Irritable bowel syndrome and visceral hypersensitivity : risk factors and pathophysiological mechanisms

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Abstract

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, characterized by abdominal pain and altered intestinal motility. Visceral hypersensitivity is an important hallmark feature of IBS and is believed to underlie abdominal pain in patients with IBS. The two main risk factors associated with the development of IBS are gastrointestinal inflammation and psychological distress.

On a peripheral level, visceral sensitivity seems to be modulated by several mechanisms. Immune cells in the mucosal wall, such as mast cells, and enterochromaffin cells may sensitize afferent nerves by release of their mediators. Furthermore, increased mucosal permeability, altered intestinal microflora and dietary habits may contribute to this feature. On a central level, an increased prevalence of psychiatric comorbidities is demonstrated in IBS patients, alongside alterations in the hormonal brain-gut axis, increased vigilance towards intestinal stimuli and functional and structural changes in the brain.

The pathogenesis of IBS is complicated and multifactorial and the treatment remains clinically challenging. Dietary measures and symptomatic control are the cornerstones for IBS treatment and may be sufficient for patients experiencing mild symptoms, alongside education, reassurance and an effective therapeutic physician-patient relationship. New pharmacological therapies are aimed at interfering with mediator release and/or blockade of the relevant receptors within the gut wall, while modulation of the intestinal flora and diet may also be of therapeutic benefit. Tricyclic antidepressants and serotonin reuptake inhibitors act both on a central and peripheral level by modulating pain signalling pathways. (Acta gastroenterol. belg., **2016**, 79, **29-38**).

Key words : irritable bowel syndrome, visceral hypersensitivity, abdominal pain.

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, characterized by chronic abdominal pain and an altered bowel habit. Visceral hypersensitivity and altered intestinal motility are presumed to underlie these symptoms. In the Western population the prevalence of IBS is 5-15% and affects slightly more women compared to men (OR 1.67, 95% CI : 1.53-1.82) (1). Specific prevalence rates for Belgium are lacking but presumably approximate those of the Netherlands (5.8%) (2). IBS negatively affects patients' quality of life as demonstrated by the SF-36 questionnaire (a patient reported survey of patient health) (3). In combination with its chronicity and high prevalence, IBS therefore undoubtedly poses an important health care issue associated with absenteeism and increased health care expenditure. In primary care 10-15% of patients consult for IBS symptoms and this amounts to 25-50% in secondary and tertiary care (1). Nevertheless, only a subgroup of patients (10-50%) consults for medical care, an indication that the true health care burden is even larger (1,4).

As currently no cure is available, treatment is directed towards symptom control. However, treatment options are limited and clinical results are often disappointing. Reassurance, understanding and patient education are the main cornerstones of treatment (5). In addition, dietary measures and symptom diaries may be sufficient for patients experiencing mild symptoms (6). In moderate-to-severe IBS pharmacological and psychological therapies are often required (7). However, the development of new therapeutic targets is hampered by the insufficiently elucidated underlying pathophysiological mechanisms (8). In this review we provide a short overview of identified risk factors and pathophysiological mechanisms in the development of IBS and visceral hypersensitivity and how these can be used to explore new therapeutic options for the treatment of IBS.

Diagnostic criteria for IBS

IBS is a functional bowel disorder for which a diagnostic marker is currently not available. Therefore, to date the diagnosis of IBS is based on symptom criteria, the Rome III criteria (Table 1), composed of the combined presence of chronic abdominal discomfort (altered visceral sensitivity) and an altered bowel habit (altered motility). In addition, IBS patients can be subtyped according to their predominant bowel pattern : constipation-predominant (IBS-C ; 20-30%), diarrhoea-predominant (IBS-D ; 38-50%) or mixed (IBS-M ; 6-16%) when alternating between loose and hard stools ; the remainder is classified as IBS-U (unsubtyped ; 24-60%) (5,9).

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Table 1. — **Rome III diagnostic criteria for the diagnosis of irritable bowel syndrome**

Rome III Diagnostic criteria
Recurrent abdominal pain or discomfort at least 3 days/month in the last 3 months associated with two or more of the following : • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to the diagnosis.

The diagnosis of IBS can only be made after a concise anamnestic interview and careful physical examination. The need for laboratory testing and/or structural evaluation should be based on the patients' age, the duration, severity and nature of symptoms, psychosocial factors and family history and may include analysis of blood and stool samples, colonoscopy and/or abdominal ultrasonography to exclude an organic cause (5). 'Alarm' signs such as fever, gastrointestinal bleeding, anaemia, weight loss, abdominal mass, nocturnal symptoms, faecal soiling or family history of colon cancer are not compatible with a diagnosis of IBS and always warrant further investigation (4, 5). Many IBS patients additionally report upper GI symptoms and there is considerable overlap between IBS and other functional gastrointestinal disorders such as functional dyspepsia in 7 to 79% of cases, suggesting a common underlying dysfunction and pathophysiology (10).

Risk factors : psychological distress and intestinal inflammation

Currently the two main risk factors associated with the development of IBS are psychological distress and intestinal inflammation (Fig. 1).

IBS is associated with a increased prevalence of adverse life events during childhood, such as emotional or sexual abuse or the loss of a parent (11,12). IBS patients with a burdened history display more psychiatric co-morbidities and tend to utilize healthcare services more frequently. These adverse life events also correlate with symptom severity and response to treatment. Hence, a history of adverse life events influences the therapeutic approach and outcome. Centrally-acting therapies are often preferred over symptom-based therapies in this group of patients (13).

A second important risk factor in IBS development is a previous gastrointestinal inflammation. In up to 35% of IBS cases, new-onset IBS follows a severe episode of gastroenteritis and symptoms may persist up to eight years post-infection (14). This post-infectious IBS (PI-IBS) is associated with disease-related factors (e.g. severity and duration of infection and invasiveness of the pathogen), as well as with host-specific factors (such as smoking, female sex, depression or adverse life events preceding the infection) (15). The fact that previous bowel inflammation can trigger new-onset IBS is further corroborated by observations of an increased prevalence of IBS-like symptoms in patients with quiescent inflammatory bowel disease (IBD). Despite mucosal healing,

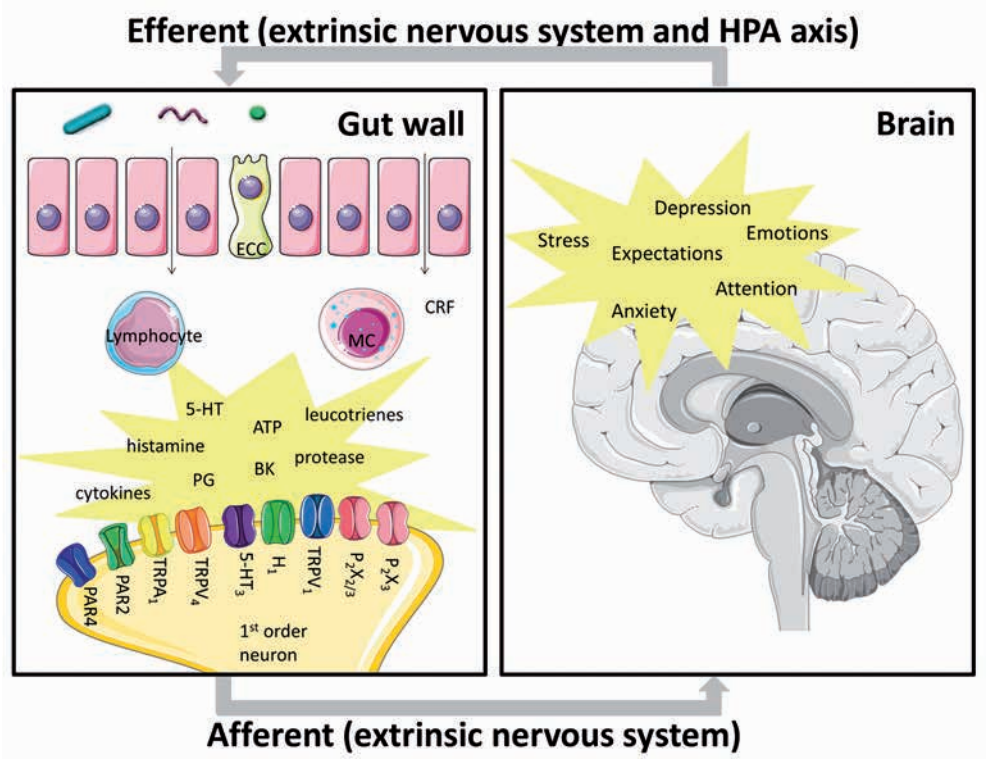

Fig. 1. — Simplified figure of the mechanisms involved in the pathogenesis of visceral hypersensitivity as discussed in this review and thus non-exhaustive.

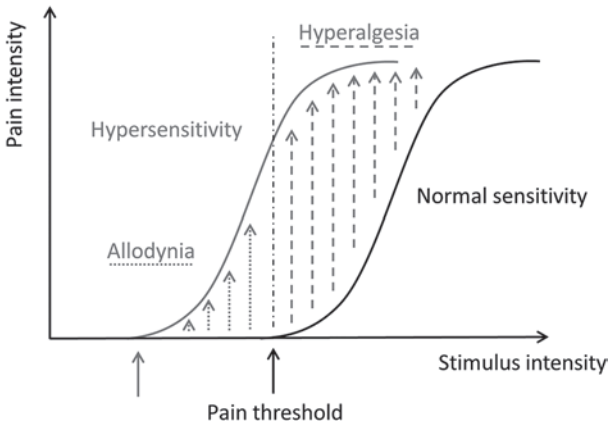

Fig. 2. — Concept of hypersensitivity. The black curve represents the normal pain perception. Only when the pain threshold is exceeded (full thickness arrow) does the stimulus induced pain. The grey curve demonstrates hypersensitivity, characterized by a decreased pain threshold (grey arrow), allodynia (dotted arrows) and hyperalgesia (dashed arrows). Based on (17).

46% of Crohn's disease patients and 36% of those with ulcerative colitis in remission continue to suffer from abdominal pain and altered bowel habits, meeting the diagnostic criteria for IBS (16).

Visceral hypersensitivity

Visceral hypersensitivity, or an increased perception of stimuli originating from the viscera, is a hallmark feature of IBS and is currently regarded as the main factor underlying abdominal pain in IBS patients (17). Visceral hypersensitivity entails both hyperalgesia and allodynia (Fig. 2) (18). Hyperalgesia refers to an increased response to a normally painful stimulus. Allodynia refers to a painful response to a normally innocuous stimulus (19). In clinical trials, visceral hypersensitivity or disturbed stimulus perception is most commonly objectified by balloon distension. A balloon is inserted in the distal colon or rectum and is inflated with increasing pressures or volumes to stimulate the sensory afferent nerve endings in the colon wall (17). After each distension, patients grade their perceived pain on a visual analogue scale. IBS patients report significant lower pain thresholds and higher pain scores compared to healthy controls. Studies report that 35-90% of IBS patients demonstrate visceral hypersensitivity and that this increased sensitivity may correlate with the severity of symptoms, such as abdominal pain and bloating (17,18).

Visceral hypersensitivity can arise from a peripheral or central level (Fig. 3). In the periphery, vagal and spinal (splanchnic and pelvic) afferent nerves register mechanical, thermal and chemical stimuli and convey this information to the spinal cord. Here, vagal and spinal afferents connect with second order neurons whose cell bodies reside in respectively the brainstem and the dorsal horn of the spinal cord (20). In the spinal cord, these secondary afferents cross the midline and ascend mainly through the spinothalamic tract to the thalamus. The signal is then transferred from the thalamus to cerebral areas involved in somatosensory perception and cognitive and affective modulation, such as the somatosensory and insular cortex, the anterior cingulate cortex (ACC) and the limbic

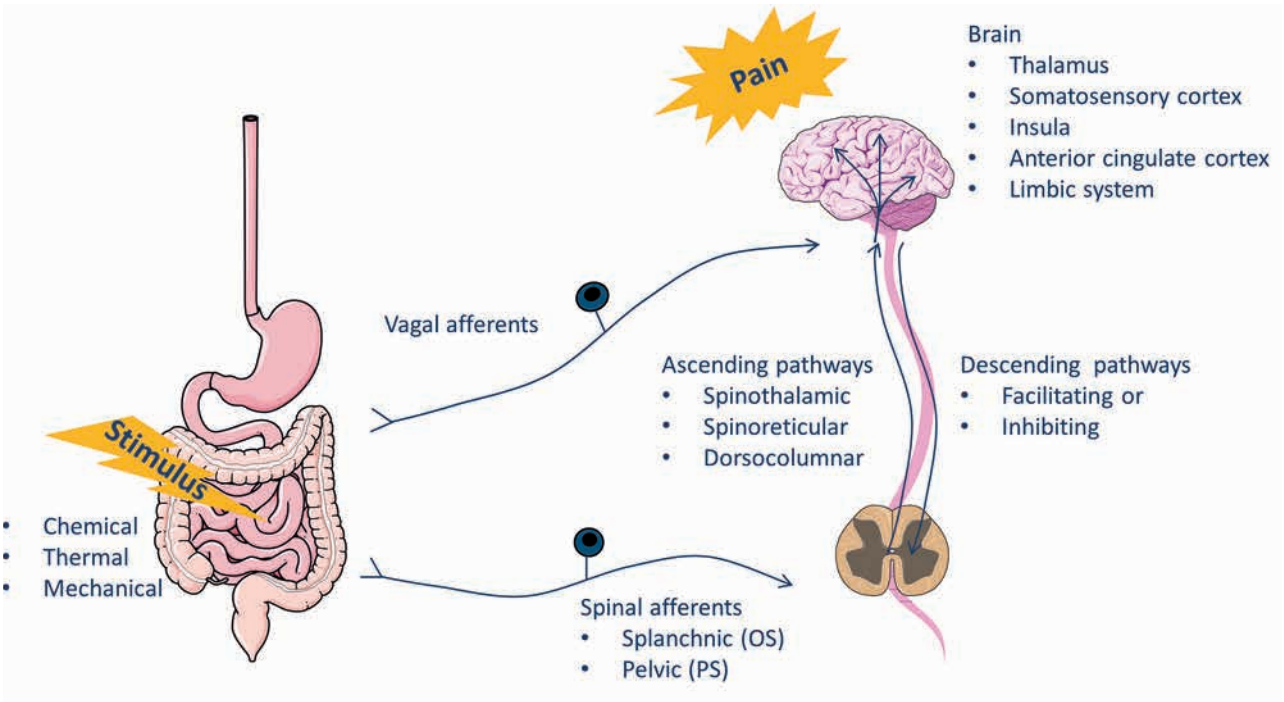

Fig. 3. — Schematic overview of the neuroanatomic pathways involved in the conduit of sensory information from the bowel to the brain and in the perception of pain. PS, parasympathetic nervous system ; OS, orthosympathetic nervous system.

system. Besides the spinothalamic tract, the ipsilateral dorsal columns are also involved in the transmission of sensory information to the thalamus (21). Finally, the central nervous systems (CNS) modulates pain transmission actively through descending pathways, which can either inhibit or facilitate the signal transduction (21). Visceral hypersensitivity may result from dysfunctional pain modulation on each of the aforementioned levels. For a more extensive description of the neuroanatomic components involved in visceral pain perception, we refer to a recent review of Vermeulen *et al*. (22).

Pathogenesis of visceral hypersensitivity

Peripheral factors

Mucosal inflammation : the role of specific cell types

The observation of new-onset IBS after an acute gastroenteritis and the increased prevalence of IBS-like symptoms in patients with quiescent IBD cultivated the hypothesis that a chronic low-grade mucosal inflammation or immune activation contributes to symptom generation in IBS (18,23). Activation of mucosal immune cells influencing neuronal activity has further nursed the concept of neuroimmune modulation as an underlying mechanism in visceral hypersensitivity (24). Corroborating evidence for this theory was delivered by multiple studies showing increased numbers of mast cells (MCs), lymphocytes and enterochromaffin cells (ECCs) in the gut wall of IBS patients (25).

Changes in the intestinal barrier function resulting in an increased uptake of luminal antigens have been suggested to represent the driving force behind the enhanced immune activation (25). The permeability of this intestinal barrier is potently modulated by stress, via the release of corticotropin releasing factor (CRF) and by mediators released by immune cells such as MCs (histamine, tryptase, prostaglandins) and T-lymphocytes (tumour necrosis factor alpha (TNF-α) and interferon γ (IFN-γ)) (26,27). The pathophysiological importance and therapeutic potential of each of these targets will be discussed in the following section.

Mast cells

The location of MCs in close proximity to afferent nerve endings in the gut wall, which convey sensory information to the CNS, together with the bidirectional communication between MCs and afferent nerves, suggest an important role for the mast cell in the pathogenesis of visceral hypersensitivity and IBS (28, 29). In addition, a positive correlation was reported between the increased number of MCs in the bowel wall and the frequency and severity of abdominal pain in IBS patients (28). MCs are activated by crosslinking of IgE antibodies (against food antigens, the intestinal microflora or invading pathogens) that bind to the IgE receptor (FcεRI) on the mast cell membrane, but MC activation also occurs through non-IgE related mechanisms, such as cytokines, neuropeptides and stress. Activation of MCs results in degranulation and mediator release (25). Conversely, treatment with the MC stabilizer ketotifen (8 mg, 8 weeks) increased the pain threshold and decreased abdominal pain in a population of 60 IBS patients (30). The most important MC mediator is histamine, acting on specific histamine receptors (H1-H4). As several studies demonstrate increased histamine release in the colonic mucosa of IBS patients, blocking these receptors may result in a new therapeutic strategy (28). Preliminary results from a phase II study corroborate this hypothesis as abdominal pain was significantly reduced by the selective histamine H1 receptor antagonist ebastine in 28 IBS patients (31). Based on these promising results, the investigators recently initiated a multicenter trial (NCT01908465). In addition, preclinical data also suggest involvement of the histamine H4 receptor in the pathogenesis of IBS (32). A recent study demonstrated a dose-dependent effect of the histamine H4 receptor antagonist JNJ7777120 on visceral hypersensitivity in a rat model for post-inflammatory IBS (33). However, clinical studies in IBS patients regarding this receptor are not yet initiated.

Tryptase, another MC mediator, binds to proteinase activated receptors (PARs) and is also believed to contribute to visceral hypersensitivity as PAR-2 antagonists and PAR-4 agonists display anti-nociceptive effects in preclinical studies (34). Furthermore, it was recently demonstrated in a preclinical study that tryptase contributes to increased rectal permeability in IBS and that the elevated permeability could be repressed by addition of the tryptase inhibitor nafamostat to rectal biopsy specimens of IBS patients (35).

T-lymphocytes

The number of T-lymphocytes is also increased in mucosal biopsies from IBS patients.

Several studies have quantified the expression of pro-inflammatory cytokines (such as interleukin (IL)-1β, IL-2, IL-5, IL-6, IL-13, IFN-γ and TNF-α) and anti-inflammatory cytokines (such as IL-10) in the intestinal mucosa, in order to gain further insight in their contribution to the local immune disturbance, however so far results are inconclusive (25,36-39). Nevertheless, the anti-inflammatory drug mesalazine, which inhibits cytokine release from T-lymphocytes, was demonstrated to be effective in the treatment of IBS (40).

Enterochromaffin cells

ECCs are sensory cells located in the intestinal mucosa. They react to luminal stimuli such as pressure and the presence of nutrients. ECCs translate these signals into neuronal responses by secretion of peptides and amines, which are able to excite enteric nerve endings (15). Several studies support the role of ECCs and their main mediator serotonin (5-HT) in the pathogenesis

of IBS. Firstly, several groups reported ECC hyperplasia in the colonic and rectal mucosa of IBS patients (41-43). Secondly, elevated levels of 5-HT were demonstrated in the supernatants of IBS mucosal biopsies (43). Thirdly, IBS has been associated with polymorphisms in the tryptophan hydroxylase, the rate-limiting step in the 5-HT biosynthesis and in the serotonin reuptake transporter, which is expressed on enterocytes and terminates 5- HT-mediated actions by removing it from the interstitial space (44-47).

In addition to motor and sensory effects in the gastrointestinal tract, 5-HT is also involved in the transmission of sensory information by afferent neurons to the CNS and acts as a neurotransmitter in the descending inhibitory and facilitating tracts in the spinal cord (48).

5-HT binds to seven receptor subtypes ; three are presumed to be involved in the pathogenesis of visceral hypersensitivity, and therefore represent interesting targets for IBS treatment : the *5-HT3 receptor, 5-HT4 receptor,* and *5-HT2B receptor*.

The *5-HT3* receptor is expressed on extrinsic afferent neurons and is involved in the transmission of sensory information to the CNS and in the peristaltic reflex (48,49). Several studies show the alleviating effect of selective 5-HT3 antagonists like alosetron, cilansetron and ramosetron on abdominal pain in IBS patients (48,50). Initially, alosetron was successfully introduced in the United States for treatment of IBS-D, but was later withdrawn from the market due to severe side effects (severe constipation and ischemic colitis) (50). Although the *5-HT4* receptor is thought to mainly mediate motor and secretory activity, the 5-HT4 agonist tegaserod also decreased visceral hypersensitivity in IBS patients (51). Tegaserod is effective in the treatment of IBS-C, but was also withdrawn from the market in 2007 due to serious cardiovascular side effects (increased risks of acute myocardial infarction and stroke) (50). The selective 5-HT4 agonist prucalopride has prokinetic properties and was demonstrated to be beneficial in the treatment of chronic constipation, although no high-quality controlled studies have addressed the efficacy of prucalopride in IBS-C yet (52).

Moreover, prucalopride is currently not reimbursed by the INAMI/RIZIV.

Preclinical data concerning the selective *5-HT2B* receptor antagonist RS-127445 demonstrate a significant reduction of visceral hypersensitivity and defecation frequency in animal models for IBS (53). Further research is required to explore the potential of this receptor antagonist in a clinical setting.

Mucosal inflammation : other possible targets

Besides MC, T-lymphocytes and ECCs and their mediators, other receptors and signal molecules are emerging as potential targets for new therapies in IBS. Prostaglandins and leukotrienes are synthesized from arachidonic acid by the enzymes cyclo-oxygenase and lipoxygenase. They stimulate afferent neurons and play an important role in the sensitization process (54). Also mediators released during acute inflammation contribute to visceral hypersensitivity. In this regard ATP and bradykinin potently activate afferent nerve endings in the intestinal wall by binding to their respective receptors (55,56). Transient receptor potential (TRP) channels such as TRPV1 receptor are expressed on extrinsic sensory afferents, enteric neurons, epithelial cells and endocrine cells and are involved in visceral sensations (57). Activation of the TRPV1 receptor by heat (> 43°C), low pH and capsaicin (the active substance in peppers) leads to calcium influx and results in the sensation of burning pain. Several mediators involved in the pathogenesis of IBS, such as histamine, 5-HT, bradykinin, prostaglandines and ATP sensitize TRPV1 receptors (50,58,59). These TRP channels are considered the integrators of sensory input. Studies on the anti-nociceptive potential of selective antagonists for TRP channels have reached the clinical phase. However a number of clinical trials with a systemic TRPV1 antagonist were terminated prematurely due to severe hyperthermia (60), indicating the need for a more specific target. In this regard, TRPV4 and TRPA1 may be of interest. TRPV4 channels seem to take part in the generation of pain and hyperalgesia in the colon and integrate with PAR-2 receptors (61). TRPA1 channels are involved in mechanical and chemical colonic hypersensitivity, provoked by inflammation and stress (57,61). Although effective agonists and antagonist have been identified for each of these channels in a preclinical setting, further research is required before clinical studies can be initiated.

Role of microflora and small intestinal bacterial overgrowth

The role of the microflora in the pathogenesis of IBS has gained increased interest over the past years. The current working hypothesis is that changes in the interaction between intestinal microbiota and permeability of the colonic wall may initiate mucosal inflammation, which results in the activation of nociceptive sensory pathways and a disruption of the enteric nerve system signalling (62).

Small intestinal bacterial overgrowth (SIBO) is associated with various aspects of IBS, such as postprandial bloating and abdominal distension, altered motility, visceral hypersensitivity, an abnormal brain-gut interaction, a disturbance of the autonomic nervous system and immune activation. SIBO as a feature of IBS pathogenesis is supported by several studies, which demonstrate that IBS symptoms decrease after eradication of SIBO (62,63). Other studies demonstrate that the non-systemic antibiotic rifaximin significantly improves IBS symptoms such as bloating and flatulence (64). Currently, rifaximin is only approved for the treatment of travellers' diarrhoea and hepatic encephalopathy.

Besides SIBO, an altered microflora is also associated with IBS. Quantitative research shows a decreased

number of *Lactobacillus* and *Bifidobacterium* species in the colon of IBS patients and an increased number of gas-producing bacteria like *Clostridium* species (4,65). *Lactobacilli* and *Bifidobacteria* are mucosa-adherent species that prevent binding of pathogens and in this way they reinforce the mucosal barrier (4). Noxious micro-organisms, such as *Clostridium* species, produce gas and short-chain fatty acids and deconjugate intraluminal bile salts. The products of this deconjugation result in changes in water and electrolyte transport, which may influence gastrointestinal motility and sensitivity (4,65). Probiotics aim to re-establish the intestinal microbiotal balance. A recent meta-analysis demonstrates a positive effect of probiotics on overall IBS symptoms (66). However, to date it remains unclear which species or dose should be administered for an optimal effect. The use of probiotics should be considered individually, secondary to dietary adjustments. When probiotics do not achieve a beneficial effect after at least 4 weeks, a different formulation can be tried (67). Long-term effects are still unclear and further research is warranted before probiotics should be incorporated in the standard of care.

Prebiotics are specific nutrients that create an optimal environment for beneficial bacterial species and could potentially prove useful in the treatment of IBS. The prebiotic trans- galacto-oligosaccharide (B-GOS) decreased IBS symptoms compared to placebo and stimulated the growth of *Bifidobacteria* in a double-blind placebo-controlled trial (68). Finally, symbiotics, the combination of prebiotics and probiotics, also seem an interesting new therapeutic approach, but again, further research is required to explore its full potential (69).

Faecal microbiota transplantation (FMT) refers to introducing faeces from healthy donors into the gastrointestinal tract of diseased individuals. There is a growing interest in FMT as a treatment for various gastrointestinal diseases, including IBS, as it may restore the intestinal microbial balance. Currently, only a few reports on the use of FMT in the treatment of IBS are available, but show promising clinical responses for IBS-D as well as IBS-C (70-72). Currently, several well-designed controlled trials are investigating the therapeutic potential of FMT in IBS (http ://clinicaltrials.gov) and the results are eagerly awaited by both patients and clinicians.

Finally, diet and nutrition can also alter intestinal microflora. Fermentable oligo- di- and monosaccharides and polyols (FODMAPs) are small, osmotically active molecules that are poorly resorbed and rapidly fermented by the intestinal flora. Reduction of nutritional FODMAPs is a simple way to interfere with the microflora and decrease luminal distension (73). A recent controlled cross-over study with 30 patients showed that a diet low in FODMAPs reduced IBS symptoms such as bloating and abdominal pain (74). These data support the proposition to include a FODMAP-low diet in the first-line treatment of IBS. Although patients frequently perceive an association between certain foods and their symptoms, this has not been objectified in clinical trials (67). Based on the individual patient history, patients may be advised to alter their dietary habits. If IBS symptoms do not improve after a period of 2-4 weeks, the diet should be revised (67). A balanced nutrition should be maintained at all times.

Herbal preparations and peppermint oil

The herbal preparation STW 5, a formula containing hydroethanolic extract of 9 herbs, was also shown to reduce abdominal pain and IBS symptom scores in a multicenter, double-blind randomized controlled trial (75,76). The effects seems to be mediated by inhibition of TNF-α (77), interaction with 5-HT3 and 5-HT4 receptors and enhanced gastrointestinal secretions (75,78).

Among the single herbal preparations, most evidence is available for the efficacy of the essential oil of Mentha piperita in IBS (75). A significant improvement of quality of life and overall IBS symptoms compared to placebo has been reported and is contributed mainly to its antispasmodic effect (79-82). Similarly, otilonium bromide was also shown to reduce abdominal pain indirectly by interfering with smooth muscle activity (83).

Central factors

Altered neuroendocrine responses

Interaction between the CNS and the gut is established by the so-called 'brain-gut axis' (BGA) consisting of a hormonal and a neuronal pathway (Fig. 1). The hormonal pathway consists of the hypothalamic-pituitary-adrenal axis (HPA-axis). CRF is released from the hypothalamus and stimulates the secretion of cortisol from the adrenal glands. In addition, CRF also has a direct effect on gastrointestinal sensitivity and motility by stimulating mast cell degranulation and altering intestinal permeability (84).

Dysregulation of the HPA-axis combined with an altered neuroendocrine response is thought to contribute to IBS symptoms such as abdominal pain and an altered bowel habit. In this respect, it was demonstrated that basal CRF levels are lower in IBS, but increase significantly more during mental stress compared to controls. These results point towards excessive activity of the HPA-axis during stress and might explain some of the stress-related symptoms in IBS (85).

CRF receptors (CRF-R1 and CRF-R2) are expressed both centrally and peripherally. Binding of CRF to these receptors has opposite effects. Binding of CRF to CRF-R1 induces anxiety on a central level, whereas binding of CRF to CRF-R2 has a more anxiolytic effect. In addition, activation of CRF-R1 promotes colonic motility, whereas CRF-R2 inhibits gastric emptying.

Furthermore, evidence suggests a pro-nociceptive effect of CRF-R1 on visceral perception in contrast to an anti-nociceptive effect of CRF-R2 and the pro-inflammatory response of CRF- R1 activation opposes anti-inflammatory influences of CRF-R2 activation (86).

Unfortunately, oral administration of the selective CRF-R1 antagonist pexacerfont to female IBS-D patients did not significantly alter bowel function (87). Thus the clinical significance of CRF receptors in the treatment of IBS remains unclear.

Psychological factors

The prevalence of psychiatric comorbidities such as depression, somatisation and anxiety seems to be significantly higher in IBS patients compared to controls. Approximately 50% of IBS patients display signs of mental distress (88). Whitehead *et al*. collected data from a computerized information system containing ICD-9CM diagnostic codes, assigned by physicians to a large group of IBS patients at each medical clinic visit or hospital admission over a 4-year period. The prevalence of depression was doubled in this group of IBS patients compared to controls (30.5% versus 16.2%) and the prevalence of anxiety was tripled (15.5% versus 5.8%) (89). IBS patients also display an increased tendency to maladaptive coping and catastrophizing (88). These psychological factors correlate with the severity of IBS and with a poorer therapeutic outcome (90). Furthermore, the presence of various psychiatric symptoms may differ between IBS subtypes, which needs to be considered in the therapeutic plan.

Ford *et al*. further corroborated the important role of psychological factors in the pathogenesis of IBS by confirming the effectiveness of antidepressants and psychological therapies in IBS patients in a meta-analysis (7). Tricyclic antidepressants (TCAs) and selective serotonin re- uptake inhibitors (SSRIs) are the most-studied psychotropic medications in IBS patients. The interest in this form of therapy for functional disorders is increasing, not only in the treatment of IBS, but also in the treatment of chronic pain syndromes like fibromyalgia and chronic fatigue syndrome (91). Table 2 shows the potential target sites of psychotropic agents, both centrally and peripherally.

TCAs and SSRIs prevent the reuptake of respectively norepinephrine and serotonin by blocking the norepinephrine and serotonin reuptake transporters on synaptic nerve endings throughout the body. On the central level, noradrenergic neurones in the locus coeruleus and serotonergic neurones in the raphe nuclei are involved in processing of sensory information and are the main targets of TCAs and SSRIs. From these areas numerous axon bundles project to the frontal cortex and limbic system where affect, attention, anxiety, agitation and pain perception are modulated (92).

TCAs are recommended as a second-line treatment for moderate to severe IBS in which pain is prominent, although the effectiveness may vary between different IBS subtypes (7). Since constipation is a well-known anticholinergic side effect of TCAs, they may especially ameliorate the bowel pattern of IBS-D patients (91). TCAs such as amitriptyline, imipramine or clomipramine are prescribed in a subpsychiatric dose of 10 mg/day, increasing to 50-100 mg/day, and can be combined with antispasmodic agents to optimize the clinical effect (91,93). However, SSRIs are often preferred over TCAs because of their more favourable side effect profile. SSRIs such as paroxetine, sertraline, fluoxetine, citalopram or escitalopram, are prescribed in a dose of 10-50 mg/day (depending on the drug) and they may be beneficial in the presence of psychiatric comorbidities (91,93). SSRIs may have an advantageous effect on a constipation-dominant pattern due to diarrhoea as a well-known side effect (91). It is important to keep in mind that the optimal therapeutic effect of antidepressants may take 4-6 weeks to achieve, despite the immediate occurrence of the side effects (94).

Likewise, the interest in behavioural therapies for the treatment of IBS has increased over the last decade. The most evidence is available for cognitive behavioural therapy (95). This form of treatment is based on the hypothesis that maladaptive cognitive patterns result in maladaptive behaviours, emotional responses and symptom exacerbation. The aim is to increase patients' awareness of these patterns and provide more adaptive ways of coping. Cognitive behavioural therapy generally consists of 6-12 sessions, on an individual basis or in group, but can also be self-administered, requiring minimal involvement of clinicians and medical staff while achieving the same positive effect (96). Other psychological therapies

Table 2. — **Potential effects of psychotropic medication in the treatment of irritable bowel syndrome**

Central effects	**Peripheral effects**
• Modulation of pain perception : analgesic or anti-nociceptive effects	• Peripheral analgesic effects : changing visceral afferent communication
• Effect on the mood : decreases fear, vigilance to gastrointestinal signals or an increased reaction to stressful events	• Effects in gastrointestinal physiology, through the effect on cholinergic, noradrenergic and serotonergic pathways.
• Effects on psychiatric co-morbidities : depression, post-traumatic stress syndrome or somatisation disorders	• Smooth muscle effects in viscera, such as relaxation of the fundus of the stomach
• Treatment of associated sleep disorders	• Neuro-immune modulation of mast cells and enterochromaffin cells by anti-histaminergic, anti-cholinergic and serotonergic effects.

used in the treatment of IBS are dynamic interpersonal psychotherapy, relaxation therapy, biofeedback therapy and hypnotherapy. For an extended review concerning the effectiveness of these various psychotherapies, we refer to the recent review of Palsson *et al*. (96).

Vigilance and gut perception

Recent data suggest that IBS patients are over-attentive (hypervigilant) towards internal gastrointestinal stimuli. IBS patients show altered brain responses to rectal stimuli, regardless of whether these stimuli are actually delivered or only anticipated. In these patients, alterations take place not only in areas involved in attention and perception, but also in subcortical regions involved in emotional and autonomous responses on the visceral stimuli (97). Furthermore, it was shown that pain perception increases when attention is specifically focussed towards the gut, whereas stimulus perception significantly decreases during distraction of the stimulus by a cognitive task (98). In this regard, the relation between anxiety and IBS may be an important factor contributing to hypervigilance and hypersensitivity. Anxiety towards painful abdominal sensations may lead to increased vigilance towards intestinal stimuli, which may in turn result in increased perception and even more anxiety, enabling a vicious circle of pain, anxiety and increased vigilance.

Functional and structural alterations in the central nervous system

Functional imaging allows us to visualise brain areas involved in the processing of pain stimuli and to study functional alterations in IBS patients. It is now established that IBS patients demonstrate increased activity in brain areas associated with emotional arousal (the perigenual anterior cingulate cortex and amygdala) and endogenous pain modulation during rectal balloon distension compared to healthy controls (99). In contrast, controls show enhanced engagement of the medial and lateral prefrontal cortex, areas involved in modulation of pain and emotion and cognitive control of emotion. Increased activity in these regions is associated with a more effective down-regulation of the emotional arousal circuit in controls (99). It was also demonstrated that IBS patients show altered activity in descending pathways in the spinal cord, which may facilitate or inhibit the transmission of sensory information to the brain (100).

In addition, structural differences in the brain of IBS patients compared to controls were reported. IBS patients show increased grey matter in the hypothalamus, which may be associated with altered function of the stress system and the HPA-axis. Furthermore, a negative correlation between dorsolateral prefrontal cortical thickness and maladaptive coping and a positive correlation between the anterior insulate cortical thickness and IBS duration were found (101). All these findings underscore the importance of the central nervous system in the pathogenesis of IBS symptoms.

Perspectives and conclusion

This review highlights possible mechanisms involved in the pathogenesis of IBS and visceral hypersensitivity in particular. Two main risk factors associated with the development of IBS are previously endured gastrointestinal infection or inflammation and psychological stress. As discussed, mediators released during intestinal inflammation (such a histamine, tryptase or ATP) may have several effects, namely 1) direct activation of afferent neurons within the gut wall, 2) an indirect effect on afferent neurons by increasing intestinal permeability, 3) a potentiating effect of signal transduction pathways by peripheral and/or central sensitization. Inhibiting the release of these mediators and antagonizing their respective receptors is an interesting approach in the development of new IBS therapies. Furthermore, the role of altered microflora and dietary factors in the pathogenesis of IBS and the therapeutic potential of pre- and probiotics is not yet fully elucidated. Finally, the involvement of central factors such as psychological distress, depression and anxiety is to be considered and warrants the use of antidepressants and psychological therapies as a second-line treatment of IBS.

In conclusion, it is clear that the pathogenesis of IBS is not yet fully understood. Without doubt, IBS is a complicated and multifactorial disorder, in which peripheral as well as central mechanisms are implicated. Figure 1 provides a simplified overview of these mechanisms and their mutual interactions. The treatment of IBS remains challenging and further research in this field is required to improve treatment strategies for patients with IBS.

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