GASTROENTEROLOGY

Current understanding of pathogenesis of functional dyspepsia

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Key words chronic gastritis, dysmotility, dyspepsia, gastric acid, placebo, Rome classification, visceral hypersensitivity.

Accepted for publication 28 January 2011.

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Abstract

Functional dyspepsia (FD) is a disorder in which upper abdominal symptoms occur in the absence of organic disease that explains them. Many pathogenic factors have been proposed for FD, including motility abnormalities, visceral hypersensitivity, psychosocial factors, excessive gastric acid secretion, Helicobacter pylori, genetics, environment, diet, lifestyle, and post-infectious FD. Many of those pathogenic factors are also common to irritable bowel syndrome and other functional gastrointestinal disorders, so understanding FD offers a glimpse into the nature of functional gastrointestinal disorders in general. Motility abnormalities and visceral hypersensitivity are thought to be important in the manifestation of FD symptoms, but the other factors are also thought to contribute by interacting and modifying motility and visceral hypersensitivity.

Functional dyspepsia: definition and current status

Dyspepsia refers to symptoms centered in the upper abdominal region, such as stomachache, heartburn, feeling bad after eating, and heavy feeling in the stomach. Many patients complain of dyspepsia despite the absence of an obvious organic cause such as ulcer, esophagitis, or cancer. Dyspepsia in a patient with no organic disease that explains the symptoms is known as functional dyspepsia (FD). FD is one of a number of functional gastrointestinal disorders.

The scientific investigation of the pathophysiology of FD began not so long ago, and research on FD from many different angles remains active. The first definition of FD was developed in 1998 by a working party of the American Gastroenterological Association and a committee of the International Congress of Gastroenterology in Rome. Subsequently, the Rome II classification system was developed in 1999, followed by the Rome III system in 2006. According to the Rome III system, which is currently in use, FD is defined as the presence of at least one of the following symptoms in the absence of organic disease that is likely to explain the symptoms, with the symptoms being present for the three months preceding diagnosis and having their onset at least six months before diagnosis: bothersome postprandial fullness, early satiation, epigastric pain, and epigastric burning. The Rome III system further subdivides FD into postprandial distress syndrome (PDS), which is the presence of bothersome postprandial fullness and/or early satiation, and epigastric pain syndrome (EPS), which is the presence of epigastric pain and/or epigastric burning.

Dyspepsia is one of the most common disorders in medicine, with dyspeptic patients seen on a daily basis not only by gastroenterologists, but also by physicians in a variety of other fields. According to the Domestic/International Gastroenterology Surveillance Study (DIGEST) published in 1999, 9% of Japanese adults experienced moderate or more severe dyspeptic symptoms at least once per week, and 34% of those persons were seen by a healthcare provider. In recent years, as health awareness has increased, medical checkups and comprehensive medical examinations (so-called “ningen [human] dock”) have become more common, and the prevalence of Helicobacter pylori infection has decreased, the proportion of dyspepsia patients with organic disease that explains their symptoms seems to be decreasing. Indeed, in a study of consecutive outpatients who visited a university hospital, about 40% of those with abdominal symptoms as their chief complaint were diagnosed with functional gastrointestinal disorders. Unfortunately, despite the large number of FD patients, there are almost no treatments for FD that have shown superiority to placebo in rigorous clinical studies. We hope that study of the pathophysiology of FD will lead to the development of effective evidence-based treatments for FD patients.

Factors related to the pathophysiology of FD

Why do FD patients experience symptoms despite the apparent absence of organic disease? Symptoms are normally perceived mainly in the brain, and one would expect dyspeptic symptoms to result from the perception of stimuli from the stomach and...
Motility abnormalities

The possibility of a relationship between motility abnormalities and dyspeptic symptoms has been investigated for a comparatively long period of time, but the results have not been particularly clear. Recently, however, it has been learned that postprandial gastric motility has two phases—a phase when an accommodation reflex occurs in the proximal stomach (fundus) after food consumption, and a subsequent phase when distal gastric distension occurs after a delay—and it is becoming clear that the proximal gastric distension that occurs in the first phase correlates fairly well with dyspeptic symptoms. By using a barostat connected to a polyethylene-vinyl balloon, the gastric accommodation reflex was found to occur in the gastric fundus when a nutrient was consumed. This reflex, which is also known as the “reservoir function of the stomach,” is thought to serve the biological purpose of food storage. However, 40% to 50% of FD patients show impaired gastric accommodation, and this impairment is thought to cause early satiation. Thinking that it might be possible to evaluate gastric accommodation with gastric scintigraphy, a method normally used to evaluate of gastric emptying, our group prepared the scintigrams in shown in Figure 1. These scintigrams show gastric food distribution in a healthy subject and an FD patient after the subjects had consumed solid food. Even though the subjects were in the upright position, most of the food was retained in the fundus of the healthy subject, indicating that the accommodation reflex occurred. In the FD patient, most of the food was transferred to the distal stomach soon after ingestion, suggesting that the accommodation reflex may have been impaired.

Delayed gastric emptying, experienced by the patient as a heavy feeling in the stomach, has been known to be a feature of FD for some time. Gastric scintigraphy with radioisotopes is the standard method used for direct evaluation of gastric emptying. Although presently there does not seem to be a strong direct relationship between gastric emptying and dyspeptic symptoms, the relationship between gastric emptying time and dyspeptic symptoms had previously attracted substantial interest. About 40% of FD patients show delayed gastric emptying after ingestion of solid food.

Visceral hypersensitivity

Visceral hypersensitivity has been shown to be involved functional disorders throughout the gastrointestinal system, including nonerosive gastroesophageal reflux disease (NERD) in the esophagus, irritable bowel syndrome (IBS), and FD. The above-mentioned balloon technique is commonly used to determine the distension volume at which pain is experienced in the stomach, and that volume was found to be significantly lower in FD patients than in healthy subjects. Indeed, 35% to 50% of FD patients are said to be hypersensitive to gastric distension stimuli. The result of the balloon distension experiment shown in Figure 2 demonstrates the gastric hypersensitivity of FD patients.

This result suggests that FD patients may experience as symptoms an increase in stomach contents of a size that normally would not be perceived. Such gastric hypersensitivity is said to be related to symptoms including postprandial pain, belching, and weight loss. In addition to hypersensitivity to gastric distension, FD patient also seems to have hypersensitivity in the stomach and duodenum to acid, bile acid, and some nutrients.

Progress is also being made in basic research on the mechanism of visceral hypersensitivity. Studies conducted so far have shown that central sensitization at the junctions of primary sensory neurons (nerve fibers from the gastrointestinal organs to the dorsal spinal roots) and secondary neurons (nerve fibers from the dorsal spinal roots to the brainstem) play an important role in hypersensitivity. In addition, the role of NMDA (N-methyl-D-aspartate)
Excessive secretion of gastric acid

Gastric acid is also attracting attention as a causative factor in FD. Proton pump inhibitors (PPIs), which inhibit secretion of gastric acid, have been reported to be extremely effective in uninvestigated dyspepsia (i.e. dyspepsia that has not been investigated endoscopically), and it was hoped that they would also prove to be effective in FD. Recently, it has been shown that perfusion of acid solution (pH 1) into the stomach or duodenum induces a variety of dyspeptic symptoms, which strongly suggests that such symptoms are related to acid. Figure 3 shows the results of a double-blind study in which acid and water were perfused into the stomachs of healthy adult volunteers, and their symptoms were investigated. The results show that intragastric perfusion of acid induced dyspeptic symptoms even in healthy adults, and that those adults manifested a variety of dyspeptic symptoms.

Nevertheless, based on the clinical trial data obtained so far, the therapeutic efficacy of PPIs in FD patients has not been especially impressive. Although PPIs showed efficacy in FD patients in studies conducted in Europe and the United States, they did not in a study conducted in Asia. PPIs are widely known to be useful as the initial treatment of patients with uninvestigated dyspepsia, but many of those patients probably have gastroesophageal reflux disease (GERD), so the efficacy of PPIs in FD should be considered separately.

Helicobacter pylori

_H. pylori_ infection is thought to be a cause of FD symptoms. Although the relationship between _H. pylori_ infection and FD has been studied vigorously, consistent results on the response of FD symptoms to _H. pylori_ eradication therapy have not been obtained. Discussion of improvement in symptoms must be based on randomized, double-blind clinical studies, but despite the fact that many rigorous, high-quality clinical studies have been conducted, the question as to whether treating _H. pylori_ infection improves FD symptoms remains highly controversial. In our randomized, double-blind study conducted to investigate this question in Japanese FD patients, no significant difference in symptoms between the treatment group and the placebo group was observed. However, a study conducted in Chinese patients found that eradication of _H. pylori_ improved FD symptoms. A meta-analysis showed that _H. pylori_ eradication therapy significantly improved the symptoms of FD patients, but the effect was not large; in order to eliminate the symptoms in one patient, it was necessary to administer the therapy to 15 patients. Given this result, it is difficult to believe that _H. pylori_ infection is an important factor in the pathophysiology of FD. Clinical practice guidelines from Asia on _H. pylori_ infection do maintain that _H. pylori_ infection should be eradicated, however, since they also recognize that the effect of such eradication on FD will be limited, the statement was probably made taking into consideration the benefit to society that results from preventing ulcers and cancer by eradicating _H. pylori_.

Genetics

It has been hypothesized that genetic factors predispose some persons to FD. The finding that manifestation of dyspeptic...
Figure 3 Induction of dyspeptic symptoms in healthy subjects by intragastric perfusion of acid. The involvement of acid in the manifestation of upper abdominal symptoms was investigated by perfusing acid into the stomachs of healthy adult volunteers, and noting the type and severity of the symptoms experienced by the subjects. Although the types of symptoms and their severity varied widely by subject, intragastric perfusion of acid induced symptoms that were significantly more severe than those induced by perfusion of water. Since significant differences between acid and water were observed for bloating, abdominal distension, nausea, and belching, which have been considered dysmotility-type symptoms, the results demonstrated experimentally that acid causes not only pain, but also dysmotility-type symptoms. Adapted from Miwa et al.31 with modifications. □, Distilled water; ■, Acid (0.1M HCl).

Figure 4 G-protein beta-3 subunit position 825 genotypes and GI symptoms. Manifestation of dyspeptic symptoms is associated with SNP genotypes at position 825 of the G-protein beta-3 subunit gene (GNB3). In the initial data, which were obtained from Germans, a higher frequency of abdominal symptoms was associated with the CC genotype (A). In Japanese, abdominal symptoms were present at higher frequency in persons with the TT genotype (B). Adapted from Holtmann et al.42 and Oshima et al.44 with modifications. □, CC; ■, CT; ■, TT.

Symptoms is associated with a single-nucleotide polymorphism (SNP) genotype at position 825 of the G-protein beta-3 subunit gene (GNB3)42 touched off much research in the field of FD. Subsequently, many studies related to genetic polymorphisms associated with predisposition to FD appeared; however, for various reasons including the fact that in most of those studies the odds ratio of the genetic mutations having an effect was only about 2 to 3,42–45 there is a need for further research on the clinical significance of genetic polymorphisms as causative factors for FD. It is interesting that the results of the studies varied by race and geographical region. The initial data on the above-mentioned GNB3 SNP, which were obtained in Germans, showed a higher frequency of abdominal symptoms in persons with the CC homozygous genotype,42 but in Japanese, abdominal symptoms were present at higher frequency in persons with the TT homozygous genotype44,45 (Fig. 4). Furthermore, a study from the United States found that the CT heterozygous genotype was involved in manifestation of abdominal symptoms.43 Thus, it is possible that genetic relationships vary by race and geographic region. It is also interesting that genetic differences may help explain regional differences in the incidence of FD.5
Pathogenesis of functional dyspepsia

Environment

It has been observed for a comparatively long time that severe stress, particularly during childhood or adolescence, contributes to development of the functional gastrointestinal disorder IBS. The frequency of sexual abuse was significantly higher in college students with IBS than in controls, and the risk of IBS was increased in persons who were exposed to wartime conditions during early life. In the neonatal maternal separation model of IBS, rats that are separated from their mothers for 2 to 3 h per day for 2 to 3 weeks during the neonatal period experience intolerable stress, and after maturing, exhibit defecation abnormalities and hypersensitivity. These results suggest that in human traumatic stress during early life may be associated with development of IBS later in life. In addition, when Persian Gulf War veterans who had experienced high stress during the war were subjected to cutaneous and visceral (rectal distension) pain stimuli, both somatic and visceral sensitivity were increased, suggesting that severe stress during adulthood can also affect visceral sensitivity. These data are not easy to interpret. Recently, there have been similar reports concerning FD. Gastric hypersensitivity was greater in FD patients with a history of physical or sexual abuse in childhood than in control FD patients, and a history of abuse after reaching adulthood was associated with changes in gastric accommodation. Although the mechanism by which traumatic stress in early life affects the development of functional gastrointestinal disorders is still unclear, such stress probably should be recognized as a pathogenic factor.

Dietary factors and lifestyle

It is highly likely that diet affects manifestation of FD symptoms, but the number of studies addressing such effects remains relatively small. Dietary factors include factors directly related to food ingestion, such as patterns of nutrient intake and potential intolerance to specific foods or macronutrients, and cognitive factors. Since FD symptoms are often triggered by ingestion of food, the relationships between FD symptoms and foods should probably receive greater attention. So far, there have been reports that ingestion of fat may worsen dyspeptic symptoms, and that abdominal fullness is correlated with ingestion of fat and amount of food ingested. Another study showed that glutamic acid promoted gastric motility after ingestion of high-protein, high-calorie food. In addition, Gonlachanvit recently proposed the interesting idea that since rice and spicy food (chili pepper) decrease dyspeptic symptoms, the consumption of large amounts of such foods in some Asian countries may explain the low prevalence of dyspeptic symptoms. It is highly likely that diet and lifestyle are related to dyspeptic symptom improvement and exacerbation (unpublished data). Lifestyle factors including poor socio-economical status, smoking, excessive caffeine consumption, poor living environment, and chronic illness are thought to cause or exacerbate dyspeptic symptoms, but it is difficult to identify the risk factors for FD among the risk factors for dyspepsia in general.

Post-infectious FD

A number of studies have focused on the risk of post-infectious FD. The risk of developing IBS was found to increase after Salmonella infection. Likewise, a cohort study found that the risk of developing FD increased in patients with acute Salmonella enteritis; this is so-called post-infectious FD. Tack et al. studied 400 dyspeptic patients by recall and found that 17% of the cases were post-infectious and that the post-infectious FD patients had certain characteristics, such as higher prevalence of early satiety. Subsequently, Mearin et al. reported that one year after an outbreak of acute Salmonella gastroenteritis, the prevalence of FD and IBS was higher in the persons who had experienced Salmonella gastroenteritis than in controls; FD occurred in one of seven post-infectious persons, which was an incidence 5.2 times higher than that in the controls. Persons who had experienced severe abdominal pain and vomiting during gastroenteritis were more likely to develop FD. Recently, a study from Japan found that infiltration of the duodenal mucosa by macrophages was significantly increased in post-infectious FD patients, and attracted attention as a step toward elucidation of the pathological mechanism of post-infectious FD.

Interaction of pathogenic factors

As discussed above, the pathophysiology of FD is thought to involve multiple factors. We think that those factors interact and cause changes in physiological function that lead to the symptoms of FD. The question is, how are the factors related? Those relationships are extremely complex, but motility disorders and visceral hypersensitivity are generally thought to be the functional abnormalities that are directly linked to symptoms. Although there are many researchers who would cite psychosocial factors as pathogenic factors equivalent in importance to motility disorders and visceral hypersensitivity, we think that rather than causing symptoms themselves, psychological factors cause symptoms by powerfully modifying physiological functions. Gastric acid provides a good example of the interaction of different pathogenic factors in FD. In healthy persons, dyspeptic symptoms usually do not occur, even though substantial amounts of gastric acid are secreted; however, if 100 mL of hydrochloric acid (pH 1) is instilled in the stomachs of healthy persons, such symptoms do occur, albeit with differences among individuals. Because the onset of the symptoms is delayed somewhat from instillation of the acid, it is inferred that the symptoms are caused by duodenal acidification as the acid enters the duodenum. Lee et al. showed that when acid was instilled directly into the duodenum though a tube, gastric accommodation occurred unrelated to ingestion of food and the threshold for perception of gastric distention was decreased. Thus, in the above-mentioned study, abnormal gastric motility and hypersensitivity were probably caused by influx into the duodenum of acid that had been instilled in the stomach. This simulated abnormality in physiological function directly caused dyspeptic symptoms. But why does gastric acid induce symptoms in FD patients but not in healthy persons? To answer this question, we instilled gastric acid in FD patients.
and healthy volunteers according to the same procedure, and
looked for differences in manifestation of symptoms. Despite
the instilled volume of gastric acid being the same, the FD
patients experienced a greater number of types of
symptoms (%P < 0.01) and greater severity of symptoms (%P < 0.01) (unpublished data, data
not shown). These results suggest that the FD patients
were hypersensitive to acid. The same effect would probably be observed
when acid is secreted to such an excess that it cannot be neutral-
ized in the duodenum. Thus, it seems that dyspeptic symptoms are
caused by effects of acid on motility and perception, with hyper-
sensitivity also playing a role. It is possible that psychological
stress, mediated by the autonomic nervous system, modifies acid
secretion, and in H. pylori infection, there is probably a period
when acid secretion is increased. Acid secretion is also affected by
diet and lifestyle, which need hardly be mentioned, and by genet-
ics. Thus, when considering acid as a pathogenic factor, one must
understand the role of acid itself, and also its interaction with a
variety of other factors.

The same is true for psychophysiological factors. The patho-
genic mechanism of such factors may be to alter the physiological
function of the stomach. Experimentally induced anxiety caused
inhibition of meal-induced gastric relaxation,28 and auditory stress
decreased the esophageal perception threshold.29 Everyone has
probably experienced early satiation and loss of appetite from
stress and anxiety in daily life. In FD patients too, anxiety and
other psychological factors probably alter the physiological func-
tioning of the stomach and duodenum, and thereby cause dyspep-
tic symptoms. It is common knowledge that psychophysiological
factors are strongly affected by genetics, and such factors also
probably affect acid secretion. Interestingly, environmental factors
such as mental or physical trauma during early life or extremely
severe mental or physical trauma have also been hypothesized to
be strongly involved in FD by their possibly causing psychological
development and altering responsiveness to stress.

Relationships among possible factors involved in FD pathogen-
esis are diagrammed in Figure 5. The factors interact in a complex
web, but we think that ultimately the symptoms of FD are directly
connected by gastric motility disorders and hypersensitivity. Nev-
evertheless, it is well understood from experience that symptoms are
often induced by psychological or physical stress. How stress is
related to the other factors is a question that should be further
explored in future research.

**Conclusion**

The pathophysiology of FD involves many factors and is complex.
The important point is that the pathogenic factors interactively
contribute to manifestation of FD symptoms. Gastric motility and
hypersensitivity have attracted attention as factors connected to
symptoms, but the factor that directly causes symptoms is prob-
ably psychological and physical stress. If research focuses solely
on the physiology of the digestive tract, the role of stress cannot be
addressed. Therefore, in addition to study of physiological abnor-
malities of the digestive tract, research on the relationship between
the digestive tract and the central nervous system must be pursued.

Elucidation of the pathophysiology of FD should lead to the
understanding of why we experience FD symptoms. We will be
very pleased if this understanding results in new treatments for FD.

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