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New Pharmaceutical Approaches to the Treatment of IBS: Future Development & Research

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SUMMARY

Current approaches to treatment of Irritable Bowel Syndrome (IBS) aim to normalise disturbed intestinal physiology. The most effective centrally acting drugs are tricyclic antidepressants. Alosetron, a 5-HT_3 receptor antagonist is effective in women with diarrhea-predominant IBS whilst tegaserod and prucalopride are 5-HT_4 agonists enhancing bowel motility in constipation-predominant IBS. Serotonergic receptor modulation has been the first targeted pharmacological intervention. The development of new drugs constitutes a major challenge as there are many targets along the brain-gut axis and the enteric nervous system (ENS). Newer tricyclic antidepressants with fewer side effects and corticotrophin releasing factor-1 (CRF-1) antagonists are examples of future centrally acting drugs. Agents that alter visceral sensitivity include kappa-opioid agonists (fedotozine, trimebutine, asimadoline), alpha-2 adrenoreceptor agonists (clonidine, lidamidine), tachykinin receptor antagonists (neurokinin A, substance P) and other experimental anti-nociceptive drugs (GABA-B receptor agonists). COX-2 inhibitors may be effective for post-infectious IBS. Drugs potentially useful in controlling intestinal motility and secretion other than serotonergic receptors modulators, include muscarinic receptors antagonists (derifenacin, zamenifenacin), octreotide and CCK-1 receptor antagonists (dexloglumide). Neurotrophins (NT-3 and brain derived neurotrophic factor) are promising factors for the treatment of IBS patients with constipation.

The development of new and effective drugs for IBS requires a more detailed understanding of pathophysiologic mechanisms, a fact that will allow us a more targeted intervention.

Key words: Irritable bavel syndrome, visceral sensitivity tricyclic antidepressants, muscarinic receptors

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INTRODUCTION

Irritable Bowel Syndrome (IBS) is common in all societies and is more frequent in women.[1] The main feature is abdominal pain or discomfort associated with a change in stool consistency and frequency but other symptoms such as bloating are common.[2] Patients are often classified as diarrhea-predominant (D-IBS), constipation-predominant (C-IBS) or alternating between diarrhea and constipation (Alt-IBS). Although IBS sufferers who consult doctors are more likely to have anxiety, depression and somatization,[3] those who do not are much less abnormal and in some studies do not differ from the normal population.[4] Thus, while IBS patients often exhibit psychopathology other factors are likely to be involved and successful treatments will need to correct both central and peripheral abnormalities.

The Brain-Gut Axis

The two-way communication between the gut and the central nervous system (CNS) has been termed the brain-gut axis.[5] The enteric nervous and enteroendocrine systems act on smooth muscle and epithelial cells to control gastrointestinal motility and secretion. Changes in the intestinal environment are monitored by immune cells, nerve endings and enteroendocrine cells which, when stimulated, secrete signalling molecules that control digestive function. Most of the sensory information passing to the spinal cord and brain via extrinsic afferent

nerves is processed in reflex circuits and does not reach consciousness but noxious stimuli may be experienced as pain or discomfort. The CNS modulates intestinal function via efferent autonomic nerves. Disturbance at one or more levels of this axis can cause abnormal perception of visceral events. Thus, CNS mechanisms controlling pain, increased sensitivity of sensory nerves in the gut or abnormal motility and secretion have all been implicated in the pathophysiology of IBS. The factors triggering these events are unknown, but stress and intestinal inflammation may be important.

Central processing

New brain imaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), can highlight regional differences in brain activation and metabolism in patients with IBS. In IBS patients brain areas involved in attention and vigilance may be activated in anticipation of colorectal distension[6] and failure to activate descending anti-nociceptive pathways has also been documented.[7] Thus future approaches may involve drugs that act on receptors specific to these regions. The brain plays a major role in determining whether nociceptive signals are consciously perceived and this is influenced by psychosocial factors including past experience, depression, anxiety and stress. The effects of stress are largely due to the action of corticotropin releasing factor (CRF) on CRF-1 and CRF-2 receptors.[8] The peripheral response to stress is mediated by the hypothalamic-pituitary-adrenal axis (HPA) and the autonomic nervous system which has important effects on the gut. Thus, vagal nerves inhibit gastric motility and stimulate distal colonic motility, while sympathetic nerves regulate intestinal secretion and permeability.[9] Enteric neurons, enteroendocrine cells and immune cells also contain CRF, which acts on smooth muscle and myenteric CRF1/2 receptors.[10] Acute stress induces delayed gastric emptying, accelerated intestinal transit and increased distal colonic motility.[11] These findings are common in some IBS patients and increased autonomic responsiveness with exaggerated colonic motor responses to stress and food are well documented.[9] However, the changes are variable and some female patients with severe C-IBS have decreased vagal activity.[12] In addition, many IBS patients have abnormal cortisol responses.[12,13] Experimental models suggest that stress induces cutaneous hypoalgesia, and visceral hyperalgesia a feature often observed IBS patients.[14]

Visceral Hypersensitivity

Altered rectal sensation is present in almost all patients with IBS.[15] Pain emanating from the gut is mediated predominantly by spinal afferent nerves which have cell bodies in the dorsal root ganglia and central terminals in the spinal cord. Most spinal afferent nerves can be made more sensitive to stimulation by inflammatory mediators (peripheral sensitization). Although intestinal biopsies from IBS patients may be normal using conventional criteria, recent studies suggest a significant proportion have low-grade inflammation especially those with a post-infective origin. Following bacterial gastroenteritis, a quarter of patients develop post-infectious IBS (PI-IBS) characterised by diarrhea and urgency[16] and a persistant increase in the numbers of enteroendocrine cells, mast cells and mucosal lymphocytes.[17] Other studies have identified increased numbers of immune cells in the lamina propria and myenteric plexus in non PI-IBS patients.[18-21] Activation of peripheral sensory nerves may cause an increase in the excitability of dorsal horn neurons which can persist even after the peripheral stimulus disappears (central sensitization). Ascending spinal pathways carry painful stimuli to the brainstem, whereas descending noradreneric, serotonergic and opioidergic anti-nociceptive pathways suppress dorsal horn excitability. Thus, drugs acting on peripheral sensory nerves act early in the pain pathway by directly blocking pain transmission or by preventing the sensitization of nerves and drugs acting on receptors at the dorsal horn or on ascending/descending pathways regulate chronic pain due to central hypersensitivity.

Motility and secretion

In patients with D-IBS high amplitude peristaltic contractions (HAPC's) occur more frequently, particularly after a meal, and are associated with accelerated colonic transit.[22] These contractions markedly increase intracolonic pressure and are frequently associated with abdominal pain. Abnormalities of small intestinal motility have also been described.[23] In contrast, patients with C-IBS tend to have fewer HAPCs and slower colonic transit.[24] Gastrointestinal transit is also dependent on secretion as up to 8 litres of saliva, gastric acid, pancreatico-biliary and intestinal secretions enter the small intestine every day although abnormalities of secretion in IBS have rarely been studied.

Challenges in developing drugs for use in IBS

The development of drugs for the treatment of IBS represents a significant challenge. Current approaches to treatment aim to normalise disturbed physiology. Thus, constipation is treated with bulking agents and pain is managed with myorelaxants. Improved understanding of

the pathophysiology of IBS will allow us to target specific central and/or peripheral receptors. Presently the most effective drugs are tricyclic antidepressants (TCADs), which are thought to act mainly centrally and 5-hydroxytryptamine (5-HT3) antagonists whose action is almost entirely peripheral. Centrally acting drugs are useful in severe IBS as they modify not only the perception of pain but also its emotional aspects and may also relieve stress, anxiety and depression. However, central side effects mean they are often poorly tolerated. Drugs that target peripheral sensory nerves are free of central effects, but may fail to counteract central hyperalgesia and may also have undesirable effects on secretion and motility. Drugs acting on motility and secretion may be less effective than predicted because co-transmitters may override the effects of specific antagonists. Receptor desensitization with loss of efficacy may also be a problem with chronic use. It is often difficult to extrapolate the results of *in vitro* studies because *in vivo* actions are usually the sum of multiple receptor effects and are subject to species differences. Drugs acting on the enteric nervous system (ENS) may have regional effects due to differences in receptor expression, whereas effects on smooth muscle tend to be more generalized and less well tolerated. By using modified release formulations specific delivery of drug to act on the ENS or in different intestinal regions is possible. Animal models of visceral hypersensitivity involve noxious distension of the colorectum (up to 80mmHg) to produce pseudoaffective responses, but extrapolating the results of these experimental models to humans may be premature, given our current level of understanding. Newer animal models of IBS are thus needed and in this respect the recent model of visceral hypersensitivity due to maternal separation looks attractive.[25]

Clinical trials have been hampered by a lack of standard criteria, although the recently modified Rome II criteria may be helpful in this respect. Study endpoints are difficult to define, as IBS symptoms are subjective and strongly influenced by psychological factors. The high placebo response in IBS means that achieving significant improvements over placebo remains difficult.

Centrally acting drugs

Antidepressants

A recent meta-analysis reported that anti-depressants were the most effective treatments for functional gastrointestinal disorders particularly in treating pain.[26] However, it should be noted that many of the trials on which the meta-analysis are based are old and of poor quality. Although the benefits of tricyclic antidepressants have often been considered to be anti-depressive, it is likely that because of their very varied actions (antihistaminic, antimuscarinic, noradrenalin & serotonin reuptake inhibition) there are additional central and peripheral actions. Tricyclics are effective analgesics particularly in neuropathic pain and can inhibit mechanosensitive pelvic afferent nerve fibre responses to colorectal distension in rat models.[27] They also slow small and large intestinal transit[28] suggesting an additional benefit in patients with D-IBS. In the only study to assess the efficacy of serotonin reuptake inhibitors (SSRI), citalopram significantly improved abdominal pain, bloating and global well being, but had no effect on bowel habit in IBS.[29] Previous studies indicate that SSRIs accelerate small bowel transit but not colonic transit[30] although they relax colonic tone.[31] In the future the development of new tricyclics with fewer side effects will help to improve tolerability. Larger trials comparing the efficacy of tricyclics vs SSRIs and conventional treatments are needed and their role in different subtypes of IBS needs to be established. Newer agents including CRF antagonists and NK antagonists have antidepressant and anxiolytic effects in addition to their effects on motility and sensation.

CRF antagonists

Activation of both central and peripheral CRF receptors is involved in the gastrointestinal response to acute stress. CRF administered centrally and peripherally induces watery diarrhea in rats by increasing colonic motility, secretion and permeability via an action on CRF-1 receptors.[10,32,33] In contrast, delayed gastric emptying is regulated by peripheral CRF-2 receptors.[34] In a manometric study, intravenous CRF increased distal colonic motility in healthy volunteers and IBS patients but the motility index and duration of symptoms were significantly longer in IBS patients.[35] The effects of CRF antagonists on gastrointestinal function in man have yet to be reported, although in a recent study of patients with major depression, a CRF-1 antagonist significantly reduced depression and anxiety scores and was well tolerated.[36] These findings suggest that centrally and peripherally acting selective CRF antagonists may have a promising role in the treatment of diarrhoea-predominant IBS, particularly when associated with features of stress, anxiety and depression.

Drugs that alter visceral sensitivity

Kappa-opioid agonists

The effects of endogenous opioids (enkephalins, beta-

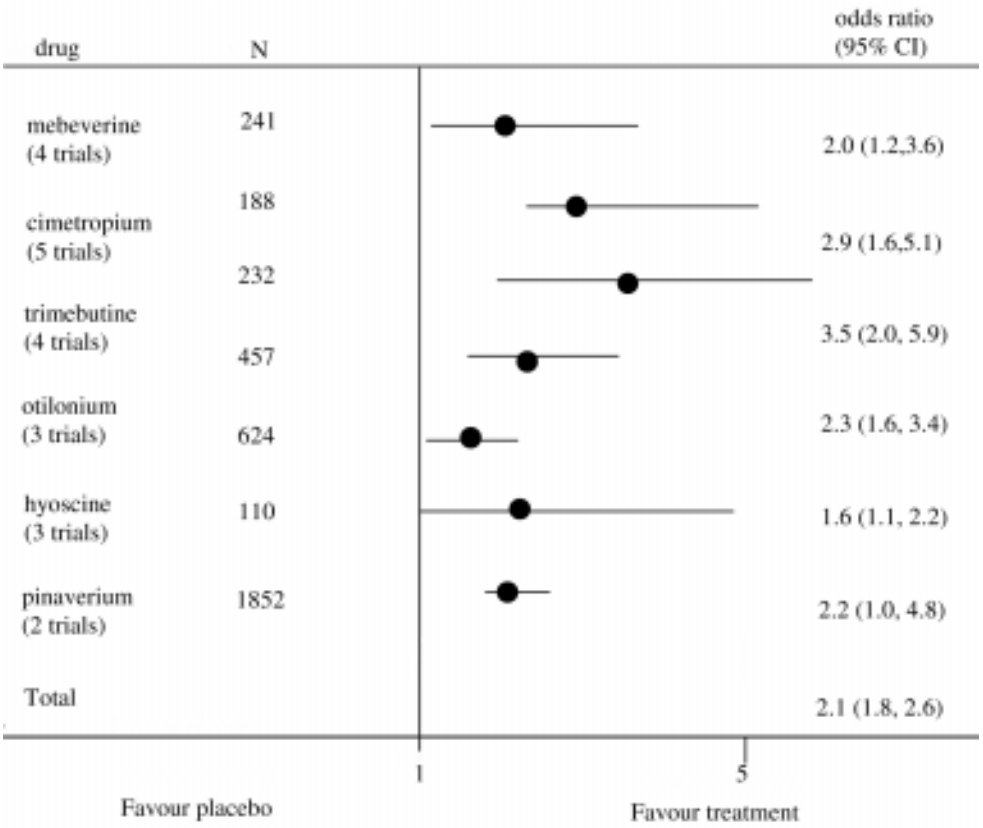

Figure 1. Meta-analysis of the effect smooth muscle relaxants on global assessment of improvement in patients with IBS (redraw from Poynard et al 2001)

endorphin and dynorphins) are mediated by m, d, and k-opioid receptors. Although centrally-acting opioid agonists benefit pain in IBS patients,[37] CNS side-effects limit their clinical use. Loperamide is a peripherally acting m-opioid agonist that improves diarrhea and urgency and delays small bowel and colonic transit without causing central effects.[38] In animal models peripheral m-opioid receptors may also mediate anti-nociceptive effects[39] although loperamide has little effect on pain in man. Peripherally acting k-opioid receptor agonists, such as fedotozine, have more potent anti-nociceptive effects than m- or d-opioid agonists and do not cause central side-effects. Fedotozine decreases the response of pelvic afferents to noxious gut distension in rats[40] and in IBS patients it increased colonic distension thresholds without any changing compliance suggesting a direct effect sensory nerves rather than colonic tone.[41] In a randomized, placebo-controlled study, fedotozine significantly improved overall disease severity, pain and bloating in patients with IBS, although the overall clinical effect was disappointingly small.[42] By acting on inhibitory enteric k-opioid receptors fedotozine also slows colonic transit. Other opioidergic drugs that have potential use in IBS include trimebutine, a weak m, d, and k agonist,[43] and the k-agonist asimadoline.[44]

Alpha2-adrenoceptor agonists

Noradrenaline acts on pre-synaptic a2-adrenoceptors to inhibit the release of substance P and glutamate from afferent nerve terminals in the spinal cord.[45] The a2-adrenoceptor agonist clonidine is thus a potent epidural anaesthetic in man.[46,47] There may be synergism between a2 and opioid receptors as the effects of peri-spinal clonidine are enhanced by mu- or delta- but not kappa-opioid agonists in rodents.[48] Studies in healthy volunteers show that clonidine reduces fasting colonic tone and significantly increases colorectal compliance, reducing the perception of gas and pain during distension. Despite these effects on visceral sensitivity, clonidine has little effect on small intestinal or colonic transit times or the colonic motor response to a meal.[49,50] The effects of clonidine on the gut are mediated by pre-synaptic alpha 2-adrenoreceptors on cholinergic enteric neurons and efferent noradrenergic axons.[51] In clinical practice the use

Table 1. The different mechanisms of action of drugs used to treat IBS

mechanism of action	example
central action	
Tricyclic antidepressants	imipramine
Serotonin reuptake inhibitors	citalopram
CRF1 antagonists	astressin
visceral sensation	
NK antagonists	saredutant
k-opioid antagonists	fedotozine
a2-adrenoceptor antagonists	clonidine
$5HT_3$ antagonists	alosetron
motility & secretion	
antispasmodics	mebeverine
m-opioid agonists	loperamide
M3 antagonists	zamenifenacin
somatostatin analogues	octreotide
CCK_1 antagonists	dexloxiglumide
$5HT_3$ antagonists	alosetron
$5HT_4$ agonists	tegaserod

of clonidine may be limited by central side-effects although pain and gas sensations appear to respond to low doses. Another a2- adrenoceptor agonist, lidamidine, slowed colonic transit and reduces stool frequency but did not improve abdominal pain in a clinical trial in IBS patients.[52]

Tachykinin receptor antagonists

The two most important mammalian tachykinins, neurokinin A and substance P, act on NK-1, NK-2 and NK-3 receptors on enteric and spinal afferent nerves. Tachykinins co-localise with acetylcholine and under normal circumstances tachykinin receptor antagonists have little effect on gastrointestinal transit.[53] However, they have a more important role in controlling GI motility, secretion, vascular permeability, immune function and visceral pain during intestinal inflammation. NK-2 antagonists are effective in animal models of visceral hyperalgesia induced by inflammation or stress[54] and also have antidepressant-like activity in rat models.[55] In a pilot study, the NK1 antagonist CJ-11974 reduced symptom intensity and rectal sensitvity following balloon distension in IBS patients[56] and further studies in IBS patients are underway.

Experimental anti-nociceptive drugs

Afferent nerves express a wide variety of receptors that are involved in peripheral and central pain transmission. Although many of these receptors are potential therapeutic targets they have yet to be tested in man (see table 2). GABA-B receptor agonists act as spinal antinociceptive agents by inhibiting the release of substance P in the spinal cord[57] and may also act on peripheral receptors.[58] Although the GABA-B receptor agonist baclofen has been shown to inhibit distension sensitive gastro-oesophageal vagal afferents,[59] its anti-nociceptive effects in IBS are untested. N-methyl-D-aspartate (NMDA) receptors are ionotropic glutamate receptors. Both peripheral and dorsal horn NMDA receptors respond to noxious colorectal distension[60,61] and NMDA receptor mediated changes in synaptic excitability at the dorsal horn are particularly important in the development of central sensitization. Fully competitive NMDA antagonists, such as ketamine, cause central toxicity, but non-competitive antagonists including racemide are well tolerated.[62]

A different approach to treating patients with persistant, low-grade inflammatory change is to use anti-inflammatory agents. In rodent models of post-infectious (PI-IBS), the inflammatory response associated with nematode infection causes marked changes in enteric nerve function and smooth muscle contractility that persist following the resolution of inflammation. Muscle hy-

Table 2. Experimental antinociceptive agents

class of drug	natural ligand	example	site of action
NMDA antagonist	glutamate	racemide	spinal
GABA-B agonist	GABA	baclofen	spinal
vanilloid VR-1 antagonist	H+, heat, capsaicin	capsazepine	peripheral
cannabinoid C1 agonist	endogenous cannabinoids	andandamide	peripheral
bradykinin B2 antagonist	bradykinin	icatibant	peripheral
cGRP antagonist	cGRP	BIBN-4096BS	peripheral
purinocept or P2X3	ATP	TNP-ATP	peripheral
PAR-2 antagonist	activated by trypsin	-	peripheral

Table 3. The effects of different motility/secretory agents.

mechanism of action	indication	effect on motility & secretion
m-opioid agonist	D-IBS	↓SB/colon transit
M3 antagonist	D-IBS	↓colonic motility
somatostatin	D-IBS	↓SB/colon transit ↓secretion
oxytocin	C-IBS ?	↑colonic motility
CCK-1 antagonist	nonD-IBS	↓colonic motility
5-HT_3 antagonist	D-IBS	↓SB/colon transit ↓secretion
5-HT_3 agonist	C-IBS ?	↑SB transit
5-HT_4 antagonist	D-IBS ?	↓colon transit (small effect)
5-HT_4 agonist	C-IBS	↑SB/colon transit ↑secretion
neurotrophin	C-IBS ?	↑colon transit

percontractility appears to be dependent on cyclooxygenase-2 (COX-2) derived prostaglandin E2 (PGE2) production by the muscle and can be inhibited by corticosteroids and COX inhibitors.[63] However, in a preliminary study assessing the effect of steroids in PI-IBS patients, 30mg prednisolone daily for 3 weeks did not improve clinical symptoms compared to placebo, despite a 25% fall in lamina propria lymphocyte count.[64] Microscopic colitis, an idiopathic chronic diarrhoeal syndrome characterised by histological mucosal inflammation despite a macroscopically normal colon, has features in common with D-IBS. In small open label study bismuth subcitrate, an agent with anti-inflammatory properties, resolved diarrhea and produced histological improvement[65] suggesting that it may also be beneficial in PI-IBS.

Drugs affecting motility and secretion

Muscle relaxants:

In a meta-analysis smooth muscle relaxants were found to significantly improve overall symptoms, abdominal pain and distension compared to placebo.[66] However, most of the studies were small and inconclusive and there is likely to be a publication bias. In a recent large, well designed study, mebeverine was found to be inferior to alosetron which itself only benefits 1 in 8 patients.[67] These drugs relax smooth muscle by a variety of mechanisms and many have additional effects on intestinal transit. Mebeverine, a reserpine derivative, was recently shown to delay transit and inhibit colonic mass movements.[68] Otilonium bromide is a combined calcium channel blocker, antimuscarinic and tachykinin NK2 antagonist.[69] Pinaverium acts as an L-type calcium channel blocker in colonic smooth muscle.[70] Alverine is a 5-HT1A antagonist that may have rectal antinociceptive properties.[71] Cimetropium and hyoscine are antimuscarinic agents.

Muscarinic modulators

Acetylcholine is the major excitatory neurotransmitter in the gut and its effects are mediated by nicotinic and muscarinic receptors. Muscarinic M1 receptors are located on myenteric neurones and are important in the coordination of colonic propulsion.[72] Smooth muscle contraction is stimulated predominantly by M3 receptors while M2 receptors have a modulatory role.[73] The acetyl-cholinesterase inhibitor neostigmine stimulates M1, M2 and M3 receptors stimulating coordinated colonic propulsion with accelerated transit.[72] By increasing colorectal tone and reducing compliance it increases pain and urgency to distension and is thus unsuitable for treating IBS. The M3 selective muscarinic antagonists darifenacin, zamifenacin, and YM905 have been developed to specifically relax gut smooth muscle while minimizing anti-cholinergic side-effects. In a manometric study, zamifenacin significantly reduced fasting and, more significantly, post prandial distal colonic motility in patients with IBS.[74] In animal models, the newer M3 agonist YM905 has similar potency to darifencin.[75] Such drugs have undergone recent clinical trials without any published evidence of success.

Somatostatin and Octreotide

Somatostatin is widely distributed in the gut and is found mainly in enteric neurones and enteroendocrine cells. The effects of somatostatin and its analogues are mediated by 5 receptor subtypes (SST 1-5) which are all present in the gastrointestinal tract. Octreotide, the most widely known analogue, is a subcutaneously administered non-selective agonist at SST-2,3 and 5 receptors. Somatostatin acts within the ENS to inhibit peristalsis by controlling nitric oxide/vasoactive intestinal peptide (NO/

VIP) release during descending relaxation an effect mediated by SST-2 receptors in the rat.[76] In healthy subjects and IBS patients, octreotide markedly inhibits intestinal motility, particularly in the small bowel.[77] It also inhibits intestinal and pancreatic secretion and the release of other gut peptides.[78] Conflicting studies of the viscero-analgesic properties of octreotide in man suggest either a direct effect on visceral sensitivity[79] or that it simply relaxes the colon.[80] Constipation may improve during lactation and and oxytocin was recently shown to stimulate colonic activity in healthy women[81] and significantly reduce thresholds for visceral perception in IBS patients.[82]

CCK antagonists

CCK is produced by enteroendocrine cells in the proximal small intestine and is released into the circulation following a meal. In the colon, CCK acts on CCK-1 receptors on enteric cholinergic neurons[22,83] and smooth muscle[84] to produce contraction. In the upper gut, CCK release following a fatty meal sensitizes vagal afferents to distension,[85] but its effect on colonic visceral afferents is unknown. CCK is not an important mediator of the gastrocolonic response in healthy volunteers or patients with IBS,[86] although in IBS patients, a fatty meal stimulates exaggerated and prolonged CCK release[87] and intravenous injection of CCK-8 into patients with D-IBS stimulates exaggerated HAPCs.[22] In a randomised placebo-controlled trial, patients with non D-IBS felt significantly better and had less pain and bloating following 12 weeks treatment with the CCK-1 receptor antagonist dexloxiglumide, but a similar benefit over placebo was not seen in the parallel D-IBS group.[88] The CCK-2 receptor is the main receptor subtype in the CNS and in man centrally acting CCK-2 agonists are anxiogenic,[89] although in a recent trial, a CCK-2 antagonist did not improve anxiety.[90] In rat models, activation of central CCK-2 receptors stimulates colonic transit[91] and, although CCK-2 receptors are also found on rat myenteric neurons, their presence in man has not been demonstrated.

Serotonergic drugs

Serotonin is present in enterochromaffin cells throughout the gut and is released into the mucosa in response to mechanical, chemical and toxic stimulation. Endogenous serotonin acts at $5\text{-HT}_{1P/4}$ receptors on mucosal intrinsic sensory neurons stimulating peristalsis and secretion. Stimulation of 5-HT_3 receptors on mucosal extrinsic afferents transmits sensory information to the CNS. In D-IBS increased numbers of enterochromaffin cells, excessive post-prandial 5-HT release and increased platelet 5-HT stores have all been documented.[17,92,93] Confusingly C-IBS patients have significantly higher mucosal 5HT levels than controls or D-IBS patients,[94] but whether this represents increased synthesis or impaired release is unknown. The most promising drugs are the 5-HT_3 antagonists for the treatment of D-IBS and 5-HT_4 agonists for the treatment of C-IBS.

Alosetron is a potent 5-HT_3 antagonist that induces constipation by increasing small intestinal absorption and reducing colonic motility.[95] 5HT_3 receptors are widely distributed in the brain and spinal cord and in rodents alosetron has antinociceptive and anxiolytic properties.[96,97]

In man, alosetron does not alter visceral sensitivity but may relieve pain by reducing colorectal tone.[98] Although alosetron has not been shown to be an anxiolytic or antidepressant in women,[99] it does improve global symptoms and quality of life.[100] In phase III studies, it produced sustained improvements in pain, stool frequency, stool consistency and urgency, although the absolute improvement over placebo response rates was modest (approximately 10%). Unfortunately, alosetron was withdrawn after several months on the market following reports of ischaemic colitis and severe constipation. Alosetron has only been demonstrated to be effective in females possibly because of inadequate numbers. However, cilansetron a 5-HT_3 antagonist, with similar properties is also effective in males with D-IBS.[101]

The mode of action of 5-HT_4 receptor agonists tegaserod and prucalopride is unclear but may involve stimulation of peristalsis, facilitation of myenteric acetylcholine release or direct effects on smooth muscle.[102] Tegaserod increases colonocyte secretion and accelerates small intestinal and colonic transit in healthy subjects,[103] although in C-IBS, patients, its effects on intestinal transit are less marked.[104] In clinical trials performed mainly in females with C-IBS tegaserod improved the overall assessment of relief as well as abdominal pain and constipation but not bloating.[105,106] The overall increase in efficacy above placebo is similar to that seen with alosetron. In healthy subjects, prucalopride, a more selective 5HT_4 agonist, increases stool frequency and looseness, accelerates colonic transit and increases both segmental and high amplitude peristaltic contractions (HAPCs).[107,108] Colonic transit is also stimulated in constipated patients.[109] Although prucalopride is effective in patients with chronic constipation,[110] its efficacy in C-IBS has not been tested in phase III trials due to concerns over teratogenicity in rats. Several 5-HT_4 antagonists have been

evaluated as antidiarrheal agents, although the effects in healthy subjects are disappointing. Piboserod did not affect small intestinal transit, only slightly delayed colonic transit and did not alter colonic sensory function or compliance.[111] In animal models, the selective 5-HT_3 agonist YM-31636 increased stool frequency and water content and increased colonic tone without increasing visceral sensitivity.[112,113] In a preliminary study in healthy volunteers, another 5-HT_3 agonist MKC-733 accelerated small intestinal transit.[114] Although 5-HT_3 agonists may act as anti-constipating drugs, their use may be limited by side-effects which include flushing, nausea and abdominal pain. 5-HT_{2B} and 5-HT_7 receptors on human colonic smooth muscle have recently been desribed, but the effects of specific agonists and antagonists have yet to be tested in man.[115,116]

Neurotrophins

Neurotrophins, including brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), promote survival and maturation of neurons in the brain, viscera and skin. In a recent study, recombinant NT-3 and BDNF significantly accelerated colonic transit and increased stool frequency in healthy volunteers. NT-3 also significantly accelerated colonic transit and improved defaecation in patients with constipation.[117] The effects of neurotrophins on nerve growth may be useful in slow transit constipation or enteric neuropathies, where there is evidence of denervation. However, there is concern that long-term use could lead to neuronal excitability and disordered motility. Both drugs are administered subcutaneously and some patients may develop injection site reactions or BDNF antibodies. Thus, a role in the treatment of C-IBS seems unlikely.

CONCLUSION

The development of new drugs for IBS requires a greater understanding of the causes and mechanisms of IBS. Better definition of IBS subgroups according to aetiology rather than symptoms will allow a more targeted approach to therapy. Patients with severe forms of IBS associated with psychopathology require drugs with both central and peripheral actions. Tricyclic antidepressants are presently the most effective drugs for such patients, but CRF antagonists and NK antagonists are currently being assessed in clinical trials. In patients whose IBS is triggered by inflammation, anti-inflammatory agents, motility drugs and visceral analgesics may all be effective. Although drugs which modify secretion and motility have been tested in clinical trials and demonstrate small but significant benefits over placebo, they have failed to make a substantial impact on the treatment of IBS. Visceral analgesics specifically target the pain pathways, alleviating the main symptom of IBS. Future research in this area is promising as many target receptors have been identified on visceral afferent nerves, although this approach is largely untested.

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