How stress affects the digestive tract: unravelling the pathophysiology of functional bowel disorders

Braak, B.

Citation for published version (APA):
Chapter 9

Summary and conclusion
Summary And Conclusion

In functional gastrointestinal disorders (FGID) like irritable bowel syndrome (IBS) and functional dyspepsia (FD), gastrointestinal sensorimotor function is disturbed in the absence of an organic cause\(^1\). IBS patients present with enhanced perception to distension of the colon and rectosigmoid\(^3\)-\(^6\), whereas FD patients have increased gastric sensitivity to distension, delayed gastric emptying or impaired accommodation\(^7\)-\(^10\). These abnormalities in function are to some extent reflected by the symptom pattern. IBS symptoms (i.e. pain, discomfort, bloating) are located in lower abdomen and associated with alterations in defecation frequency, stool passage and stool form\(^1\). FD symptoms like pain, bloating, early satiety and nausea are located in the upper abdomen and are frequently associated with meal ingestion\(^2\). IBS and FD are present in 6-20% and 15-40%\(^1\),\(^2\) of the Western population respectively and are considered the most frequently diagnosed disorders in gastroenterological outpatient clinics\(^11\),\(^12\). Although life-expectancy is not affected, quality of life is significantly reduced in IBS and FD patients.

From clinical experience, it is obvious that stress is an important trigger initiating or exacerbating symptoms, suggesting that FGID patients may have an altered response to stressful situations. Dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis has indeed been reported in IBS patients\(^13\)-\(^15\), with events in early life as an important risk factor\(^16\)-\(^19\). Moreover, traumatic life events such as childhood abuse and parental neglect are more frequently reported by IBS patients when compared to healthy volunteers\(^20\). It is however unclear whether early life events contribute to an altered stress response in IBS patients. Furthermore, evidence supporting early life events as a risk factor for IBS is largely based on retrospective studies of IBS patients at an outpatient clinic. Therefore, better-documented studies are required to objectively identify early-life events as a risk factor for IBS. During the World War II (1940 – 1945), the western part of The Netherlands went through a short period of severe famine, lasted from November 1944 until May 1945. This famine was most severe in cities and was associated with high mortality rates especially amongst children and elderly. The record keeping of the Dutch medical services was despite the war still collecting detailed records of patients, newborns, and mothers from that period. These patient files are, therefore, an ideal data source to reliably investigate the long-term effects of early life events (i.e. stressful wartime conditions) on the prevalence of IBS. In chapter 2 we investigated the hypothesis that a stressful environment because of severe war conditions during gestation and in early life increases the prevalence of IBS in adulthood. In addition, we evaluated whether the development of IBS is associated with dysregulation of the HPA axis. We provide evidence that exposure to wartime conditions in early life is associated with an increased prevalence of IBS in adulthood. Exposure to war, however, was not associated with alterations in the HPA-axis. Moreover, no differences in HPA-axis, at baseline or during psychological stress, were found in IBS patients compared to those without IBS. These findings, however, do not exclude that FGID patients may experience more events as stressful due to aberrant coping with stressful situations and as such being repeatedly exposed to stress. Therefore the role of stress in FGID needed further investigation, by addressing the prevalence of (experienced) daily life stress, a history of traumatic events, parental neglect and social support and their relation with FGID symptoms. This was investigated in chapter 3. To this end, 45 FD and 42 IBS patients, accompanied with 52 healthy volunteers (HV) were studied. First, every participant had to fill in several questionnaires about their daily life stress,
social support, coping mechanisms and parental relationship. These data allowed us to obtain information on the psychological profile of our patients. We identified 3 subgroups of patients with a different psychological profile, namely that of ‘parental rejection’, a ‘neurotic’ and a ‘normal’ profile. The ‘parental rejection’ profile was characterized by increased feeling of rejection and neglect by one or both parents. The ‘neurotic’ profile on the other hand showed high scores of social inhibition and negative affectivity (both associated with depression and anxiety), lack of social support & more daily hassles. Second, each subject underwent a series of 3 psychological stress tasks (i.e. Stroop word test (word-color conflict test), mirror drawing test and public speech test) to investigate the relationship between stress responsiveness towards the relative contribution of traumatic life events, psychological profile and IBS/FD diagnosis. We observed that as a group, FD and IBS patients showed blunted stress responses (cortisol, diastolic blood pressure) compared to HV. Furthermore, participants with history of traumatic life events showed decreased heart rate response and higher subjective stress scores. In addition, subjects with a ‘neurotic’ profile showed an increased cortisol response and higher subjective stress scores. Taken together, these results suggest that not only FGID diagnosis is associated with the stress response, but also a history of traumatic events and psychological profile are relevant. Finally, we determined whether these stress responses are associated with gastrointestinal symptom severity, when controlling for history of traumatic life events and psychological profile. We observed that stress response, history of traumatic events and psychological profile were significantly and independently associated with the severity of (upper) gastrointestinal symptoms. Therefore, this study provided evidence that all these factors are indeed relevant in gastrointestinal symptom generation and should taken into account in prospective studies when the severity of gastrointestinal symptoms or even therapeutic effects are determined.

Knowing that the psychological factors and the stress response significantly contribute to symptom generation, visceral hypersensitivity is an important mechanism underlying abdominal symptoms in functional bowel disorders too. Several studies have evaluated whether acute stress affects visceral perception, but the data are however rather conflicting. Moreover, it should be emphasized though that the functional test, i.e. rectal barostat, by itself is experienced as a stressful event introducing an important factor of variability, and making it rather difficult to evaluate the response to the stressor. The aim of this study therefore was to determine the stress response and to study the possible association between gastrointestinal sensitivity, assessed by rectal barostat or drink test on a separate occasion, and the acute psychological stress response. In chapter 4 we therefore determined the gastrointestinal sensorimotor function in 42 FD patients and 20 HV via a nutrient drink test with high caloric fluid, and in 42 IBS patients and 20 HV with rectal barostat, and investigated whether gastrointestinal sensorimotor function was associated with the stress response. Compared to HV, IBS and FD patients had significantly lower discomfort thresholds and drinking capacity, respectively. In all analyses, a main effect of stressor moment was found, due to the enhanced response during the 3 stress moments (especially public speech), compared to the 2 recovery periods. For rectal sensitivity and blood pressure responses, the threshold-by-stressor interaction effects on blood pressure responses were significant with a significant positive association between thresholds and BP responses during the 3 stress moments (especially public speech), but not during the 2 recovery periods. The drinking capacity did not show an association. Therefore we can concluded that rectal sensitivity, but not drinking capacity, is positively associated with an altered response to acute psycho-
logical stress in HV and FGID patients. Although this is a cross-sectional study not allowing to make any conclusions about the causality of these associations we may speculate that an altered stress response contributes to the development of rectal hypersensitivity, but not impaired drinking capacity.

As shown in chapter 2 – 4, psychological stress is an important factor in the generation of FGID symptoms and visceral sensitivity, but the mechanisms involved are still unclear. Several studies have shown alterations in brain activation in IBS and FD patients, especially associated with psychobiological factors like anxiety, depression or history of abuse. Similarly, the processing of sensory information by the brain in animals was altered by acute stress leading to stress-induced visceral analgesia. In the brain, emotional cognitive functions (i.e. pain, pleasure, motivation) are processed in the mesolimbic system (ventral tegmental area, nucleus accumbens, anterior cingulate cortex). This brain area is rich in dopamine D2 receptors (D2Rs), and is part of the dopaminergic pathway considered to be important in the regulation of (visceral) pain. Importantly, stress has a detrimental impact on the normal function of the dopaminergic system. Both acute and chronic stress are able to influence levels of dopamine and dopamine receptor function in rodents and humans. In chapter 5, we hypothesized that abnormalities in the central dopaminergic system could be involved in the pathogenesis of FD. We first analysed the in-vivo expression of central D2Rs with [123I] IBZM single photon emission computed tomography (SPECT) in 8 FD patients compared to 20 HV and investigated central D2Rs were related with gastric function, assessed with nutrient drink test. We observed a lower striatal binding potential (BP_{NP, average L+R}) for caudate nucleus, but not for putamen, in FD patients. Moreover, the D2R BP_{NP} of the caudate nucleus was correlated to maximal ingested volume (higher drinking capacity with increased binding potential), whereas the D2R BP_{NP} of the putamen was correlated to meal-evoked nausea. To further evaluate the role of dopamine in visceral sensorimotor function, we studied the effect of dopamine depletion on drinking capacity and meal evoked symptoms in HV and hypothesized that the drinking capacity during dopamine depletion will be altered. To this end, we performed a nutrient drink test during an alpha-methyl-para-tyrosine (AMPT) challenge, known to induce acute reversible dopamine depletion. We showed that drinking capacity and evoked gastrointestinal symptoms were not affected by dopamine depletion. Taken together, our data suggest that chronic rather than acute alterations in the dopaminergic system may be involved in the pathogenesis of FD. However, further studies are required to reproduce our novel findings.

Furthermore, several studies showed that stress can induce visceral sensitivity associated with dysregulation or activation of the peripheral immune system. Our next step was, therefore, to evaluate how stress may lead to increased visceral perception in humans. Animal studies have indeed suggested that repeated stress alters mucosal barrier function (increased mucosal permeability) with increased exposure of the mucosal immune system to intraluminal antigens. The latter is believed to lead to the development of microscopic inflammation and subsequent visceral hypersensitivity. In the past decade, the interest in microscopic inflammation as potential mechanism of abnormal visceral perception has increased exponentially. Different studies have shown an increased number of mast cells and T lymphocytes in mucosal biopsies of IBS patients. Knowing that inflammatory mediators released from immune cells (i.e. tryptase, histamine) can sensitize visceral afferent nerves, microscopic inflammation may indeed lead to changes in visceral perception and IBS symptoms. However, the relationship between stress response, microscopic inflammation
and visceral sensitivity has not been studied in detail in IBS. Therefore, in chapter 6 we hypothesized that visceral hypersensitivity was associated with microscopic inflammation and an increased response to an acute stressor. We first assessed the relationship between visceral hypersensitivity, determined by rectal barostat, and the number of mast cells, macrophages (CD68 and CD163), T-lymphocytes (CD3 and CD8), T-regulatory cells (FOXP3) and the number of mast cells crosslinked with of IgE-, IgG antibodies or free light chain immunoglobulins (IgFLC) in 66 IBS patients and 20 HV. Second, we determined the possible relationship between visceral perception, microscopic inflammation and stress response to a psychological stress test, in a subgroup of the participants. In contrast to our expectations, we observed a decreased number of mast cells, macrophages and T lymphocytes in IBS compared to HV. In addition, the IgFLC positive mast cells were decreased, but not IgE- and IgG positive mast cells, suggesting that antigen-specific activation of mast cells is not involved in IBS. Moreover, the number of inflammatory immune cells was not associated with the cortisol stress response and did not correlate with rectal discomfort thresholds arguing against an important role for microscopic inflammation in the generation of visceral hypersensitivity. That the number of mast cells is decreased in IBS is actually surprising, especially as an increased number of mast cells and increased release of their mediators has previously been reported by others. Nevertheless, our findings do not exclude a role for mast cells, as we believe that their activation or even their interaction with nerves may be more important than the number of cells. Our results are corresponding with previous observations in maternally separated rats in which, the development of stress induced visceral hypersensitivity did not coincide with an increased number of mucosal mast cells, but was reversed by treatment with a mast cell stabilizer (doxantrazole). Taken together, our data question the role of microscopic inflammation and rather suggest immune dysregulation with mast cell activation as pathophysiological mechanism in IBS.

Based on this finding and previous studies providing evidence supporting an important role for mast cells in IBS, mast cells should be considered as an important target for treatment of IBS. In chapter 7, we therefore performed a double blind placebo controlled trial in 60 IBS patients, to evaluate the effect of mast cell stabilizer ketotifen on the sensitivity of the gut and clinical IBS symptoms. We demonstrated that 8 weeks of treatment with the mast cell stabilizer ketotifen, but not placebo, increased the threshold of discomfort in hypersensitive IBS patients. Normosensitive IBS patients did not show this effect. In addition, ketotifen reduced IBS symptoms (i.e. abdominal pain, diarrhoea, bloating, incomplete evacuation) and improved quality of life. However, ketotifen did not affect the release of mast cell mediators, like histamine and tryptase. These data would argue against mast cell stabilization as the mechanism underlying symptom improvement. As ketotifen has histamine 1 (H1) receptor blocking properties, we hypothesize that the clinical improvement may result from this pharmacological effect. To further test this hypothesis, we are currently performing a clinical study evaluating the effect of the H1 receptor antagonist ebastine in IBS patients. Based on the ketotifen study, we conclude that the mast cell is an important target for treatment suggesting that mast cell stabilizing agents or H1 receptor antagonists should be further studied as potential new therapeutic strategy to relief IBS symptoms.

Finally, antidepressants like amitriptyline are currently used in IBS and FD with variable clinical success, but, especially in FD, clinical placebo controlled studies are currently lacking. Moreover, the mechanism of action and their effect on gastric sensitivity or drinking capacity in FD patients remains unknown. Previously, we have shown that symptoms like nausea,
pain, satiety and bloating evoked by a drink test are more intense in FD compared to HV\textsuperscript{46}. In addition, the drink test is able to indirectly assess gastric function by measuring the maximal ingested volume, irrespective of the underlying pathophysiological mechanism\textsuperscript{46, 47}. In chapter 8 we performed a double blind placebo controlled trial in 38 FD patients to evaluate the hypothesis that 8 weeks of treatment with amitriptyline improves drinking capacity and reduces dyspeptic symptoms. We observed that the drinking capacity of liquid meal was not affected by either amitriptyline or placebo treatment. Postprandial symptoms evoked by the drink test were not significantly different between amitriptyline and placebo. However, during the entire treatment, total symptom score and nausea were significantly reduced by amitriptyline compared to placebo. In conclusion, amitriptyline did not affect drinking capacity, but improved overall symptom score and especially nausea. However, larger clinical trials, with inclusion of patients with nausea as predominant symptom, are needed to further confirm our findings.

In conclusion, in this thesis, we investigated the pathophysiological mechanisms of FGID, both in the periphery and at the level of the brain, and investigated two therapeutic approaches in FD and IBS. We provided additional data stress as an important risk factor, both early in life as in adulthood. We demonstrated that changes the central dopaminergic system of FD patients, possibly related to chronic stress. To what extent these changes explain the beneficial effect of treatment with antidepressants remains to be proven. Our finding that dyspeptic symptoms, especially nausea, improved with amitriptyline may however be in line with this hypothesis. Next, we provided data suggesting immune dysregulation in IBS and hypothesized that mast cell activation rather than increased number of cells is an important pathophysiological mechanism. In a proof-of-concept study, we indeed showed that treatment with the mast cell stabilizer ketotifen improved abdominal symptoms in patients with IBS, confirming that mast cells may be an important new target for treatment.

The Future

It is becoming increasingly clear that the pathophysiology of the two most prevalent FGIDs, i.e. FD and IBS, is multifactorial. Not only psychosocial factors, traumatic events, psychiatric diseases but also the stress response to psychological stressors is relevant in the generation of FGID symptoms. Moreover, stress seems to be a key factor in physiological alterations, like visceral hypersensitivity, immune dysregulation, dysfunction of the HPA-axis, and even abnormal brain activation. However, despite increased insight in the risk factors and the underlying pathophysiological mechanisms, the current treatment options are still purely symptomatic and insufficiently effective in relieving gastrointestinal symptoms. Therefore, there is a large need to continue and even to intensify our search for new treatments. Especially as FGID are multifactorial and most likely a collection of different subtypes with different underlying pathophysiological mechanisms, one of the first challenges would be to develop tools allowing us to identify these subtypes. To this end, we definitely need biomarkers that will help us to better characterize our patients and to better determine the optimal treatment. Ultimately, this should lead to individualized and better targeted treatment of FGID patients. Ideally, we should be able to differentiate patients with altered brain function from for example those with mucosal immune dysfunction following a gastrointestinal infectious episode (post-infectious IBS), as both populations most likely require a different
therapeutic approach. To date however, the only biomarker available in clinical practice, at least for IBS, is stool consistency, of which the impact on clinical management and certainly outcome is rather limited. Hopefully, our insight on the role of immune dysfunction and the role of mast cells in this process will further increase. Ideally, this will yield biomarkers such as microRNAs or mast cell mediators in biopsies, blood and/or feces that will help to select individuals responding to mast cell stabilizers and/or H1 receptor antagonists. In the same line, insight in the alterations in brain processes and neurotransmitters/receptors involved in symptom perception will not only generate new targets for central acting compounds, but will hopefully also yield peripheral markers identifying those patients that will benefit from these compounds. In this thesis, we have tried to add a small piece to the large puzzle, but obviously, a lot of work remains to be done to better treat our patients.
Reference List