Novel mechanisms in functional dyspepsia

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Abstract

Functional dyspepsia (FD) is a highly prevalent but heterogeneous disorder in which multiple pathogenetic mechanisms are involved. Although there are many studies that have investigated various pathophysiologic mechanisms, the underlying casual pathways associated with FD remain obscure. The currently proposed pathophysiologic mechanisms associated with FD include genetic susceptibility, delayed gastric emptying, visceral hypersensitivity to acid or mechanical distention, impaired gastric accommodation, abnormal fundic phasic contractions, abnormal antroduodenal motility, acute and chronic infections, and psychosocial comorbidity. A greater understanding of the abnormalities underlying FD may lead to improved management. The aim of this editorial is to provide a critical overview of current pathophysiologic concepts in functional dyspepsia.

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EDITORIAL

INTRODUCTION

Dyspepsia, or pain or discomfort centered in the upper abdomen, is a common condition accounting for 2-5% of all primary care consults; the annual prevalence is 25%[1,2]. Dyspepsia is a major cause of morbidity and economic loss in the community[3,4]. A heterogeneous group of pathophysiologic mechanisms have been implicated in the etiology of functional dyspepsia (FD).

Delayed gastric emptying[5], antral hypomotility and altered intestinal motility[6], diminished gastric accommodation[7], Helicobacter pylori infection[8], abnormal duodenal sensitivity to acid[9], enhanced visceral sensitivity[10], carbohydrate malabsorption[11], food intolerance[12], and psychological factors[13] have all been identified in subgroups of patients with functional dyspepsia, with much overlap.

Despite the high prevalence of FD and its significant impact on social and health care costs, the underlying causative pathways are still obscure. Therefore, our objective here is to briefly provide an overview of the known pathophysiology of FD, and highlight recent advances in our knowledge.

GENETICS

Recent evidence supports the relevance of a genetic milieu in FD. A case-control study by Holtmann et al[14] suggested that there is a significant link between GNβ3(C825T) CC genotype and functional dyspepsia (OR = 2.2, 95% CI = 1.4-3.3). Although their study[14] had some limitations including the high prevalence of the CC genotype among control subjects and the relatively modest excess of the genotype in FD subjects, their findings do represent the first identification of a putative genetic predisposition. The association has been independently confirmed[15]. Further studies of the relationship between genetic polymorphisms and other pathophysiologic factors in FD are now needed.

ABNORMALITIES IN UPPER GUT MOTOR FUNCTION

A prevalence of disturbances in gut motor function of about 20-40% in FD patients is now accepted[6,7,16]. The disturbances of gastric motor function most often reported in FD include delayed gastric emptying[17], abnormalities in antral contractility[18] and an impaired accommodation response (a vagally-mediated reflex relaxation of the fundus in response to a meal)[19].

Gastric emptying

Delayed gastric emptying has been described in 25-50% of patients with FD[16,19]. The majority of small sample sized investigations failed to identify association between delayed gastric emptying and any dyspeptic symptoms[20-23]. Stanghellini et al[16], in a large study with 343 patients with FD, showed that female sex, relevant and severe postprandial fullness, and severe vomiting were independently associated with delayed gastric emptying of solids. Other European studies have generally confirmed...
these findings but studies from the US have not recently, accelerated gastric emptying in FD has also been associated with postprandial fullness, bloating, nausea, and pain, presumably through an early dumping syndrome. These findings imply that administration of a prokinetic agent to accelerate gastric emptying may actually lead to worsening, rather than to improvement of symptoms, in at least a proportion of patients with FD.

**Impaired gastric accommodation**

Gastric accommodation is a vagally mediated reflex that occurs post-prandially, results in reduction of tone, and provides a reservoir for the meal; it enables the stomach to handle increases in intragastric volume without proportional increases of intragastric pressures. Studies by the barostat, scintigraphy, ultrasonography, single photon emission computed tomography (SPECT), and non-imaging assessments (satiation drinking test) have all suggested abnormal accommodation in up to 40% of patients with functional dyspepsia. The mechanism of impaired gastric accommodation is, however, not clearly understood. Tack et al. proposed that impaired proximal stomach accommodation of an ingested meal was associated with early satiety and weight loss in FD, but other studies have not confirmed these symptom associations.

Relaxation of the proximal stomach can be activated by duodenal distension or nutrient infusion, or via a vagovagal reflex pathway, and it requires activation of intrinsic nitrergic neurons in the stomach. Recent reports have suggested that a defect at the level of the gastric intrinsic nitrergic neurons may be relevant. Abnormal vagal reflexes may also play a role, because postvagotomy patients have a similar impairment of gastric accommodation, and abnormal vagal function is observed in patients with FD.

**Abnormal phasic contractility of the proximal stomach**

Phasic fundic contractions induce transient increases in gastric wall tension and can be perceived in FD. In the recent study using a gastric barostat, unsuppressed postprandial phasic activity in the proximal stomach was present in a small subgroup of patients with FD. This was associated with symptoms of severe postprandial bloating. However, the mechanisms underlying unsuppressed phasic contractility are unclear and further studies will be required.

**Abnormalities of gastric myoelectrical rhythm**

Electrogastrography obtains a cutaneous recording of gastric myoelectrical activity from abdominal surface electrodes. Some studies have reported gastric myoelectrical abnormalities are found in up to two-thirds of patients with FD. A close relationship between the presence of delayed gastric emptying and abnormalities of gastric electrical rhythm has been reported. However, their relevance to symptom generation is still uncertain.

**Antral hypomotility**

Manometric studies have demonstrated antral hypomotility in a large proportion of those with FD. Antral hypomotility could be associated with gastric stasis manifested by a slower emptying rate of meals, but its correlation with specific symptoms is poor.

**DISTURBANCES IN VISCERAL SENSITIVITY**

The gut wall contains three kinds of neural receptors: chemoreceptors in the mucosa, which respond to chemical stimuli; mechanoreceptors in the smooth muscle layer, which respond to stretch or compression; and nociceptors, the most numerous receptors in all layers, which are commonly silent, but can be recruited by any stimulus strong enough to induce pain.

**Visceral hypersensitivity to mechanical distension**

Increased perception to visceral physiological or minor noxious stimuli, i.e., a lower threshold for sensation, has been considered one of major pathophysiologic mechanisms in the functional gastrointestinal disorders. The level of abnormality where visceral hypersensitivity is located is not clear, but several observations suggest that alterations exist at the level of the central nervous system or in addition to hyperexcitability of visceral afferents.

Several studies have found dysspeptic patients have lower thresholds for first perception and discomfort or pain during isotonic gastric distension or jejunal distension. Mertz et al. reported that hypersensitivity to gastric balloon distension was specific for FD, and Holtmann et al. have shown a failure of sensory thresholds to increase in patients with FD. While Tack et al. have shown hypersensitivity to gastric distention was associated with a higher prevalence of post-prandial pain, belching and weight loss. The symptom correlations remain to be confirmed.

Abnormal central nervous system processing ofafferent information during gastric stimuli has been suggested to be one of the mechanisms of visceral hypersensitivity. Ladabaum et al. performed PET scanning during distal gastric distension in healthy volunteers, and found increases in activation of somatic and visceral pain processing areas that were proportional to the distension-evoking stimuli. Vandenberghe et al. also performed PET scanning after proximal gastric distention in healthy volunteers, and found a neuronal network processing distention stimuli from the proximal stomach. Further study is needed to assess whether abnormalities in central processing of visceral stimuli occur in FD.

**Visceral hypersensitivity to chemical stimuli**

Several studies have been conducted to evaluate chemical sensitivity in FD, but its mechanism is not clear. In both healthy subjects and in patients with FD, perception of gastric distension was enhanced by nutrient lipids but not by glucose. Feinle et al. studied the effects of lipid on gastrointestinal sensation in healthy and dyspeptic subjects and suggested that cholecystokinin A (CCK-A) and serotonin (5-HT3) receptors mediate, at least in part, gastrointestinal sensation. They reported that intravenous administration of a CCK-A receptor antagonist reduced the effects of duodenal lipid on gastric...
relaxation and gastrointestinal sensations during gastric distension. Although they studied only small numbers of patients, these findings support changes in chemical sensitivity in FD; this needs to be validated in larger studies.

In a subset of FD patients, but not in healthy controls, intraduodenal infusion of hydrochloric acid (HCl) was found to induce nausea [6], suggesting duodenal hypersensitivity to acid. Some patients had impaired clearance of acid from the duodenum and impaired duodenal motor response to acid. Recently, Tack et al. [9] observed that duodenal acidification increased proximal gastric mechanosensitivity, induced proximal gastric relaxation, and inhibited proximal gastric accommodation to a meal. However, the underlying mechanisms remain to be elucidated in future studies.

INFECTIONOUS AGENTS

Acute and chronic infections may be involved in the pathogenesis of the functional bowel disorders [31,60-62].

Helicobacter pylori infection

Many studies and several meta-analysis have tried to establish a relationship between Helicobacter pylori (H pylori) infection and FD [60-64]. The most recently published meta-analysis [64] suggests that H pylori eradication at 12 months has a small but statistically significant benefit in the treatment of FD (relative risk of remaining symptomatic with H pylori eradication therapy = 0.91; 95% CI = 0.87-0.99). While statistically significant, the clinical significance of this finding is less clear because the effect is small, that is, 15 H pylori-positive dyspeptic patients will need to be treated to achieve just one cure.

The association between H pylori infection and pathophysiologic mechanisms has been investigated; however, no consistent differences in the prevalence and severity of individual symptoms, gastric emptying rate, or gastric relaxation after a meal were found between H pylori-positive and H pylori-negative subjects [61,63].

Post-infectious dyspepsia

It has now been well established that irritable bowel syndrome may follow an acute intestinal infection. Post-infectious dyspepsia has been recognized as a possible clinical entity by Tack et al. [31]. In a large retrospective, tertiary referral center study, they showed that a subset of dyspeptic patients has a history suggestive of post-infectious dyspepsia. Compared with patients with unspecified-onset dyspepsia, patients with presumed post-infectious dyspepsia have more prevalent symptoms of early satiety, weight loss, nausea, and vomiting and had a significantly higher prevalence of impaired accommodation of the proximal stomach, whereas both groups did not differ in the prevalence of delayed gastric emptying, or hypersensitivity to gastric distention [31]. They suggested that impaired accommodation in patients with presumed post-infectious dyspepsia is attributable to a dysfunction at the level of gastric nitricergic neurons. In this study, the lack of prospective design limited the validity of the results.

In a prospective cohort study, Mearin et al. [66] found that development of dyspepsia was increased 5-fold at 1 year after acute Salmonella gastroenteritis as compared with control subjects without baseline infection. There were some limitations because of the low response rate in the 1-year follow-up survey and lack of information on psychological status and stressful events [60]. Further studies are needed to identify the underlying pathophysiology and risk factors, and define the long-term prognosis.

PSYCHOSOCIAL ABNORMALITIES

In FD patients, a number of psychological and personality factors have been observed, including somatization, depression, and anxiety as well as health seeking behavior and alterations in illness behavior and coping styles [65-69]. These psychosocial factors are influenced by and influence GI symptoms; this bidirectional flow is mediated through the brain-gut axis [49]. The value of psychological therapies in FD, to date, is promising, but further studies of psychological treatment of FD are needed [70].

CONCLUSIONS

FD is a highly heterogeneous disorder. Traditional pathophysiological paradigms are still inadequate to explain the variation in the symptoms observed. Current symptom subclassifications have also largely failed to identify responders to specific therapies. A new classification based on mechanisms and specific symptoms needs to be considered to further advance the field. The contributors to this heterogeneity need to be better defined, and be environmental, pathological, psychological, or genetic. This could lead to better targeting of treatment in FD patients with unexplained epigastric pain or discomfort.

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