Gut feelings: visceral hypersensivity and functional gastrointestinal disorders
Kuiken, S.D.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date: 21 Dec 2018
GENERAL INTRODUCTION
Functional gastrointestinal disorders (FIGDs) represent a major clinical problem, not only because of the large quantity of patients presenting with these disorders, but also because of the lack of therapeutic options due to the limited understanding of the pathophysiological mechanisms involved. The most frequent of these disorders are the Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD). Depending on the definitions applied, reported prevalences within the general population range up to 22% and 50% for IBS and FD, respectively.\textsuperscript{1,2} Although the majority of patients do not seek medical help, FD accounts for 5% and IBS for 12% of primary care consultations.\textsuperscript{1,2} Together, FIGDs form the largest diagnostic group seen in a gastroenterologist’s practice, comprising 35 to 41% of the symptomatic outpatients’ diagnoses.\textsuperscript{3,4}

FIGDs are generally characterised by chronic or recurrent gastrointestinal symptoms, in the absence of a detectable underlying organic cause.\textsuperscript{5} Because reliable biological markers are not available, the diagnosis is based on symptom-based criteria such as the Rome II criteria, which currently serve as the gold standard.\textsuperscript{6} According to the Rome II criteria, IBS is defined as ‘abdominal discomfort or pain associated with defecation or a change in bowel habit, and with features of disordered defecation’.\textsuperscript{5} FD is defined as ‘persistent or recurrent pain or discomfort centred in the upper abdomen’.\textsuperscript{7} Symptom patterns alone are unable to adequately discriminate organic disease from FIGDs. Therefore, patients need to have been investigated to rule out relevant organic disease.

Because the pathophysiological mechanisms are largely unknown, treatment of FGIDs is often disappointing. To understand the difficulties that are encountered in the management of FGIDs, it should be emphasised that these disorders are very heterogeneous and probably represent different subgroups with distinct underlying pathophysiologies. Therefore, it is unlikely that a single mechanism would be responsible for the development of symptoms. Consequently, it is unlikely that a single treatment would be successful in all patients with IBS or all patients with FD, respectively.

To optimise treatment outcome, several attempts have been made to define subgroups of patients with IBS and FD based on their clinical presentation. Such recommendations have also been incorporated in the Rome II consensus. For IBS, sub-classification has been proposed based on predominant bowel habits. IBS patients may present with predominantly diarrhoea (IBS-D) or constipation (IBS-C), or may alternate between diarrhoea and constipation (IBS-A).\textsuperscript{5} Patients with FD are sub-classified based on their most bothersome symptom into ulcer-like dyspepsia (predominantly pain), dysmotility-like dyspepsia (predominantly non-painful symptoms) or unspecified dyspepsia (without a predominant symptom).\textsuperscript{7} In FD, the relevance of these sub-classifications to clinical practice with respect to treatment remains controversial, mainly because the relationship with proposed underlying pathophysiological mechanisms is unclear. In IBS however, recent studies have shown that the investigational serotonin agonists and antagonists were only effective in IBS-C and IBS-D, respectively, suggesting that these different subgroups indeed respond to different treatments.\textsuperscript{8,9}
Subgroup selection may also be based on the proposed mechanisms underlying the generation of symptoms. These mechanisms show considerable overlap between IBS and FD. Common mechanisms that have been proposed to play a role in both IBS and FD include abnormal motility, visceral hypersensitivity, autonomic dysfunction, altered central nervous system modulation and psychosocial factors including mental stress. More specifically, post-infectious neuro-immune modulation of gut functions has been shown to play a role in the development of IBS, whereas H. pylori infection and dysregulation of acid secretion have been related to symptoms in FD.

At present, the concept of visceral hypersensitivity provides the leading hypothesis regarding the generation of symptoms in both IBS and FD. Several studies have shown that patients with IBS exhibit hypersensitivity to distension of the colon and recto-sigmoid, whereas patients with FD exhibit hypersensitivity to gastric distension, indicating that normal, physiological stimuli may be perceived with increased intensity or may even cause pain. In addition, gut hypersensitivity may lead to alterations in gut motility by disturbing regulatory reflex pathways and secretory functions. The prevalence of visceral hypersensitivity among patients with IBS and FD is similar, roughly involving 50 to 60% of patients. In the remainder of patients, visceral sensitivity appears to be normal. Therefore, it has previously been suggested that hypersensitive patients with IBS or FD may represent a distinct subpopulation of FGIDs based on the underlying pathophysiology. The possible mechanisms involved in the development of visceral hypersensitivity have been summarised in CHAPTER 1.

From a therapeutic point of view, restoring normal sensitivity could provide an attractive approach to treat these patients. Several drugs have been shown to successfully reduce visceral sensitivity in experimental studies, but the proof of the concept has not been well established in clinical practice. In addition, the relationship between visceral hypersensitivity and symptoms in FGIDs is still unclear.

This thesis focuses on visceral hypersensitivity as a target for the treatment of FGIDs. CHAPTER 1 discusses the currently available evidence with respect to the clinical efficacy of drugs that have been proposed to interfere with visceral sensitivity in FGIDs. Associations between the presence of visceral hypersensitivity and specific symptoms in FGIDs may further support its relevance to symptom generation. In addition, such associations could help to classify or select hypersensitive FGID patients based on symptom patterns, for example to improve the outcome of treatments aimed at reducing visceral sensitivity. Therefore, we studied the relationship between visceral hypersensitivity and symptoms in FGIDs. In CHAPTER 2, we assessed possible associations between dyspeptic symptoms and proximal gastric dysfunction (i.e. impaired relaxation to a meal and hypersensitivity to distension) in patients with FD. In CHAPTER 3, the relationship between IBS symptoms and hypersensitivity to rectal distension was evaluated.

To guide future treatments aimed at restoring normal sensitivity in FGIDs, it is important to identify the receptors and mediators implicated in visceral perception.
in humans. At present, most of our understanding of the (patho-) physiology of the viscero-sensory system is derived from animal studies, and cannot simply be extrapolated to humans. Based on the available experimental data, we further explored the roles of N-methyl-D-aspartate (NMDA) receptors and nitric oxide (NO) in visceral sensitivity in man. In CHAPTERS 4 and 5, we studied the effects of two different NMDA receptor antagonists on the gastric sensitivity in healthy volunteers. The effects of the NO synthase inhibitor L-NMMA on gastric and rectal sensitivity in healthy volunteers are described in CHAPTERS 6 and 7, respectively. In addition, to study possible differential effects of NO in (abnormal) hypersensitive states, we also studied the effect of L-NMMA on rectal sensitivity in hypersensitive IBS patients (CHAPTER 7). Finally, to further address the concept of targeting visceral hypersensitivity in clinical practice, we studied the proposed viscero-sensory effects of the SSRI antidepressant fluoxetine on symptoms in hypersensitive and normosensitive IBS patients (CHAPTER 8).

REFERENCES


