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Novel Therapeutic Approaches in IBS

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Summary of recent advances

Irritable bowel syndrome (IBS) remains an incompletely understood, common syndrome with significant unmet medical needs. Significant progress has been made in the development of novel therapies aimed at normalizing bowel habit alterations and abdominal discomfort, even though some of the most effective treatments are currently only available for patients under a restricted access program from the FDA. Preclinical evidence supports the potential usefulness of several compounds in development for the treatment of chronic abdominal pain. Recent new evidence for a possible role of altered microflora and altered host microbial interactions may provide new treatment targets in the future.

Introduction

Despite its high prevalence, considerable impairment of health related quality of life (HRQoL), and burden of illness [1], the available treatment options for IBS are limited and effective therapy remains a challenge to clinicians. IBS as defined by current criteria is likely to be a heterogeneous disorder with a core group of patients having a generalized brain gut disorder, while smaller subgroups may have similar symptoms arising from celiac disease, microscopic colitis or bacterial overgrowth. In the majority of patients, IBS symptoms result from a complex dysregulation of the brain gut axis, involving variable contributions of peripheral, spinal and supraspinal abnormalities [2][3][4]. Alterations in gastrointestinal motility have been identified in some patients, and together with alterations in intestinal fluid handling, may play an important role underlying IBS-related bowel habit irregularities. Enhanced perception of signals arising from the gastrointestinal (GI) tract ("visceral hypersensitivity") is considered a key factor underlying abdominal pain and discomfort [4]. Considerable preclinical and clinical evidence supports the presence of altered central arousal/stress circuits which may play a key role in central pain amplification, and in frequently associated symptoms of anxiety [5]. Recent evidence implicates a possible alteration in host microbial interactions and in mucosal neuroendocrine immune interactions [6]. Despite the initial enthusiasm about potentially novel treatment approaches, it remains to be determined which of the various reported abnormalities truly contribute to IBS symptoms, to health care seeking and to HRQoL impairment, which targets are relevant for

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Conflicts of interest
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drug development, and which of the growing list of abnormalities represent secondary effects or epiphenomena.

Serotonin and noradrenaline modulators

1. Serotonergic receptor modulators

More than 80% of the organism's serotonin (5-HT) is stored in enterochromaffin cells (ECC) of the gastrointestinal tract and serotonin can be released from these cells in response to a variety of physiological and experimental stimuli [7]. Upon stimulation of ECCs, 5-HT acts in a paracrine fashion on serotonin receptors on terminals of afferent neurons. 5-HT is also contained in certain enteric neurons and can modulate enteric neuron discharge. The effect of 5-HT on motor, secretory, and sensory functions within the gut makes 5-HT receptors potentially interesting targets for IBS drug development, even 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). 5-HT$_3$R antagonists are thought to interfere with 5HT signaling to IPANs, thereby attenuating peristaltic and the secretomotor reflexes, and in turn decreasing intestinal motility and secretion [8]. Several 5-HT$_3$Rs 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, in particular diarrhea has been reported (reviewed in [9]). Meanwhile, efforts aimed at understanding the mechanisms of action of 5-HT$_3$R antagonists and of the role of several receptor subtypes [10] have only been partially successful. Due to rare but potentially serious side effects (ischemic colitis), one of these compounds is only available through a restricted access program [11], while development of other compounds has been suspended (news release April 2005) (http://salesandmarketingnetwork.com/news_release.php?ID=2004126&key=Solvay).

5-HT$_4$R agonists—There is both clinical and preclinical evidence that serotonin, via 5-HT$_4$R, plays a pivotal role in the modulation of gastrointestinal motor function, in particular the peristaltic reflex [7] Less well supported is a possible role of 5-HT$_4$R in the modulation of visceral afferent function. Presumably by facilitated release of acetylcholine via presynaptic 5-HT$_4$R on cholinergic neurons, the partial 5-HT$_4$R agonist tegaserod accelerates upper and lower gut transit in healthy subjects, promotes gastric emptying, small bowel and colonic transit in constipation-predominant IBS (IBS-C) patients and increases fecal water and intestinal secretion in female subjects [7]. The efficacy of tegaserod in the treatment of IBS-C patients has been evaluated in several large, multicentre, randomized, double blind, placebo controlled trials in which a beneficial effect of the drug was demonstrated in terms of global symptoms improvement, relief of abdominal pain and discomfort, improvement in stool frequency and consistency, as well as significant improvement of daily bloating scores (reviewed in [12]). The drug was originally approved for the treatment of IBS-C in 55 countries and for the treatment of chronic constipation in 15 countries, in both cases including the US, but is now only available via a restricted access program. This restriction was triggered by a small apparent increase in cardiovascular mortality in post marketing surveys (http://www.fda.gov/CDER/drug/advisory/tegaserod.htm).

More specific and more potent, full agonists of the 5-HT$_4$R receptors such as prucalopride have been demonstrated to show efficacy in stimulating colonic transit and in treating chronic constipation [3]. Several compounds are currently in clinical development.

5-HT_4R agonist/5-HT_3R antagonists—Renzapride is a compound that shows mixed 5-HT_4R agonist and 5-HT_3R antagonist activities. Based on treatment success with the component drug categories, one would expect that this combination may be superior to each of the individual approaches, while minimizing the primary side effect of 5-HT_3R antagonists, e.g. constipation. Renzapride is currently under development for the treatment of IBS-C with a prokinetic effect expected from its 5-HT_4R agonist properties. Preliminary data from two phase IIb trials in the UK showed evidence for relief of abdominal pain and discomfort in IBS-C patients, and for male and female patients with mixed symptoms of diarrhea and constipation [13]. Renzapride was shown to stimulate colonic transit associated with improvement of bowel function in female IBS-C patients.[14] The compound is currently in clinical development for IBS-C (http://www.alizyme.com/alizyme/products/renzapride/).

2 Selective and non-selective monoamine uptake inhibitors

SSRIs may have beneficial effect in IBS patients through central effects by reducing pain perception and frequently comorbid symptoms of anxiety and depression. Their antihyperalgesic action is thought to be mediated in part by their enhancement of serotonergic descending pain inhibition systems. Preliminary evidence indicates that paroxetine may have some overall benefit in IBS patients with moderate to severe symptoms [15][16, 17]. Newer monoamine reuptake inhibitors, such as the 5-HT and norepinephrine (NE) reuptake inhibitors (SNRIs) duloxetine, venlafaxine and milacipram have been proposed as more effective treatments for chronic pain conditions associated with depression [18], and have been evaluated in patients with painful diabetic neuropathy [19] and most recently in fibromyalgia (reviewed in [20]). Despite the attractive rationale of targeting ineffective endogenous pain modulation systems, as well as frequently comorbid anxiety and depression, supportive evidence from well designed clinical trials in IBS patients is currently not available.

Beta3 adrenoceptor agonists—Beta(3)-adrenoceptors (AR) (β_3-AR) have been under investigation as novel targets for functional gastrointestinal disorders in which motility disturbance and pain are key features. In a recent study, Cellek et al. [21] demonstrated the expression of β_3-ARs on cholinergic neurons in the myenteric plexus and submucosal plexus of human colon. A β_3-AR agonist caused the release of somatostatin from human isolated colon, and this was associated with inhibition of cholinergically mediated muscle contraction. In a rat model of visceral pain induced by intracolonic mustard oil, the β_3-AR agonist elicited somatostatin-dependent visceral analgesia and reduced chemically induced diarrhea in vivo in a rat model. The combination of decreased intestinal motility and secretion and visceral analgesia constitutes a promising profile of activity for β_3-AR agonists. In addition, in view of several older reports on the viscero-analgesic effect of the somatostatin analogue octreotide in human subjects [22] and the preliminary results about a favorable effect on IBS symptoms [23], this class of drug holds promise for IBS therapy.

Neuropeptide receptor modulators

1. Neurokinin receptor modulators

The neurokinins are a family of neuropeptides, which bind with different degrees of specificity to their respective neurokinin receptors (NKRs), NK_1R, NK_2R and NK_3R. The wide distribution of NKRs throughout the autonomic and central nervous systems, and the general role of the neurokinin signaling system as a modulatory rather than a primary transmission system make the neurokinin receptors a potentially interesting target for the pharmacological modulation of sensory and motor dysfunctions.

NK_1R antagonists—Despite consistent pre-clinical data showing potential benefit of NK_1R antagonists for a range of pain and affective disorders, clinically beneficial effects could only been demonstrated for chemotherapy induced nausea [24] while clinical trials for somatic pain [25]and depression [26, 27] have largely been disappointing. Similarly, even though NK_1R antagonists reduce gastrointestinal hypermotility and hyperalgesia in sensitized rodent models [27, 28] the published data supporting the possible use of NK_1R antagonists in the treatment of IBS symptoms are limited [29]. Several new NK_1R antagonists are in development.

NK_2R antagonists—Extensive preclinical data from rodent models support the concept that NK_2R antagonists can attenuate increased intestinal motility, secretion and visceral sensitivity by acting at the peripheral level [30]. In addition, significant preclinical evidence supports a role for these compounds in the treatment of CNS disorders, including anxiety [31]. Results from a phase I clinical trial with nepadutant have demonstrated an inhibitory effect on human intestinal motor response and IBS-like symptoms induced by intravenous administration of NKA without affecting basal motility [32]. To date, there are no published data on the effect of NK_2R antagonist on visceral sensitivity in humans.

NK_3R antagonists—A number of pre-clinical studies using selective NK_3R receptors antagonists have revealed a potential role of NK_3Rs in the regulation of intestinal motility and nociception in rodent models [30]. Similar to the findings with NK_1R antagonists, these effects have been seen in pathological situations (sensitized models) whereas the role of NK_3Rs seems limited under normal conditions. Talnetant (SB-223412), a selective orally active NK_3R antagonist under development by GlaxoSmithKline for the potential treatment of several disorders, including urinary incontinence and IBS, showed no effect on rectal sensory function and compliance in healthy humans [33] and no effect on IBS symptoms in two well designed randomized controlled trials (RCTs)[34].

2. CRF_1 receptor antagonists

Convergent evidence from extensive preclinical studies has established the role of the brain CRF-CRF_1R signaling system in mediating the endocrine, autonomic, behavioral, and visceral responses to stress, suggesting that these receptors might be an ideal target in the context of functional bowel disorders [35]. In addition to its central effects, CRF, via the activation of CRF_1R on myenteric neurons, plays an important role on colonic secretory and motor functions as well as colonic permeability [36]. In humans, a recent study from Sagami et al. reported an inhibitory effect of intravenous injection of the non-CNS penetrable CRF receptor antagonist -helical CRF9–41 on exaggerated motility induced by colonic distension and electrical stimulation of the rectal mucosa in IBS-D patients[37]. A significant reduction of abdominal pain and anxiety scores was also reported. Unless the IBS patients participating in this study exhibited increased permeability of the blood brain barrier, this study suggests that antagonism of *peripheral* CRF_1R alone 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 [38]. Even though these initial observations need to be confirmed, the extensive preclinical evidence for the crucial role of the CRF_1R in mediating the majority of altered behavioral, perceptual and visceral alterations implicated in IBS pathophysiology are encouraging for the development of CRF_1R antagonist for the treatment of IBS [39].

3. Alpha adrenergic agonists

A potential benefit of α2 adrenergic receptor (α2AR) agonists in the treatment of IBS is based on preclinical and clinical evidence for beneficial effect on gastrointestinal motility and on chronic pain [40]. Additional support for this treatment approach comes from recent evidence showing a possible association of functional α2AR polymorphisms with constipation and with high somatic symptom scores in patients with lower functional bowel disorders [41]as well as in other functional pain disorders [42]. The effect of α2AR agonists on colonic and rectal motor and sensory functions had been suggested by results from studies showing that the α2AR agonist clonidine induced colonic and rectal relaxation and a reduction in the perception of colonic or rectal balloon distension in healthy volunteers [43, 44]. In an exploratory RCT of clonidine in IBS-D patients, clonidine was associated with satisfactory symptoms relief compared to placebo [45]. However, the strong hypotensive effect of this class of compounds as well as the common side effect of fatigue significantly limit the clinical usefulness of currently available compounds in this class for the treatment of IBS.

Epithelial and luminally acting agents

1. Chloride channel activators

Intestinal fluid secretion plays a key role in intestinal homeostasis and is driven primarily by active chloride transport from the basolateral to the apical side of enterocytes. Based on the potential benefit of normalizing intestinal fluid and electrolyte handling, Cl^- channels openers have been developed for the treatment of gastrointestinal dysfunction and chronic constipation. Lubiprostone is a selective type-2 Cl^- channel activator that significantly increases small intestinal fluid volume and also elevates intestinal fluid Cl^- concentration without altering serum electrolyte concentrations in animals[46]. Double-blinded, randomized human studies have demonstrated that lubiprostone accelerates small bowel and colonic transit. Well-designed RCTs and larger open-label trials have established lubiprostone as a safe and effective treatment for chronic constipation and has been approved on January 31, 2006 for both men and women (age 18 and over) with chronic constipation [46, 47]. The effect of lubiprostone in IBS-C has been evaluated in a randomized double-blinded, 12-week study in 50 IBS-C patients. The study showed improvements in abdominal discomfort/pain scores and bowel movement frequency more than doubled in all lubiprostone treatment groups as compared with placebo, during the first 8 weeks of the study. These improvements seemed to be dose related. Symptom scores and adverse events were not reported.[48]

2. Guanylate cyclase C agonists

GC-C activation induces intestinal fluid secretion and inhibits colonic fluid absorption, and may therefore be beneficial for the treatment of chronic constipation. Linaclotide is an agonist of the human guanylate cyclase-C (GC-C), a transmembrane protein located in the gut epithelium. Preliminary preclinical reports showed that linaclotide accelerates gastrointestinal transit and decreases visceral hyperalgesia. In human phase I studies, linaclotide was safe and well tolerated, decreased stool consistency, and increased stool frequency. In a randomized, double blind, placebo controlled study in 36 women with IBS-C, linaclotide 1000 μg significantly accelerated ascending colon emptying and colonic transit at 48hr, improved stool consistency, stool frequency, ease of passage and time to first bowel movement [49].

3. TRPV1 antagonists

The transient receptor potential ion channel of the vanilloid type 1 (TRPV1) represents another promising target with therapeutic potential for the treatment of gastrointestinal

dysfunctions. TRPV1 is a non selective cation channel with high permeability for calcium, is activated by a range of various stimulus including acidosis and lipid mediators and is characterized as a polymodal nociceptor. Direct and indirect evidence indicates 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[50]). Published data on the compounds potential benefit for IBS are not available.

4. Probiotics and antibiotics

The term “probiotic” refers to ‘micro-organisms, which when ingested, may have a positive effect in the prevention and treatment of a specific pathological condition’ [51]. Clinical benefits have been reported in gastrointestinal infections, particularly in the treatment of acute infantile diarrhea, inflammatory bowel diseases or pouchitis [52]. Possible beneficial effects of probiotics in IBS patients, particular on bloating related symptoms, have been reported from small clinical trials, and symptomatic improvements have been reported after treatments with *Lactobacillus plantarum*, *Bifidobacterium infantum*, and the composite probiotic VSL#3 [53–56]. Several mechanisms have been proposed to explain a therapeutic effect of probiotics in IBS, including a modulation of mucosal immune function (evidence for the modulation of pro-inflammatory cytokines), a trophic effect on colonic mucosal and epithelium, and a nutritional effect on the gut microflora. However, the heterogeneity, and small sample size of the various studies makes it difficult to draw definitive conclusions about the effectiveness of probiotics in IBS treatment.

Antibiotics—The rationale for the use of antibiotics in the treatment of IBS is based on the observation that small bowel bacterial overgrowth may be present in a significant number of patients who meet diagnostic criteria for IBS. In a series of studies, the antibiotic neomycin was found to improve IBS symptoms in about 25% of patients. The proposed mechanism for these effects was elimination of bacterial overgrowth demonstrated by normalization of the lactulose breath test results [57]. Side effects and low efficacity of neomycin has led to further investigation using rifaximin, a gut selective antibiotic with negligible systemic absorption and a broad spectrum activity. In a recent study, an overall improvement of IBS symptoms for 10 weeks after a 10 days treatment with rifamycin (400 mg/3x/day) compared with placebo was reported [58]. Several methodological concerns have been raised regarding the primary outcome measure (global scores) and the lack of effect of treatment on secondary end points specific to IBS such as pain [59]. Before this treatment approach can be recommended for IBS patients, further studies on the IBS population showing bacterial overgrowth, the possible role of bacterial overgrowth on IBS symptoms, and the potential benefit from antibiotics therapy are needed.

Conclusions

Considerable progress has been made in the development of different categories of novel agents which have been shown to improve specific IBS symptoms, in particular bowel habits and abdominal discomfort. This includes effective treatments for constipation (Cl^- channel agonists, guanylate cyclase C activators, 5-HT_4R agonists), diarrhea (5-HT_3R antagonism, and bloating type symptoms (probiotics and possibly antibiotics). Considerable preclinical data suggest the potential benefit of several compounds which are in development for the treatment of chronic abdominal pain (antagonists for CRF_1R, NK_1 and NK_2R, α2AR receptor agonists, and β3AR agonists). It remains to be determined which of these treatment approaches has an impact on global IBS endpoints (such as adequate relief of symptoms), and which are symptom specific. Most importantly, in view of the zero tolerance of regulatory authorities for side effects of new IBS drugs, it will need to be seen if the development of effective IBS drugs without side effects is a realistic goal.

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