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TOPIC HIGHLIGHT

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Functional dyspepsia: The role of visceral hypersensitivity in its pathogenesis

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Abstract

Functional, or non-ulcer, dyspepsia (FD) is one of the most common reasons for referral to gastroenterologists. It is associated with significant morbidity and impaired quality of life. Many authorities believe that functional dyspepsia and irritable bowel syndrome represent part of the spectrum of the same disease process. The pathophysiology of FD remains unclear but several theories have been proposed including visceral hypersensitivity, gastric motor dysfunction, *Helicobacter pylori* infection and psychosocial factors. In this review, we look at the evidence, to date, for the role of visceral hypersensitivity in the aetiology of FD.

Key words: Visceral hypersensitivity; Motor dysfunction; *Helicobacter pylori*; Psychosocial

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INTRODUCTION

Functional dyspepsia is a common clinical condition in the community and is one of the most common disorders encountered by gastroenterologists worldwide. It forms part of the functional gastrointestinal disorders (FGID's), a spectrum that includes irritable bowel syndrome (IBS), non-cardiac chest pain, and non-ulcer or functional dyspepsia and that overlaps to a significant extent with non-erosive reflux disease (NERD)[1]. Studies of FD prevalence have provided varied rates but one study estimated that as many as 25% of Americans may be affected[2]. However not all of those affected seek medical attention for their symptoms. While the individual symptoms may be included within the concept of FD are also varied and include post-prandial fullness, bloating, early satiety, nausea, and vomiting, the hallmark of functional dyspepsia is the presence of persistent or recurrent pain or discomfort centred in the upper abdomen for which there is no organic cause. According to the most widely employed definition of FD, Rome II, this symptom should have been present for at least 12 wk within the preceding 12 mo in order to be classified as FD[3]. The advent and widespread use of the Rome criteria has facilitated clinical studies, including studies of pathophysiology, by ensuring, as far as possible, the inclusion of a relatively homogenous population within any given study. In the evaluation of any study of the role of visceral hypersensitivity, or indeed, any other factor in the pathophysiology of FD, it is critical to be fully apprised, not only of the criteria that were employed in the definition of the study population, but also of their geographic origin and the location of the study. These and other features, such as age, socio-economic status and ethnicity, can lead to tremendous variations in the relative contributions of various factors to the pathophysiology of FD, in a given population. For decades, general practitioners and specialists alike dismissed these patients as malingerers or as having some form of somatization disorder. However, it is only in the last decade or so that attempts have been made to elucidate the true pathophysiology of this heterogeneous disease. A number of putative mechanisms have been elucidated, including visceral hypersensitivity, delayed gastric emptying, impaired gastric accommodation, acid sensitivity, *Helicobacter pylori* (*H pylori*) infection and disturbed central perception of peripheral visceral events.

With regards to the relative contributions of these factors, Stanghellini *et al* found delayed gastric emptying in 33% of FD patients, and this was associated with female gender, low body weight, the presence of severe postprandial fullness, and vomiting, and the absence of pain as a dominant symptom[4]. Impaired gastric accommodation is thought to be present in approximately 40% of patients and is associated with early satiety and weight loss[5-7]. As regards *H pylori*, its role in the generation of symptoms remains controversial but certainly there is evidence to show that persistent infection may alter gastric

motor and sensory physiology; however, the benefits of eradication remains somewhat controversial[8-10]. The prevalence of hypersensitivity to gastric distension has been reported to be of the order of 30%-40%. Attempts to link mechanisms with symptoms have met with mixed results; proposed symptom associations with various pathophysiologic mechanisms are outlined in Table 1 below[11].

Method

An extensive review of the role of visceral hypersensitivity in the pathogenesis of functional dyspepsia was undertaken. For this purpose a systematic search of Pubmed databases 1966-2003 for relevant literature was performed, using the following key word combinations: functional dyspepsia or non-ulcer dyspepsia and visceral hypersensitivity. Relevant literature was reviewed and cited accordingly.

Table 1 The mechanism and associated symptoms in functional dyspepsia

Mechanism	Associated symptoms
Delayed gastric emptying	Postprandial fullness, nausea, vomiting.
Hypersensitivity to gastric distension	Epigastric pain, belching, weight loss.
Impaired accommodation	Early satiety, weight loss.
Helicobacter infection	Epigastric pain
Duodenal lipid hypersensitivity	Nausea
Duodenal acid hypersensitivity	Nausea
Unsuppressed phasic contractility	Bloating, absence of nausea
Atypical nonerosive reflux disease	Epigastric pain

VISCERAL HYPERSENSITIVITY

In order to fully understand visceral hypersensitivity we must first return to neurophysiology and understand how stimulation of the gut wall results in conscious perception. The perception of somatic pain involves a three-neuron chain, as illustrated in Figure 1. For visceral pain, a similar mechanism is operative. The signal is initiated at sensory receptors in the mucosa, muscle layer or serosa and relayed *via* intrinsic primary afferent neurons (IPAN's), vagal or spinal sensory afferent neurons to second order neurons in the enteric nervous system, brain stem or spinal cord, respectively.

Theories abound regarding potential sites of abnormal sensory signalling in FD. While most studies have involved mechanical stimuli, such as distension, there is evidence of sensitivity to other stimuli. For example, Samsom and colleagues have previously shown that FD patients are more sensitive to the introduction of exogenous acid into the duodenum[12]. Firstly, the existence of hypersensitivity, at the level of gut mechanoreceptors, has been nicely illustrated by Tack and colleagues[13]. In this experiment, they took fifty patients with documented visceral hypersensitivity by barostat studies and treated half with fundus-relaxing drugs, sumatriptan and clonidine. When re-tested, those treated with gastric relaxing drugs now demonstrated a significant reduction in gastric sensitivity, thereby, illustrating the role of the mechanoreceptor in the generation of symptoms from a hollow viscus in the gastrointestinal tract, as had been previously shown by others, in healthy volunteers[13-15].

Much of the initial work on visceral hypersensitivity involved balloon distension of the stomach. The development of the barostat allowed investigators to measure gastric tone and sensory responses accurately and reproducibly for the first time[16]. It has long been known in clinical practice that patients with irritable bowel syndrome (IBS) have a low threshold for the development of pain when subjected to certain stimuli, such as digital rectal examination, sigmoidoscopy and colonoscopy. This was confirmed some time ago by balloon inflation studies in IBS[17]. More recent studies have suggested that both visceral hypersensitivity[18], and visceral hyperalgesia[19], the phenomenon whereby innocuous stimuli become painful, are highly specific for IBS. Another related phenomenon characteristic of IBS is that of viscero-somatic referral, whereby the pain elicited by a given stimulus is experienced at a site remote from that of its application.

Similar observations have been made in functional dyspepsia, thereby, advancing the visceral hypersensitivity hypothesis in this disorder also. Several studies have looked at balloon distension of the stomach using the gastric barostat and have all found increased sensitivity to distension at lower distending pressures relative to normal healthy controls[20-25]. Mearin and colleagues nicely illustrated this phenomenon. In their study, one can clearly see the distinct difference in abdominal discomfort scores between the FD patients and the control subjects as intragastric pressure is increased[22].

Mearin's group also, rather interestingly, showed that there were no differences in terms of somatosensory responses between controls and dyspeptics thus suggesting that this was truly a visceral phenomenon. Some would even suggest that visceral hypersensitivity to distension appears to be organ specific, with the response to rectal distension being specific for IBS and that to gastric distension being similarly specific for FD. However, a subsequent study by Bouin *et al* looked at somatic sensation by hand immersion in cold water, and found that those with functional gastrointestinal disorders perceived pain earlier and had a lower pain tolerance than normal controls[26]. These findings suggest, in contrast, that hypersensitivity is not just a visceral problem, but, perhaps, forms part of a more generalised sensory dysfunction. Whether differences in patient populations or testing methodology can explain these apparently discordant results remains unclear.

Mertz and colleagues compared sensory responses in a group of FD patients with both healthy controls and a group of patients with organic cause for their dyspepsia[24]. They examined both sensory thresholds to gastric balloon distension and the nature of the symptoms perceived during gastric distension. While there was no real difference in the prevalence of symptoms between the organic and functional groups (apart from nausea as a primary complaint being significantly more common in the FD group), only those with functional dyspepsia

had lowered perception thresholds to gastric distension, 87% versus 20%. In addition, they showed, rather nicely, the presence of viscerosomatic referral in the FD patient group alone. This could explain how patients with functional dyspepsia may perceive pain at sites distant to the stomach.

THE BRAIN-GUT AXIS

Other potential sites for sensory abnormalities in functional dyspepsia are the sensory afferent neurons, the spinal cord, and the brain itself. More and more research is now focusing on the so-called brain-gut axis. Normally, most visceral sensation to the central nervous system (CNS) does not reach conscious perception but patients with FD are thought to perceive visceral stimuli in an abnormal manner[27]. Vandenberghe and colleagues demonstrated, in their study, that visceral hypersensitivity may originate at sites other than the gut wall and involve a multimodal pathway[28]. They showed that both painful and non-painful gastric distension resulted in higher symptom scores among a group of FD patients with visceral hypersensitivity, yet gastric compliance was similar to that in a group of FD patients without hypersensitivity, suggesting that altered perception was more than a gut wall phenomenon.

Research in animal models has furthered our knowledge of the visceral sensory pathways (Figure1). Previously it had been thought that nocioception was mediated by spinal afferents and the sympathetic system[29], until animal studies established the role vagal afferents played in the modulation of nociception[30,31]. The advent of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scanning have greatly increased our knowledge of the final sensory pathways in the spinal column and the brain[32]. Two recent studies, in healthy volunteers, have demonstrated the activation of several areas of the brain in individuals subjected to gastric distension[32,33]. Some of the areas of activation included the thalamus, the insula, the left and right postcentral gyrus, and the anterior cingulate gyrus. The latter, interestingly, was previously shown to be an area of low activation, in IBS patients, in response to a painful stimulus[34]. Similarly, non-painful oesophageal balloon distension activates the primary somatosensory cortex, the insula bilaterally, and the operculum and painful stimuli activate the right anterior insular cortex and the cingulate gyrus[35,36]. These studies illustrate the complexity of central nervous system processing of visceral pain.

FOOD HYPERSENSITIVITY IN FUNCTIONAL DYSPEPSIA

Typically, and almost by definition, FD patients report the occurrence of most their symptoms in relation to food ingestion. Accordingly, studies have shown that about 60%-70% of patients with FD are hypersensitive to an infusion of lipid into the duodenum[37,38]. Another study found more dyspeptic symptoms in patients following the ingestion of high-fat versus low-fat soups[39]. It would also appear that hypersensitivity is nutrient specific as the intraduodenal infusion of an emulsion of long-chain triglycerides induced fullness, nausea, and bloating in patients with FD, whereas an infusion of glucose did not[40]. A role for fat was further illustrated in a recent study on healthy volunteers where the lipase inhibitor, orlistat, markedly reduced the perception of fullness and nausea induced by duodenal lipid infusion and gastric distension[41].

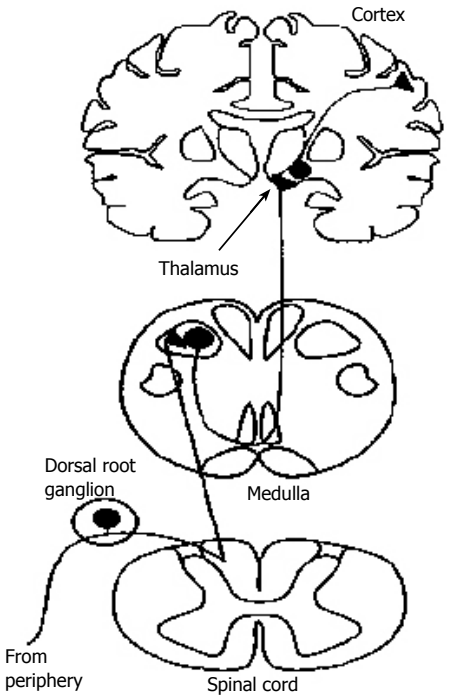

Figure 1 Sensory pathway showing one route of visceral sensation from the periphery, via a spinal sensory afferent neuron to the central nervous system.

Duodenal infusion of acid was also found by Samson and colleagues to induce nausea in FD; these patients also demonstrated impaired clearance of exogenous acid from the duodenum[12]. It is clear from these studies and others that small intestinal sensing of certain nutrients and fat, in particular, as well as the motor response in the foregut to their instillation, may play a role in the induction of symptoms in FD. In this way motor and sensory phenomena may interact and prove synergistic in symptom induction.

Helicobacter pylori

H pylori infection is purported in several studies as a possible mechanism in functional dyspepsia. However, recent large scale controlled trials and a meta-analysis failed to show any improvement in dyspeptic symptoms with *H pylori* eradication[42-44].It is unclear what role *H pylori* plays in the symptom profile of the FD patient, and whether any of the proposed pathophysiological mechanisms mentioned earlier are related to *H pylori* infection. These particular questions were addressed in a recent study by Sarnelli and colleagues[45] in which they compared the symptom profile of FD patients with and without *H pylori*, and looked at various pathophysiological mechanism including gastric emptying, sensation and accommodation.

They found no association between *H pylori* infection and the overall prevalence of symptoms or the gastric sensory-motor functions. This is in keeping with the previous observations that eradication of *H pylori* is not associated with with improvement in the dyspeptic symptoms.

In conclusion, clearly, a vast amount of knowledge regarding FD has been garnered from detailed studies of the last decade or so. The level of complexity involved in visceral sensation is only now being fully understood and therapies aimed at ameliorating the hypersensitive gut are crucial. These will involve visceral analgesics and agents that block the various neurotransmitters involved. The development of enhanced neuroimaging will allow us better understand the mechanisms of actions of some of these agents. Functional dyspepsia often leaves the clinician despondent due to the lack of clinical efficacy of many of the drugs used, but novel agents and targets of treatment offer hope for the treatment of this complex condition.

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