—Review—

Pathophysiology of Functional Dyspepsia

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Abstract

Functional dyspepsia is a highly prevalent and heterogeneous disorder. Functional dyspepsia involves many pathogenic factors, such as gastric motility disorders, visceral hypersensitivity, psychological factors, *Helicobacter pylori* infection, and excessive gastric acid secretion. The present article provides an overview of pathogenetic factors and pathophysiologic mechanisms.
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Key words: functional dyspepsia, gastric emptying, ghrelin, post-infectious functional dyspepsia

Introduction

Functional dyspepsia (FD) is divided into two subgroups according to the Rome III criteria: epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS)[1]. Most patients with FD complain of symptoms related to the intake of meals; however, the pathophysiology of FD remains poorly understood[2–4]. A number of potentially important abnormalities have been reported in FD patients, including impaired fundic accommodation[5], gastric hypersensitivity to distention[6], abnormal duodenojejunal motility[7], duodenal motor and sensory dysfunction[8], duodenal hypersensitivity[9] and *Helicobacter pylori* infection[10]. Although the Rome III criteria exclude gastroesophageal reflux symptoms from the symptoms of FD patients, some degree of overlap between the symptoms of non-erosive reflux disease (NERD) and FD is inevitable. In addition, the symptoms of both FD and NERD can include impaired gastric motility. Most patients with FD and NERD complain of several symptoms related to meals, however the pathophysiology of these diseases remains poorly defined[2,3]. Forty to sixty percent of patients with FD also have *H. pylori* gastritis[11,12], but whether *H. pylori* is the cause of the symptoms associated with FD is unclear[13,14]. Impaired gastric motility is strongly associated with gastric emptying and gastric accommodation and has been implicated in the pathophysiology of functional dyspepsia, a common gastrointestinal disorder[15]. Delayed gastric emptying is reportedly present in 25% to 50% of patients with FD[16].

FD and Gastric Emptying

The standard method for measuring gastric

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emptying is the radioactive isotope method[17]. The ^{13}C-acetate breath test is a reliable and non-invasive tool for analyzing gastric emptying rates without radiation exposure and is comparable to scintigraphy[18]. Most studies following the Rome II criteria have failed to find a good correlation between clinical symptoms and gastric emptying[19]. However, Sarnelli et al. have reported that female sex, postprandial fullness and vomiting are strong independent predictors of slow gastric emptying[20]. Three large-scale single-center studies from Europe have shown that patients with delayed gastric emptying for solids are more likely to report postprandial fullness, nausea and vomiting[21,22], although two other large multi-center studies in the United States found no association or found only a weak association[23,24]. Because the most important characteristic symptom in patients with PDS patients is postprandial fullness, a clearer understanding of the mechanics of gastric emptying would help elucidate the etiology of PDS.

Patients with NERD and FD

Several mechanisms have been proposed for the pathogenesis of NERD patients, including visceral hypersensitivity, prolonged contraction of the esophagus and psychological factors[25–27]. Previous studies have correlated FD and NERD symptoms with psychological distress[28,29]. In our study, scores of the Self-Rating Questionnaire for Depression (SRQ-D) reflecting distress and a state of depression were significantly higher in patients with FD and NERD than in healthy volunteers[30]. Quigley et al. have reported that the precise prevalence of delayed gastric emptying remains to be defined in gastroesophageal reflux disease[31]. Our data show that 33% of patients with NERD exhibit delayed gastric emptying. Therefore, administration of mosapride citrate in addition to omeprazole decreased gastro-esophageal reflux and improved gastric emptying in patients with proton pump inhibitor-resistant NERD and delayed gastric emptying[32]. Uemura et al. have reported that the CYP2C19 genotype has no significant effect on the rate of complete resolution of heartburn in patients with NERD[33].

Ghrelin and FD Patients

Ghrelin is a 28-amino acid peptide produced in the stomach. It is an endogenous ligand for the growth hormone secretagogue receptor (GHSR) in the oxyntic gland of the stomach[34]. In rodents, central or peripheral administration of ghrelin stimulates gastric contraction and emptying[15] and shows prokinetic effects in a postoperative ileus model in rats[35]. In human studies, ghrelin infusion also increases food intake and the sensation of hunger compared with saline infusion alone. These widespread physiological functions have encouraged research to assess the efficacy of exogenous ghrelin administration as a novel therapy for various disorders such as growth hormone (GH) deficiency, cachexia, anorexia nervosa, gastroparesis, functional dyspepsia and cancer anorexia. Administration of physiological doses of exogenous ghrelin to humans dose not significantly alter gastric motility[36,37]. However intravenous administration of high doses (40 μg) of ghrelin in healthy volunteers induces a premature gastric phase III of the migrating motor complex and increases proximal stomach tone[38]. Thus, several studies have shown that infusion of ghrelin as opposed to placebo accelerates gastric emptying and decreases meal-related symptoms in patients with gastroparesis[39–41]. In addition, repeated intravenous infusions of ghrelin (3 μg/kg) twice a day to five patients with functional dyspepsia for 2 weeks increased daily food intake by approximately 30% compared with levels before and after ghrelin treatment[42]. We also believe that impaired gastric emptying is reflected by low levels of acylated ghrelin in patients with PDS[30]. Suzuki et al. have reported that plasma ghrelin levels correlate well with the serum pepsinogen I/II (PGI/II) ratio[43] and decrease as gastric mucosal atrophy worsens. Therefore, we have to consider that the degree of advance of gastric atrophy is negatively correlated with serum levels of ghrelin. Acylated ghrelin has been shown to accelerate gastric emptying, increase gastric tone, and induce premature interdigestive migrating motor complex activity[44,45]. In contrast,

desacylated-ghrelin has been reported to inhibit gastric emptying without altering small intestinal transit[46,47]. We have previously reported that there was a significant relationship between low levels of acylated ghrelin linked to appetite and Tmax value[30]. However, we have found that the score for feeling of hunger is not significantly (p=0.473) associated with acylated-ghrelin levels[48]. Takeda et al. have reported that the cisplatin-induced decreases in the plasma acylated-ghrelin level and food intake are mediated by 5-HT2B/2C receptors and suppressed by flavonoids in Rikkunshito[49].

H. pylori Infection and FD

Several studies and meta-analysis have tried to establish a relationship between *H. pylori* infection and FD. The relationship between *H. pylori* infection and FD patients is still controversial. McColl et al. have reported that *H. pylori* eradication therapy is effective for resolving symptoms in patients with FD[14]. On the other hand, Blum et al. have reported that in patients with FD, the eradication of *H. pylori* is not likely to relieve symptoms[50]. A recently published meta-analysis suggests that *H. pylori* eradication at 12 months has a small but statistically significant beneficial effect on symptoms in FD[51]. The main reason for *H. pylori* eradication in patients with FD may be related more to other potential beneficial effects than to symptomatic improvement[52].

Post-infectious FD

Post-infectious FD has first been proposed as a possible clinical entity based on a large retrospective, tertiary referral center study, which showed that a subset of dyspeptic patients has a history suggestive of post-infectious dyspepsia[53]. Indeed, in a population with an outbreak of salmonella gastroenteritis, the prevalence of FD was significantly increased up to 1 year after the acute event[54]. Tack et al. have reported that 25% of the patients with FD report an acute onset and that 17% of FD patients report an acute onset accompanied by signs suggestive of an acute gastrointestinal infection. These findings suggest that FD, similar to other functional bowel disorders, such as irritable bowel syndrome (IBS) and gastroparesis, may occur following an acute intestinal infection[28]. Spiller et al. have reported that numbers of mucosal T cells are increased in patients with post-infectious IBS[55]. In contrast, in our study, duodenal Vδ1 T cells and CD3-positive T cell counts did not differ among patients with post-infectious FD, EPS, or PDS and healthy volunteers[56]. In addition, Spiller et al. have also reported that numbers of enteroendocrine cells are increased in post-infectious IBS patients[55]. 5-HT is thought to be linked to the regulation of secretion, motility and sensory events. However, in the present study, there was no significant difference in numbers of serotonin producing cells of the duodenum amongst the study groups (EPS, PDS, post-infectious FD and healthy volunteers). Considering our results, we speculate that the duodenitis of post-infectious FD patients may depend on the accumulation of macrophages and eosinophils and an accompanying partial loss of villi[56]. Talley et al. and Toukan et al. have reported that there is a significant association of the number of migrated eosinophils in the duodenum in subjects with non-ulcer dyspepsia[57,58]. We have reported that numbers of eosinophils and of CCR2-positive macrophages in post-infectious FD are significantly higher than those in healthy volunteers. CCR2 expression level is regulated by monocyte chemoattractant protein-1 (MCP-1)-stimulated prostaglandin E2 production[59,60]. Kindt et al. have also reported that macrophage accumulation in the duodenum is increased in post-infectious FD patients[61]. In turn, these mediators which migrate inflammatory cells such as macrophages and eosinophils may cause sensory-motor dysfunction and produce such clinical symptoms as epigastric burning.

Duodenal Sensitivity to Lipids or Acid

In both healthy subjects and in patients with FD, duodenal perfusion with nutrient lipids, but not with glucose, enhances the perception of gastric distention[62]. These effects of duodenal lipid infusion

require lipid digestion and the subsequent release of a cholecystokinin A receptor antagonist[63]. Based on these observations, it has been proposed that increased sensitivity to duodenal lipids infusion may be a relevant pathophysiologic mechanism in FD[64].

Conclusions

The pathophysiology of FD involves many factors such as gastric motility, hypersensitivity, psychological factors and genetics. These factors interactively contribute to the manifestation of FD symptoms. Understanding of the underlying pathogenetic mechanisms might lead to better targeting of treatment in these patients with FD.

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