Gut feelings: visceral hypersensivity and functional gastrointestinal disorders
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Citation for published version (APA):
SUMMARY & CONCLUSIONS
The concept of visceral hypersensitivity has become an established factor in our understanding of the development of symptoms in functional gastrointestinal disorders (FGIDs). Since the original paper by Ritchie in 1973, several independent research groups have confirmed that patients with irritable bowel syndrome (IBS) exhibit increased sensory responses to mechanical distension of the bowel. A similar phenomenon was later described in patients with functional dyspepsia (FD), who showed hypersensitive responses to distension of the proximal stomach. In the presence of a hypersensitive gut, normal, physiological stimuli may be perceived with increased intensity or may even cause pain, whereas regulatory reflex pathways of gut motility and secretion may become disturbed. Indeed, abdominal pain or discomfort, unexplained by any structural abnormalities and associated with alterations in gut motility, are key features in the symptom pattern of both IBS and FD. It is important to acknowledge that visceral hypersensitivity is not a generalised feature among patients with IBS and FD, but involves about 50% to 60% of patients. Hypersensitivity may therefore only play a role in a distinct subpopulation of patients with FIGIDs, who may need to be distinguished from normosensitive patients with regard to their underlying pathophysiology and treatment. In this thesis, we have critically reviewed the clinical evidence reported in the literature favouring visceral hypersensitivity as a therapeutical target in FIGIDs. In addition, we further assessed the possible relationship between visceral hypersensitivity and symptoms in FGIDs. Finally, we obtained evidence to guide future pharmacological strategies aimed at reducing visceral hypersensitivity in clinical practice.

In CHAPTER 1, we reviewed the available literature to find proof for the concept that restoring normal sensitivity could provide benefit in patients with IBS and FD. Five drug classes with proposed visceral analgesic properties and of which controlled data were available addressing their clinical efficacy were selected. These included opioid substances, serotoninergic agents, antidepressants, somatostatin analogues and α2-adrenergic agonists. Several well designed clinical trials were identified convincingly showing that contemporary compounds such as alosetron and tegaserod, but also existing drugs such as tricyclic antidepressants and loperamide are efficacious in FIGDs (in particular in IBS). However, we were unable to find convincing evidence that these particular drugs also reduce visceral sensitivity in humans. Conversely, other drug classes of which the visceroanalgesic properties in humans seem well established, such as kappa-opioid agonists and somatostatin analogues, appeared to display limited clinical efficacy. It should be emphasised though that the proposed visceroanalgesic effects of many of the selected compounds have not been fully characterised in humans. In addition, the presumption that selected subgroups with documented visceral hypersensitivity should benefit most from these interventions has not been well explored. Therefore, in contrast to what seems generally accepted, we conclude that targeting visceral hypersensitivity as a treatment for FIGIDs is still controversial and requires further validation. This should involve high quality clinical trials with true visceral analgesics and careful selection of patient subgroups.

To support the hypothesis that FIGIDs with and without visceral hypersensitivity represent different subgroups with distinct pathophysologies, we
studied the association between the presence of visceral hypersensitivity and specific symptoms. Such possible associations may further support the relevance of hypersensitivity to symptom generation, and may also provide a rationale for subgroup selection based on clinical parameters, when evaluating visceral analgesic compounds in future studies. In CHAPTER 2, we showed that despite the substantial demonstrable differences in gut sensitivity, hypersensitive and normosensitive IBS patients present with comparable, heterogeneous symptom patterns. Therefore, selection based on clinical parameters is unlikely to discriminate individual IBS patients with visceral hypersensitivity from those with normal visceral sensitivity. Similarly, in CHAPTER 3, no correlation could be demonstrated between specific dyspeptic symptoms and hypersensitivity to gastric distension in patients with FD. In addition, impaired accommodation to a meal, another proposed mechanism underlying the development of symptoms in FD, was also not associated with specific symptoms. Although these findings contrast with comparable studies in FD, our data suggest that there is no clear relationship between dyspeptic symptoms and proximal stomach dysfunction.

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 viscerosensory system is derived from animal studies, and cannot simply be extrapolated to humans. Based on these available experimental data, we chose to further explore the roles of two candidate mediators of visceral perception in humans, namely the N-methyl-D-aspartate (NMDA) receptor and nitric oxide (NO).

Activation of NMDA receptors plays a role in chronic and 'wind-up'-like somatic pain. In contrast, there is experimental evidence that in the viscera, NMDA receptors are involved not only in mediating hypersensitive states, but also in the processing of both acute noxious and non-noxious stimuli from normal, non-inflamed viscera. With this in mind, we studied the effects of two different NMDA receptor antagonists on gastric sensitivity in healthy volunteers. In CHAPTER 4 we studied the effect of dextromethorphan, a non-opioid antitussive agent with NMDA receptor antagonistic properties, on the sensitivity to gastric balloon distension. In contrast to what we anticipated, dextromethorphan increased rather than decreased gastric sensitivity. Whether this reflected an NMDA mediated effect or a non-specific effect of dextromethorphan remained unclear, since the compound displays high affinity to several other receptors. Therefore, in CHAPTER 5, we performed a similar study with oral S(+)-ketamine, another non-competitive NMDA receptor antagonist yet with high affinity to the receptor. In contrast to dextromethorphan, S(+)-ketamine did not alter gastric perception in our healthy volunteers, suggesting that the effect of dextromethorphan reflects a non-specific action via non-NMDA mediated binding sites. Taken together, these data suggest that NMDA receptor blockade does not reduce visceral sensitivity in health. The role of NMDA receptors in conditions characterised by visceral hypersensitivity, such as FIGIDs, needs to be further studied.
The effects of the NO synthase inhibitor L-NMMA on gastric and rectal perception in healthy volunteers are described in CHAPTER 6 and CHAPTER 7, respectively. In the stomach, no effect of L-NMMA on the perception of distension-induced sensations was seen. Similarly, L-NMMA did not alter the sensitivity to rectal distension, indicating that at least in healthy volunteers, NO has no major role in visceral perception. With regard to maintaining fundic and rectal tone, differential effects of NO synthase inhibition were observed. L-NMMA decreased basal fundic volume and reduced fundic relaxation both after ingestion of a liquid meal and during intra-duodenal lipid infusion, whereas basal rectal volumes remained unaltered. Thus, we concluded that NO is involved in modulating fundic, but not in rectal tone.

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). In contrast to healthy volunteers, L-NMMA significantly increased the threshold for discomfort/pain during rectal distension in IBS patients, whereas rectal tone and rectal compliance remained unaltered. In concert with experimental studies on visceral hypersensitivity in rats, these findings suggest that NO may be involved in maintaining visceral hypersensitivity in IBS.

In CHAPTER 8, we studied the proposed viscero-sensory effects of the selective serotonin reuptake inhibitor (SSRI) antidepressant fluoxetine on symptoms in IBS patients. Our main finding was that fluoxetine had no demonstrable effect on visceral sensitivity, questioning its visceral analgesic properties in IBS patients. In addition, no effect on IBS symptoms could be demonstrated in the overall treated patients. However, in patients with hypersensitivity to rectal distention, fluoxetine reduced the number of patients reporting significant abdominal pain, which was not observed in patients with normal rectal sensitivity. Although these data should be interpreted with caution because of the limited number of patients, this may have implications for future study designs further evaluating the antinoceptive effects of SSRIs in FIGDs, since patients characterized by visceral hypersensitivity may respond better to this type of treatment. Whether this can be confirmed in larger studies and how this can be explained needs to be awaited.
CONCLUSIONS

Despite the lack of convincing evidence that visceral analgesic drugs are efficacious in clinical practice and the poor correlation with symptoms, visceral hypersensitivity may still play an important role in the pathogenesis and treatment of FIGDs. Therefore, drug development should continue to focus on new agents with visceral analgesic properties, mainly based on data obtained from animal models. When new agents have been selected for human use, it should be emphasised that differential effects may be expected in normosensitive and hypersensitive subjects. Indeed, we showed that L-NMMA was only effective in IBS patients with documented hypersensitivity but not in healthy volunteers, suggesting that visceral analgesic agents may only be effective in hypersensitive states. This knowledge is of course very important in the process of future drug evaluation.

So far, clinical trials evaluating the effect of visceral analgesics have only been performed in unselected populations of patients with FIGDs. We believe that in order to find ultimate proof for the concept of visceral hypersensitivity, the design of clinical trials should be changed such that only patients with proven visceral hypersensitivity should be included. This of course raises the question how patients with visceral hypersensitivity should be selected. As we showed that clinical presentation or non-invasive techniques currently available are unable to distinguish hypersensitive from normosensitive patients, gut distension using the barostat remains the investigation of choice. It should be stressed though that this is an invasive and unphysiological technique, which is expensive, time-consuming and often bothersome for patients. Clearly, this approach will make large scale clinical trials in FIGDs even more difficult to perform, further stressing the need for future research developing new non-invasive tools evaluating visceral sensitivity in a more physiological manner.