Towards an integrated psychoneurophysiological approach of irritable bowel syndrome

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9

SUMMARY AND DISCUSSION

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Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by recurrent episodes of abdominal pain or discomfort accompanied by disturbed bowel habits. It is among the most frequently occurring functional bowel syndromes, with a prevalence ranging from 5 to approximately 20%. Diagnosis is made according to the Rome criteria. Despite the growing body of literature, the pathophysiology of IBS remains poorly understood. A variety of mechanisms have been proposed in symptom generation, including enhanced visceral sensitivity, disturbed intestinal motility, autonomic dysfunction, mucosal inflammation, altered immune activity, altered processing of afferent sensory information, and psychological disturbances. These alterations probably reflect dysfunction at different levels of 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. The studies presented in this thesis highlight different aspects of the brain-gut axis in order to gain further insight in the pathophysiological mechanisms underlying IBS.

In **Chapter 2**, we studied involvement of baroreflex sensitivity (BRS), a measure of autonomic (dys)function, in IBS patients and healthy controls under baseline conditions and during a gastrointestinal stressor, i.e. rectal balloon distension. As BRS not only modulates sympathetic and parasympathetic autonomic outflow, but also affects cortical arousal and somatic and visceral pain perception, it might play a role in the pathophysiology of IBS. A previous study in rats demonstrated increased sympathetic outflow and decreased BRS during electrical stimulation of abdominal vagal afferents[1]. In contrast, we found an increase in BRS under mild rectal stimulation in healthy subjects and in IBS patients, which persisted in controls during intense stimulation, whereas BRS returned to baseline in patients. The interpretation of these contrasting results is unclear, but the differences may be related to the use of anaesthesia in these rats[1], which affects cortical perception and depresses the arterial baroreflex. More importantly, we demonstrated that resting BRS is significantly larger in IBS patients compared to healthy subjects. This is opposite to our assumption that resting BRS is lower in IBS (as is the case in most chronic diseases[2,3]), which renders the hypothesis that IBS patients are hypersensitive due to diminished baroflex function unlikely. In contrast, a recent study demonstrated decreased BRS in IBS patients compared to controls, both at baseline and during ramp en phasic rectal balloon distension[4]. Differences in balloon distension protocol may, at least in part, account for this discrepancy. Our study does not provide information on the basis of which (the difference between) these results can be explained. One theory is that the frequently experienced viscerosensory stimuli in IBS, such as abdominal pain, may entail a training-effect, possibly materialized in chronic elevated substance P concentrations at the level of the nucleus tracti solitarii (NTS)[5,6]. Such a training-

mechanism can only be further investigated in animal models of visceral afferent stimulation. Alternatively, it may reflect an intrinsic autonomic characteristic in which IBS patients differ from healthy individuals, which may occur at the NTS level, as has previously been shown for the oesophagus[7]. It is tempting to interpret the enhanced baseline baroreflex response in patients as an anticipatory phenomenon and to expect benefits from that anticipation in the form of inhibition of cortical arousal and visceral pain perception during irritating stimuli such as abdominal pain. However, our finding that no differences in BRS values exist between IBS patients and control subjects during rectal distension makes such a hypothesis unlikely. Whether these autonomic changes are either a consequence of IBS or play a role in the pathophysiology should be the focus of future investigations.

Several gut peptides are involved in the regulation of gastrointestinal motor and sensory function. We studied plasma levels of gut peptides released from the upper (cholecystokinin (CCK) and motilin) and lower (peptide YY, PYY) small intestine under fasting and postprandial conditions in IBS patients and controls, the results of which have been presented in **Chapter 3**. Both fasting plasma CCK levels and the incremental postprandial CCK response were elevated in IBS patients compared to controls. These results support previous studies in IBS showing disturbed CCK release and altered organ sensitivity[8], excessive intestinal motor activity[9] and reduced pain thresholds[10] during infusion of CCK. Furthermore, neither fasting nor postprandial CCK levels were significantly different between patients who were classified as either hypersensitive or normosensitive to rectal balloon distension, which renders a contribution of increased CCK secretion to the pathogenesis of enhanced visceral perception less likely. However, CCK infusion has been shown to aggravate symptom severity in IBS patients[11]. It is therefore possible that CCK release after a meal is involved in the exaggerated postprandial colonic motor response that has been demonstrated in IBS patients[12]. Although postprandial CCK concentrations were merely twofold increased in IBS compared with controls, the combination with increased end-organ sensitivity may be responsible for postprandial symptom aggravation in IBS. Against the background of the female predominance in IBS, another interesting finding was that the elevated fasting and postprandial plasma CCK levels were almost completely attributable to female IBS patients. Differences in the effect of CCK on gastrointestinal motility between males and females have been reported (for instance increased sphincter of Oddi motility during CCK infusion in female compared to male dogs)[13], but the interpretation of this finding remains unclear. Fasting and postprandial motilin levels did not differ between patients and controls, which is supported by the literature. Remarkably, fasting motilin levels were significantly elevated in patients with a diarrhoea predominant bowel habit compared to other subgroups. This may be clinically relevant as motilin stimulates human colonic

motility[14] and may therefore play a role in the accelerated colonic transit that has been demonstrated in patients with diarrhoea[15]. Overall, no differences were found in fasting and postprandial PYY-levels, which is in line with previous data. Our observation that patients who were hypersensitive to rectal balloon distension have a greater postprandial PYY response, together with data showing increased numbers of PYY-containing enteroendocrine cells in rectal biopsy specimens from patients with post-infectious IBS[16], may imply a role for this hormone in the development of post-infectious visceral hypersensitivity and/or IBS.

With increasing evidence to suggest a role of mucosal inflammation and immune system alterations in the pathophysiology of IBS, we studied genetically determined immune activity by comparing the prevalence of gene promoter single nucleotide polymorphisms (SNPs) of interleukin 10 (IL-10, anti-inflammatory cytokine) and tumor necrosis factor alpha (TNF-α, pro-inflammatory cytokine) between IBS patients and controls. In **Chapter 4**, we demonstrated that the high producer TNF-α genotype is more prevalent in IBS patients compared to healthy controls, particularly the heterozygous genotype which is associated with a high TNF-α production phenotype (41% versus 26%). The previously demonstrated fivefold increase in TNF-α producing intraepithelial activated macrophages in patients with post-infectious IBS[16], together with the potency of enteric pathogens such as Campylobacter jejuni, Salmonella and Shigella to stimulate macrophage TNF-α production[17], supports a role of this cytokine in persisting bowel symptoms in these patients after infection. Low-producer genotype frequencies for IL-10 were similar between patients and controls. The combined high-producer TNF-α and low-producer IL-10 genotype (i.e., 'high risk profile' for inflammation) was three times more prevalent in patients compared to controls but occurred in only 9% of cases. This implies that other mechanisms and/or cytokines are also involved. Yet, this genotype combination tended to occur more often in patients with a diarrhoea predominant bowel habit compared to the constipation and alternating types (20% versus 4% and 3%, respectively). This is supported by a recent study showing enhanced baseline TNF-α and Escherichia coli lipopolysaccharide-induced TNF-α and IL-6 levels in diarrhoea predominant IBS-patients reporting more than 3 bowel movements per day, urgency, watery stools, and pain associated with diarrhea[18]. While statistical significance was not reached, these data indicate that IBS subgroups may exhibit different cytokine producer genotypes that might be involved in disease expression.

Motor disturbances of the gut have been demonstrated in IBS, but the role of this abnormality in the pathogenesis of IBS and particularly in postprandial symptom deterioration has not been established. With the recent characterization of a rectocolonic inhibitory reflex in healthy individuals, the study presented in **Chapter 5** was performed to investigate this phenomenon in IBS. We found that rectal pain dur-

ing balloon distension after a standard high-caloric meal was increased in patients compared to controls. Rectal distension inhibited colonic motor activity (measured by tone and phasic volume events using barostat) in an intensity-dependent manner in both IBS patients and controls. Most interestingly, the magnitude of this response was comparable between patients and controls under fasting conditions, but was significantly impaired in patients versus controls after a meal, with more postprandial phasic motor activity occurring in patients. A possible explanation for this finding is that exaggerated postprandial colonic motor activity impairs the ability of the colon to relax and thereby attenuates rectocolonic reflexes in IBS patients after a meal. The role of the (impaired) rectocolonic inhibitory reflex in the pathophysiology of IBS awaits further elucidation. Altered reflexes at other locations in the gastrointestinal tract have already been demonstrated in patients with functional bowel disorders. For instance, impaired reflex fundic relaxation following intestinal administration of nutrients has been shown in patients with functional dyspepsia[19]. Our finding that the rectocolonic reflex is impaired in IBS after a meal, together with the increased rectal pain during balloon distension in IBS, is consistent with the hypothesis of a generalized disturbance of postprandial colonic sensori-motor functions in IBS.

Visceral hypersensitivity is one of the few reproducible phenomena in IBS and has been put forward as a biological marker. Processing of afferent visceral information and emotional pain management both occur in similar brain regions, but little is known about the relationship between psychological variables and visceral hypersensitivity. **Chapter 6** explored the prevalence of rectal hypersensitivity, levels of psychological distress and symptom severity in IBS. In addition, we aimed to address which demographical, clinical and psychological variables predict the occurrence of visceral hypersensitivity in IBS. We found that rectal compliance and pain thresholds are reduced and that the intensity of pain perception but not urge is increased in IBS patients when compared to healthy controls. The latter is consistent with previous reports demonstrating decreased perception thresholds in IBS only for noxious stimuli, and not for stool[20]. Furthermore, visceral hypersensitivity (defined by pain perception threshold ≥ 2 standard deviations below the mean threshold in controls) was present in one third of patients. This finding is remarkable, since some report up to 95% percent of IBS patients being hypersensitive to balloon distension[20]. The difference is probably due to the use of different parameters to define visceral hypersensitivity (for instance, inclusion of intensity of sensations and altered viscerosomatic referral in the definition[20] besides reduced perception thresholds). Logistic regression analysis showed that only symptom severity predicts the occurrence of visceral hypersensitivity and that no correlation exists with any of the investigated psychological and demographical characteristics. A recent study in 109 adult IBS patients also demonstrated a significant correlation between symptom

severity and hypersensitivity to rectal balloon distension[21]. In contrast, another recent study in children with IBS and functional abdominal pain did not find an association between symptom severity and rectal pain perception thresholds[22]. Taken together, these data challenge the view that visceral hyperalgesia is a biological marker of IBS, since hypersensitivity may be absent in Rome II positive patients with mild symptoms. They also show that psychological characteristics such as anxiety, somatization, and neuroticism do not correlate with sensory thresholds. In particular, neither vigilance nor dysfunctional cognitions were different between hypersensitive and normosensitive patients, suggesting that symptom perception and management do not differ between these groups. Yet, these findings do not exclude a common neuropsychological basis in the clinical expression of IBS because several studies show that psychological distress is more prevalent among patients who seek health care[23]. Therefore, the role of psychological factors in IBS symptom presentation remains an interesting subject of investigation.

Pharmacotherapy for successful treatment of IBS is often disappointing, but cumulative evidence suggests efficacy of psychological interventions such as cognitive behavioural therapy, dynamic psychotherapy and hypnotherapy in treating IBS. Most of these interventions incorporate a relaxation technique. In **Chapter 7** we presented the results of a randomized controlled trial to determine short and long-term efficacy of relaxation training (RT), a brief psychological group intervention, when added to standard medical care, on symptom severity and psychological wellbeing in IBS patients. We found that RT leads to significant symptom improvement up to 12 months after treatment, with a 34% reduction in IBS composite symptom score in the RT group compared to only 12% in patients receiving standard medical care. Quality of life (general health, health change) also improved significantly more in patients treated with RT compared to those receiving standard treatment. According to the Jacobson and Truax criteria for clinically significant symptom improvement, 12 RT-treated patients (23%) were improved at 12 months after treatment, compared to 1 patient (3%) who received standard medical care. These results are at least similar, if not better, when compared to the beneficial effects of other psychological interventions[24,25]. Although treatment duration is short (4 weeks), consolidation of symptom improvement probably lies in routine use of relaxation techniques in daily life. When embedded in a clear rationale, this provides patients with a useful tool to cope with their symptoms and establishes long-term symptom reduction.

One of the first attempts to conceptualize the multifactorial pathogenesis of IBS comes from Naliboff and colleagues in 1998. They proposed a biobehavioral model which integrates the central nervous system, visceral sensory and motor functioning, and cognitive-behavioral systems into one comprehensive working model. In **Chapter 8**, we tested the validity of an operationalized version of this model using

a path analysis method based on Structural Equation Modeling (SEM). This method allows calculation of reciprocal and chronological relationships between model variables. Initial analysis indicated poor model fit, rejecting the validity of this model when applied to our patient population. In particular, ANS functioning (represented by BRS) was not associated with IBS symptom severity. In view of the convincing evidence showing ANS alterations in IBS patients, it is probable that autonomic dysfunction takes place through different mechanisms than those proposed in the working model. Our finding that ANS functioning was significantly correlated to (hyper)vigilance without affecting IBS symptom severity is supported by a recent study showing that repeated exposure to aversive visceral stimuli in IBS patients leads to habituation of visceral perception, while central processing of anticipation of visceral pain (i.e., vigilance) remains activated[26]. Further evaluation of the model confirmed that visceral pain during rectal balloon distension is related to IBS symptoms (which is consistent with the results presented in **Chapter 6**), but no association with a history of 'abdominal trauma' (sexual or physical abuse, inflammatory processes), autonomic dysfunction, or vigilance was found. We also hypothesized that illness behavior influences cognitions, which in turn modulate symptom severity. The results showed that a better fit was achieved when illness behavior was positioned in the model as a mediator between cognitions and IBS symptoms, suggesting that dysfunctional cognitions do not affect symptom severity by themselves but are modulated by a patient's approach to his or her symptoms (illness behavior). Another interesting finding was that the well-known association between a history of 'abdominal trauma' and increased IBS symptom severity does not involve visceral hyperalgesia, but is also mediated by illness behavior. These data not only suggest a central role for illness behavior in the pathyphysiology of IBS, but also highlight behavioral interventions such as relaxation training as potentially beneficial treatment options.

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