of IBS.

z2-adrenergic receptor agonists

Growing interest in the potential therapeutic activity of z2-adrenergic receptor (z2AR) agonists in the treatment of IBS is based on the well-documented effects of this class of compound on pain perception, autonomic function and anxiety states. An important role of central noradrenergic pathways (in particular the crucial role of the locus coeruleus complex) in the pathophysiology of IBS has been suggested, and recent preliminary findings suggest a possible association of functional z2AR polymorphism with constipation and high somatic symptoms in patients with lower functional bowel disorders, as well as in other functional pain disorders. The z2AR agonist clonidine induced colonic and rectal relaxation and a reduction in the perception of colonic or rectal balloon distension in healthy volunteers. In a randomized, controlled exploratory study of the effect of clonidine in diarrhoea-predominant IBS patients, Camilleri et al. showed a satisfactory symptom relief associated with clonidine 0.1 mg b.d. compared with placebo. However, the typical side effect profile of clonidine (hypotension and fatigue) limits the clinical usefulness of this approach in the treatment of IBS. Newer agents with better side effect profiles remain an attractive strategy in drug development.

Cholecystokinin-A antagonist

The involvement of cholecystokinin (CCK) in sensory and motor responses to distension of the intestinal tract, as demonstrated in a broad range of preclinical and clinical studies, has led to the development of CCK antagonists for the treatment of functional bowel disorders including the IBS. CCK-A receptor antagonists were found to accelerate the gastric emptying and colonic transit time and have also been shown to inhibit gall-bladder contraction in healthy volunteers. Even though not part of the initial development rationale, an extensive literature in humans has implicated CCK-A receptors on vagal afferents in the development of satiety. Thus, CCK-A receptor antagonism may be relevant in the relief of the symptom of early satiety in patients with functional dyspepsia. While early phase II studies suggested a possible therapeutic effect in IBS (reviewed in Varga et al.), this finding could not be confirmed in a subsequent study. One limitation of drug development for IBS and other functional disorders may be the relatively narrow therapeutic window between the desired effects on visceral perception and motility and the inhibition of gall-bladder function resulting in the development of gallstones.
NMDA (N-methyl-D-aspartate) receptor antagonists

NMDA receptor-mediated central sensitization is a well-established mechanism underlying the development of hyperalgesic states in both animal and human models of somatic and visceral pain. In addition to the well-characterized role of spinal NMDA receptors in the sensitization of dorsal horn neurons, NMDA receptors have also been identified on peripheral and central terminals of primary afferents. The role of these peripheral NMDA receptors in pain transmission is incompletely understood. Preclinical evidence in rodents suggests that peripherally administered NMDA antagonists may have an analgesic effect in visceral pain models. In a recent clinical study, a low dose of ketamine was shown to prevent and reverse the oesophageal hypersensitivity induced by acid infusion in healthy volunteers, suggesting that NMDA-mediated central sensitization is involved in this acute hypersensitivity model. Despite the attractiveness of NMDA receptor antagonists to selectively reverse pathological pain states associated with central sensitization, while leaving normal pain transmission intact, clinical applications have been limited by high dose-related central side effects and poor oral bioavailability. Future development of peripherally restricted and tissue and subunit selective antagonists hold some potential for the treatment of visceral hyperalgesic states, including the IBS.

TRPV1 receptor antagonists

The transient receptor potential ion channel of the vanilloid type 1 (TRPV1) represents another promising target with therapeutic potential for the treatment of GI dysfunctions. TRPV1 is a non-selective cation channel with high permeability for calcium, is activated by a range of various stimuli including acidosis and lipid mediators and is characterized as a polymodal nociceptor. While initial studies have focused on a possible role of TRPV1 located on the peripheral terminals of spinal afferents, the role of central TRPV1s is poorly understood. Direct and indirect evidence indicate a possible role of TRPV1 in visceral pain and preliminary data have raised great interest in the potential role of TRPV1 in visceral hyperalgesia (for review see ). For example, increased TRPV1 expression in the rectum has been reported in patients with chronic rectal urgency and with oesophagitis. Several antagonists are currently under investigation in clinical trials.

SUMMARY AND CONCLUSIONS

In the past 10 years, major efforts have been undertaken to identify promising targets within the brain–gut axis, and well-designed clinical trials have been used to evaluate the effectiveness of novel treatments. Based on recent advances in the characterization of IBS pathophysiology, the list of candidate compounds with potential usefulness for IBS therapy has rapidly grown. However, while most of the currently available medications used for the treatment of IBS provide relief for a specific symptom, converging data support the concept that global symptom relief and improvement of HRQoL may be the more relevant endpoints for individuals who suffer from IBS. The fact that the majority of currently available drug treatments have failed to provide robust measures of patient satisfaction and HRQoL improvements may in part be related to their reported relative small efficacy combined with an unfavourable side effect profile. The main challenges associated with successful drug development strategy for FGIDs include: the likely heterogeneity of patients meeting the diagnostic symptom criteria for IBS, and the need for drugs targeting multiple symptoms, individual symptoms, providing significant overall improvement of HRQoL and patient satisfaction.

Contrary to the earlier focus on peripherally restricted drugs, a growing number of compounds with partial or predominant central effects are currently in development and clinical evaluation. The advantages of compounds targeted at multiple sites within the brain–gut axis (such as SST2 receptors, opioid receptors, 5-HT3 receptors, NKRs and CRF1 receptors; for a schematic summary, see Figure 2) in a syndrome-like IBS with symptoms involving the GI, pain and emotional system are obvious: (i) such compounds are likely to affect both the alterations in reflex responses involving GI motor and secretory functions, as well as abnormal perception of, and autonomic responses to visceral stimuli; (ii) they are likely to affect multiple symptoms rather than the current mono-symptomatic therapy aimed at peripheral targets; (iii) they are more likely to reverse abnormal modulatory mechanisms rather than interfere with essential homeostatic functions, such as normal pain transmission or homeostatic reflexes; and (iv) they could have a greater impact on global endpoints and health-related quality-of-life measures.
because of simultaneous treatment of non-GI-specific symptoms such as fatigue, loss of energy and excessive worry, all of which have been identified as having a greater impact on quality-of-life impairment than specific GI symptoms, such as altered bowel habits.158

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