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Towards an integrated psychoneurophysiological approach of irritable bowel syndrome

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INTRODUCTION

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EPIDEMIOLOGY

Irritable bowel syndrome (IBS) is among the most frequently occurring functional bowel disorders and is characterized by recurrent abdominal pain or discomfort accompanied by altered bowel habits¹. Its prevalence ranges from 6% in the Netherlands² to 22% in other Western countries³. Approximately two-third of patients is female and symptom onset generally occurs below the age of 35. IBS has considerable economic impact, accounting for total annual direct costs of £ 45.6 million on average in the United Kingdom⁴. In the Netherlands, health care utilization and absence from work in IBS patients is approximately twice that of the general population⁵.

DIAGNOSIS

In 1978, Manning was the first to introduce diagnostic criteria for IBS after an era in which diagnosis was made by exclusion of organic disease⁶. The Manning criteria required onset of abdominal pain associated with more frequent and looser bowel movements, pain relieved with defecation, visible abdominal bloating, and subjective sensation of incomplete evacuation and mucous stools more than 25% of the time. In 1992, an international committee of specialists known as the Rome Working Team refined the Manning criteria and formulated the Rome I criteria for IBS. These were re-evaluated in 1998 (Rome II criteria, applied in this thesis; Table 1)¹ and recently in 2006 (Rome III criteria)^{7,8}. According to Rome III criteria, irritable bowel syndrome is defined as recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months, associated with 2 or more of the following: 1) improvement with defecation and/or 2) onset associated with a change in frequency of stool and/or 3) onset associated with a change in form (appearance) of stool⁸. Additional symptoms that support the diagnosis but are not part of these criteria include abnormal stool frequency (≤ 3 times per week or ≥ 3 times per day), abnormal stool form (hard/lumpy stool or loose/watery stool), defecation straining, urgency, sensation of incomplete bowel movement, passage of mucus, and bloating. In daily practice, subgroups are recognized according to predominant bowel habit, i.e. IBS with diarrhoea (IBS-D), IBS with constipation (IBS-C), alternating or mixed IBS (IBS-A, both hard/lumpy and loose stools) and unsubtyped IBS (insufficient abnormality of stool consistency to meet criteria for IBS-D, IBS-C or IBS-A). From a clinical point of view, the Rome criteria help physicians to make a more firm diagnosis of IBS. In research, they allow standardization of patient recruitment and comparison of patient groups between studies.

Table 1. Rome II criteria for irritable bowel syndrome**Diagnostic criteria**

At least 12 weeks, which need to be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two of three features:

1. Relieved with defecation; and/or
2. Onset associated with a change in frequency of stool; and/or
3. Onset associated with a change in form (appearance) of stool

Supportive symptoms of the irritable bowel syndrome

1. Fewer than three bowel movements a week
2. More than three bowel movements a week
3. Hard or lumpy stools
4. Loose (mushy) or watery stools
5. Straining during a bowel movement
6. Urgency (having to rush to have a bowel movement)
7. Feeling of incomplete bowel movement
8. Passing mucus (white material) during a bowel movement
9. Abdominal fullness, bloating or swelling

Diarrhoea-predominant

1 or more of 2, 4, or 6 and none of 1, 3, or 5

Constipation-predominant

1 or more of 1, 3, or 5 and none of 2, 4, or 6

PATHOPHYSIOLOGY

Despite the growing body of literature, the pathophysiology of IBS remains poorly understood. Currently, IBS is viewed as a multifactorial condition in which clinical expression results from interplay between physiological and neuropsychological factors^{9,10}. These factors are integrated in the brain-gut axis, a conceptual framework which has recently emerged in an attempt to improve our understanding of the etiology, pathogenesis and clinical expression of IBS. They include autonomic dysfunction^{11,12}, altered processing of afferent sensory information^{13,14}, disturbed intestinal motility^{15,16}, enhanced visceral sensitivity^{17,18}, inflammatory processes^{19,20}, altered immune activity^{21,22}, and psychological disturbances^{23,24}. Dysfunction at different levels of the brain-gut axis may be responsible for these alterations.

Autonomic dysfunction

Several studies have demonstrated some form of autonomic dysregulation in IBS^{11,12,25,26}, but the nature of autonomic dysfunction remains elusive and results have been far from congruent. For instance, spectral analysis of heart rate variability has suggested increased sympathetic activity in IBS patients²⁵, both during waking and sleep²⁶. These data are supported by findings showing hypertensive episodes during sigmoidal balloon distension in both IBS and health, pointing to upregulated

sympathetic tone²⁷. In contrast, it has also been shown that rectal balloon distension depresses blood pressure in IBS patients (but not in controls)¹¹, suggesting down-regulated sympathetic activity during visceral stimulation.

Autonomic control of gastrointestinal motor and sensory functioning is complex. In short, it is governed by the dorsal vagal complex²⁸, an integrated central structure comprising the motor nucleus of the vagus from which autonomic outflow to the colon arises, and the nucleus tracti solitarii (NTS) which integrates viscerosensory input from the gut and other organs²⁹. Physiological information from the gut *proximal* to the splenic flexure is carried by cranial nerve afferents that terminate in the NTS, while noxious viscerosensory information is transmitted by sympathetic spinal fibers. From the NTS, interneurons project to the ventrolateral medulla (VLM), which controls sympathetic outflow, and to higher centers. Sensory information originating *distal* from the splenic flexure (descending colon and rectum) is exclusively conveyed by spinal afferent fibers that terminate in the thalamus, but collaterals also reach the NTS and VLM^{30,31}. This key role of the NTS suggests that the altered autonomic outflow observed in IBS may result from either a normal or abnormal reflex response to disturbed afferent viscerosensory information from the gut.

Altered intestinal motility

Both small intestinal and colonic motility are altered in IBS^{32,33}. Intraluminal small intestinal pressure recordings have revealed shorter intervals between fasting migrating myoelectric complexes, more clusters of jejunal pressure activity and more ileal propulsive waves in IBS-D compared to controls, implying increased small bowel motility. The latter abnormality was associated with cramping abdominal pain³². Manometry of the left hemicolon in IBS patients has demonstrated increased colonic frequency patterns, a higher motility index, and an increase in mean number and peak amplitude of high amplitude propagating contractions (HAPCs), which coincided with the occurrence of abdominal pain in more than 90%³³. Other studies, however, have not been able to demonstrate significant differences in colonic motility between IBS patients and healthy controls³⁴. Autonomic dysfunction may be seen as circumstantial evidence for altered intestinal motility in IBS. However, it remains elusive which intestinal motor abnormalities contribute to symptom generation.

Visceral hypersensitivity

Visceral hypersensitivity is considered a hallmark in IBS^{35,36} and has even been proposed as a biological marker¹⁷. Typical findings in IBS patients are increased visceral sensitivity to noxious stimuli, such as rapid rectal balloon distension, while physiological stimuli elicit similar responses as in controls¹⁷. The pathophysiology of this visceral hyperalgesia is poorly understood, but it may result from disturbances at

different levels of the brain-gut axis. First, sensitization of peripheral nerve endings at the intestinal level may occur during or after acute inflammation^{37,38}, leading to higher excitability and/or increased firing of these neurons. Second, alterations in the spinal dorsal horn neurons and upregulation of spinal nerve endings may play a role in the extended viscerosomatic referral pattern that is often seen in IBS^{17,37}. Third, altered processing of afferent visceral information in the brain, particularly in the prefrontal cortex, anterior cingulate cortex, and thalamus, has repeatedly been demonstrated in IBS patients^{14,39,40}. These regions are not only involved in pain processing but are also part of the emotional limbic system and are therefore involved in numerous psychological and cognitive events^{41,42}. Although the prevalence of visceral hypersensitivity in IBS patients differs between studies and its role in the pathophysiology is not clear, it is one of the few reproducible phenomena in IBS.

Inflammation and immune system alterations

The role of low-grade inflammation and (mucosal) immune system activation in the pathogenesis of IBS has received much attention over the last decade. The risk to develop IBS after dysenteric illness is increased^{19,20,43}. Histological studies found increased numbers of immunocompetent cells in colonic and small bowel mucosa of patients with post-infectious IBS (PI-IBS)^{21,44,45}. Even more interestingly, large bowel mucosal samples in subgroups of IBS patients show activated mast cells with signs of degranulation and inflammatory mediator release in the proximity of mucosal nerve endings, especially in patients who are hypersensitive to balloon distension^{21,46}. This implies that mucosal inflammation may contribute to symptom generation. In addition, increased or decreased secretion of several pro- and anti-inflammatory cytokines that are known to modulate the (intestinal) immune response⁴⁷ may play a role in this mucosal inflammation. For instance, a number of single nucleotide polymorphisms (SNPs) in the promoter region of the gene coding for the anti-inflammatory cytokine interleukin-10 (IL-10), leading to increased production of IL-10, appear to be less prevalent in IBS patients²². Very recent data involving microarray gene expression profiling of sigmoid colon mucosa even suggest stable alterations in colonic mucosal immunity in IBS⁴⁸. These data strongly suggest that inflammation of the gut mucosa plays a role in the clinical expression of IBS in at least a subset of patients.

Psychopathology

Symptoms in IBS are associated with psychological factors, which may affect clinical outcome²³. Whether psychological disturbances contribute to the pathophysiology of IBS as such or only occur as comorbidity is not yet clear. Although an increased prevalence of several psychiatric conditions such as anxiety, depression and somatization has been demonstrated in IBS⁴⁹⁻⁵¹, these disorders may particularly be

related to health care seeking⁵¹. There is also evidence to suggest that psychological disorders do not play a significant role in the pathophysiology of IBS when levels of visceral hypersensitivity are accounted for⁵². Alternatively, altered processing of afferent visceral information in the prefrontal cortex, anterior cingulate cortex, and thalamus has been demonstrated in IBS^{39,40}. Nociception (becoming aware of a painful stimulus) and emotional pain management both occur in these brain regions, which are also part of the emotional limbic system^{41,42}, suggesting that psychological disturbances may be related to visceral hypersensitivity and IBS.

AIMS AND OUTLINES

The concept of the brain-gut axis as a model to improve our understanding of the pathophysiology of IBS has been the basis of research in IBS over the last decades and the framework for this thesis. The primary objective was to gain further insight in the many parameters and variables that are involved in this model, and their relationship. The second goal was to study the efficacy of a brief psychological group intervention for the treatment of IBS symptoms. Third, we aimed to test the validity of a previously published comprehensive working model of IBS, based on the brain-gut axis.

Evidence for abnormal activity of the autonomic nervous system, reflected in the cardiovascular system by altered heart rate variability (HRV)^{25,26} and in the digestive system by disturbed motility^{32,33}, suggests disturbed viscerosensory-autonomic reflexes in IBS. In rats, electrical stimulation of abdominal vagal afferents increases sympathetic outflow and also decreases baroreflex sensitivity (BRS), pointing to the possible involvement of the arterial baroreflex in IBS⁵³. Altered baroreflex functioning during gastrointestinal stress (i.e., abdominal pain) may constitute a pathophysiological key in IBS, as the arterial baroreflex not only modulates sympathetic and parasympathetic autonomic outflow, but also affects cortical arousal⁵⁴ and somatic^{54,55} and visceral⁵³ pain perception. Since this topic has not been studied in humans, we evaluated systolic blood pressure, heart rate and BRS involvement in IBS patients and healthy controls under baseline conditions and during a gastrointestinal stressor (rectal balloon distension). The results of this study are presented in **Chapter 2**.

Several gut peptides are known to be involved in the regulation of gastrointestinal motor and sensory function. For instance, cholecystokinin (CCK) stimulates colonic motility and increases rectal sensitivity to balloon distension in healthy individuals^{56,57}. Motilin is involved in the regulation of interdigestive motility of the stomach and small intestine⁵⁸, but also affects colorectal motor function⁵⁹. Peptide YY (PYY)

delays proximal gastrointestinal motility⁶⁰ and the number of PYY-containing colonic enteroendocrine cells is increased in symptomatic IBS patients after an acute infectious gastroenteritis⁴⁴. **Chapter 3** investigates plasma levels of gut peptides released from the upper (CCK and motilin) and lower (PYY) small intestine under fasting and postprandial conditions in IBS patients, as well as the influence of age, gender, IBS subtype and visceral hypersensitivity on gut hormone secretion.

With an increased risk of developing IBS after acute gastroenteritis^{19,20,43}, it has become increasingly clear that inflammation and mucosal immune system activation may be important in IBS symptom generation⁶¹. Larger numbers of immunocompetent cells are found in rectal mucosa of patients with post-infectious IBS up to 1 year after infection⁴⁴. Since pro- and anti-inflammatory cytokines are important modulators of the (intestinal) immune response, imbalances in cytokine secretion may play a role in the ongoing mucosal inflammation. A recent study showed that the high producer IL-10 genotype (anti-inflammatory cytokine; -1082 G/G Single Nucleotide Polymorphism, SNP) is less prevalent in IBS patients compared to healthy controls²². The study described in **Chapter 4** was conducted to investigate the prevalence of gene promoter SNPs of IL-10 and TNF- α (pro-inflammatory cytokine) that are known to be associated with low IL-10 or high TNF- α secretion, in IBS patients and in healthy controls.

Chapter 5 studies reflex rectocolonic motor inhibition in IBS patients and healthy controls under both fasting and postprandial conditions. This inhibitory reflex has previously been demonstrated in healthy individuals^{62,63}. Our study was undertaken to characterize this inhibitory reflex in IBS in an attempt to better understand the motor disturbances that occur in these patients, and in particular postprandial symptom deterioration⁶⁴.

Visceral hypersensitivity appears to play an important role in the pathophysiology of IBS^{35,36} and has even been proposed as a biological marker¹⁷. Although processing of afferent visceral information and emotional pain management both occur in the same brain regions^{41,42}, little is known about the relationship between psychological variables and visceral hypersensitivity. Such information is relevant because it may provide a better understanding of the pathogenesis of IBS and its treatment. In **Chapter 6**, we explore the prevalence of rectal hypersensitivity, levels of psychological distress and symptom severity in IBS patients, and we attempt to address which demographical, clinical and psychological variables predict the occurrence of visceral hypersensitivity in IBS.

Curative treatment for IBS is not available⁶⁵ and therefore therapeutic interventions are directed towards reducing predominating symptoms. These include medication such as antispasmodics, laxatives or antidiarrhoeals in addition to patient education, reassurance, and dietary advice⁹. Novel therapies focus on serotonergic and psycho-

tropic agents, but therapeutic gain is at best restricted to subgroups of patients⁶⁶⁻⁶⁹. The efficacy of psychological interventions such as cognitive behavioural therapy, dynamic psychotherapy and hypnotherapy has been demonstrated in a number of studies⁷⁰⁻⁷⁴. As most forms of psychotherapy incorporate a relaxation technique, we conducted a randomized controlled trial to determine short and long-term efficacy of relaxation training, a brief psychological group intervention, when added to standard medical care, on symptom severity and psychological wellbeing in IBS patients. The results of this study are described in **Chapter 7**.

With disturbances at different levels of the brain-gut axis as the central, conceptual framework for understanding the pathogenesis underlying IBS, a biobehavioral model would be of great assistance to verify different pathophysiological hypotheses. One of few attempts to construct such a model came from Naliboff and colleagues in 1998, who proposed an initial but comprehensive working model of IBS, incorporating the central nervous system, visceral sensory and motor functioning, and cognitive-behavioral systems⁷⁵. In **Chapter 8**, we evaluate a modified version of this model by using Structural Equation Modeling (SEM) in order to calculate reciprocal and chronological relationships between the model variables and thereby test its validity.

Finally, **Chapter 9** summarizes the various studies presented in this thesis and discusses the new insights that have been obtained in the light of the current knowledge on the pathophysiology and clinic aspects of IBS.

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