Role of Digestive Tract Hormone in Functional Dyspepsia

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ABSTRACT

Dyspepsia is a complaint commonly found in daily practice. Functional dyspepsia is considered if the organic cause of dyspepsia is not found. The pathophysiology of functional dyspepsia has not been fully understood. However there are three main pathophysiology, which are: motility disturbance, non-motility disturbance, and psychosocial factor. Several digestive tract hormones are ghrelin, motilin, cholecystokinin (CCK), peptide YY (PYY), somatostatin, glucagon-like-peptide 1 (GLP), are thought to play role in the pathophysiology of functional dyspepsia, particularly in the regulation of digestive tract motility. Currently, a new paradigm in digestive tract disturbance treatment is developing, such as motilin receptor agonist therapy (for example mitemcinal) and ghrelin receptor agonist therapy, which is used as one of the new modalities in treatment of dyspepsia.

Keywords: *dyspepsia, functional dyspepsia, motilin, ghrelin, cholecystokinin, motilin receptor agonist, ghrelin receptor agonist*

ABSTRAK

Dispepsia adalah keluhan yang kerap ditemui dalam praktik sehari-hari. Dikatakan sebagai dispepsia fungsional jika penyebab organik tidak ditemukan. Patofisiologi dispepsia fungsional belum sepenuhnya dimengerti namun terdapat tiga patofisiologi utama yakni gangguan motilitas, gangguan non-motilitas dan faktor psikososial. Dewasa ini diketahui adanya peran hormon saluran cerna seperti hormon ghrelin, motilin, cholecystokinin (CCK), peptida YY (PYY), somatostatin, glucagon-like-peptide 1 (GLP) dalam patofisiologi dispepsia fungsional khususnya dalam pengaturan motilitas saluran cerna. Pengetahuan akan hormon-hormon ini menjadikan adanya paradigma baru dalam terapi gangguan saluran cerna yakni dengan dikembangkannya terapi agonis reseptor motilin (misalnya mitemcinal) dan ghrelin (TZP-101) sebagai salah satu modalitas baru dalam terapi dispepsia.

Kata kunci: *dispepsia, dispepsia fungsional, motilin, ghrelin, cholecystokinin, agonis reseptor motilin, agonis reseptor ghrelin*

INTRODUCTION

Dyspepsia is explained as sensation of discomfort or pain in the upper abdomen area.[1,2] This complain commonly happen in general population, with the average of 25% (ranging from 13-40%) incidence annually.[1,3] The organic cause of dyspepsia, such as duodenal ulcer, is found in only 40% of patients with dyspepsia. This means, the rest or about 60% experience functional dyspepsia.[5,6,7] Functional dyspepsia (FD) is a condition which cause and pathophysiology have not yet been fully understood.[2,3] Several digestive tract hormones, such as: ghrelin, motilin, cholecystokinin (CCK), Peptide YY (PYY), somatostatin, glucagon-like-peptide 1 (GLP) are thought to play role in

functional dyspepsia, particularly in the regulation of digestive tract motility. Therefore, knowledge on these hormones may help us in the management of functional dyspepsia.

Definition of Functional Dyspepsia

Based on Rome III consensus in year 2005, it is agreed that dyspepsia is explained as sensation of pain or discomfortness in the mid-upper abdomen, either acute or chronic.[1] If this dyspepsia complaint is not caused by organic abnormality, systemic, or metabolic disease, thus it is considered as functional dyspepsia (FD).[1-3,7,13,14] Currently there are two categories of FD, which are: dyspepsia complaints which are induced by meal or also known as postprandial distress syndrome (PDS) and epigastric pain or epigastric pain syndrome (EPS).[1,7]

PATHOPHYSIOLOGY OF FUNCTIONAL DYSPEPSIA

Several theories about pathophysiology of FD has been known, such as: gastric emptying disturbance, hypersensitivity towards gastric distention, accomodation disturbance of proximal gaster towards food, gastric acid hypersection, *H. pylori* infection, disturbance in duodenojejunal motility, duodenal hypersensitivity towards acid or particular nutrients, and disturbance of central nervous system.[1,4,11,16,17] In summary, these different pathophysiology is explained in figure 1 below.

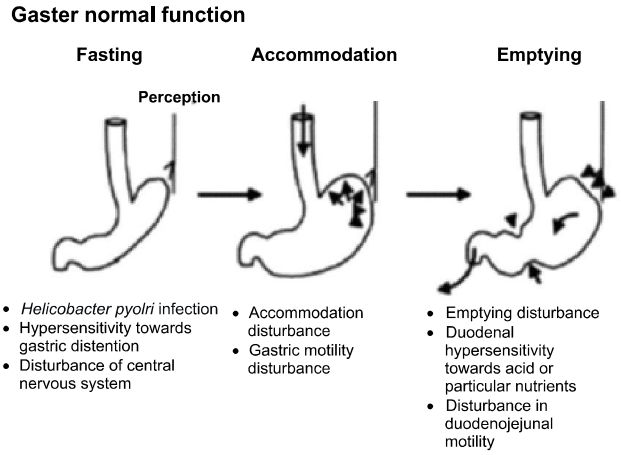

Figure 1. Pathophisiologic mechanism in functional dyspepsia

There are three main mechanism in the pathophysiology of FD, including: digestive tract motility, visceral hypersensitivity, and psychosocial factor.[5,17,18,19]

1. **Motility disturbance**
   Mostly reported motility disturbances are gastric emptying disturbance and gastric accomodation refleks disturbance.[14,17] Gaster has two different motoric function depending on the location, which are: proximal and distal part. Distal part of the gaster regulates mixing and grinding gastric contents into smaller form, so that it will be easier to distribute to duodenum, while the proximal gaster is more act as food reservoir.[14,17] This food reservoir reflex is known as accomodation reflex.[21] About 30 to 70% FD patients experience disturbance in this reflex. Consumed food is directed to the distal part of the gaster, thus causing sense of satiety.[21,22.] Presence of digestive tract motoric disturbance, such as delayed emptying will cause food distribution disturbance in the gaster. Besides, it may also cause disturbance in food accomodation process, antrum hypomotility, and gastric dysrhythmias and duodenum and jejunum motility changes.[19,22]
2. **Visceral hypersensitivity**
   Thirty five up to 50% of FD patients experience hypersensitivity towards gastric distention stimuli. FD patients will experience complaints, such as postprandial pain and burping as there is addition of gastric volume, which in normal condition not being complained of.[21,23] FD patients also has gastric and duodenal hypersensitivity towards acid, bile acid, and particular nutrients, such as fat.[12,17,19] Presence of fatty acid in the duodenum through the role of cholecystokinin (CCK) hormone will stimulate relaxation in the proximal part of gaster and increase sensitivity to gastric distention. This will finally cause complaint of nausea.[12,14,20]
3. **Psychosocial factor**
   Brain gut-axis (BGA) regulates communication between brain and digestive tract system (intestine). This BGA comprises of three parts, which are: enteric nervous system (ENS), autonomic nervous

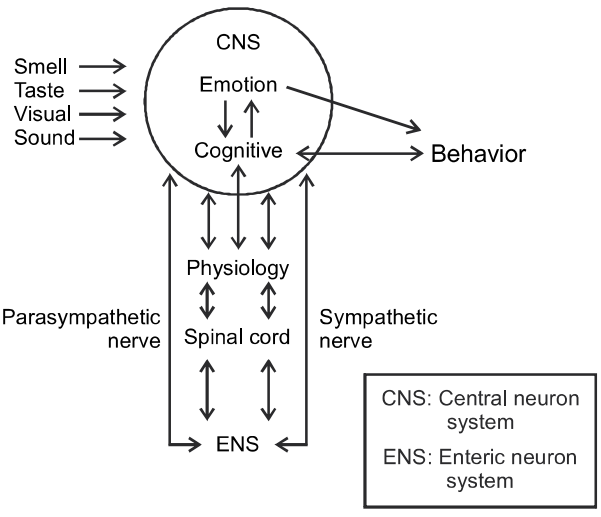

Figure 2. Brain-gut-axis[24]

system (ANS), and central nervous system (CNS). ANS distribute information which is received from the intestine to the intestine through vagus and spinal afferent pathway. Further, after being processed in brain level, information is sent back to the digestive tract through ANS, particularly parasympatic and sympathic efferent (Figure 2).[24]

HORMONES WHICH INFLUENCE UPPER DIGESTIVE TRACT FUNCTION

Several hormones produced by the intestine, especially as response to food, influence digestive tract sensoric and motoric function, both in fasting and postprandial condition.[11] Motilin, somatostatin, and ghrelin play role in digestive tract motoric activity in fasting condition, while cholecystokinin (CCK), gastrin, leptin, Peptide YY (PYY), glucagon-like-peptida 1 (GLP-1), GLP-2, neurotensin, pancreas polypeptide and others influence postprandial activity. GLP-1, PYY, and ghrelin, also play role in the regulation of gastric motoric function (see Figure 3).[8,10,18,19,21-23]

Gastrin

Gastrin in large amountis produced by specific endocrine cell (G cell) in gastric antrum as response to the presence of food in small amount which can be found in proximal gaster, duodenum, jejunum, ileum, and pancreas.[8,22,26] These hormones play role in the gastric acid secretion.[10,11,13,26] Besides, gastrin also has effect in stimulating cell growth in gastric mucosa and few cancers.[26] In FD patients, it is known that there is higher level of gastrin compared to healthy individuals.[8-10] This increase of gastrin level is especially found in postprandial compared tofasting condition.[9]

Elevation of gastrin level in FD is assumed as impact of autonomic nervous system disturbance and role of *H. pylori* infection.[8,9,22,27] Gastrin may also not increased significantly in FD patients compared to healthy individuals.[27] This is caused by CCK inhibition effect towards production of gastrin due to *H. pylori* infection. Currently, *H. pylori* eradication is recommended as a therapy modality of FD.[13,22]

Ghrelin

Ghrelin, a hormone which is relatively new to be discovered, is produced by oxyntic cell in the gaster. This hormone is produced during fasting, together with motilin, somatostatin dan xenin. The function of this hormone is to increase gastric emptying rate and also may increase appetite.[8,11,26] Its role in FD pathophysiology is still not widely known considering that in FD patients, this hormone level during fasting might be low, normal, or even increased.[8]

Secretin

The role of this hormone towards FD pathophysiology is not much known. This hormone may cause gastric dysrhythmias, particularly hinderance in gastric emptying process.[8] Secretin is produced by special enteroendocrine cell in the small intestine (called as S-cell) and has main function in stimulating pancreatic fluid and bicarbonate, particularly to neutralize gastric acid as it enters duodenum (negative feedback).[26]

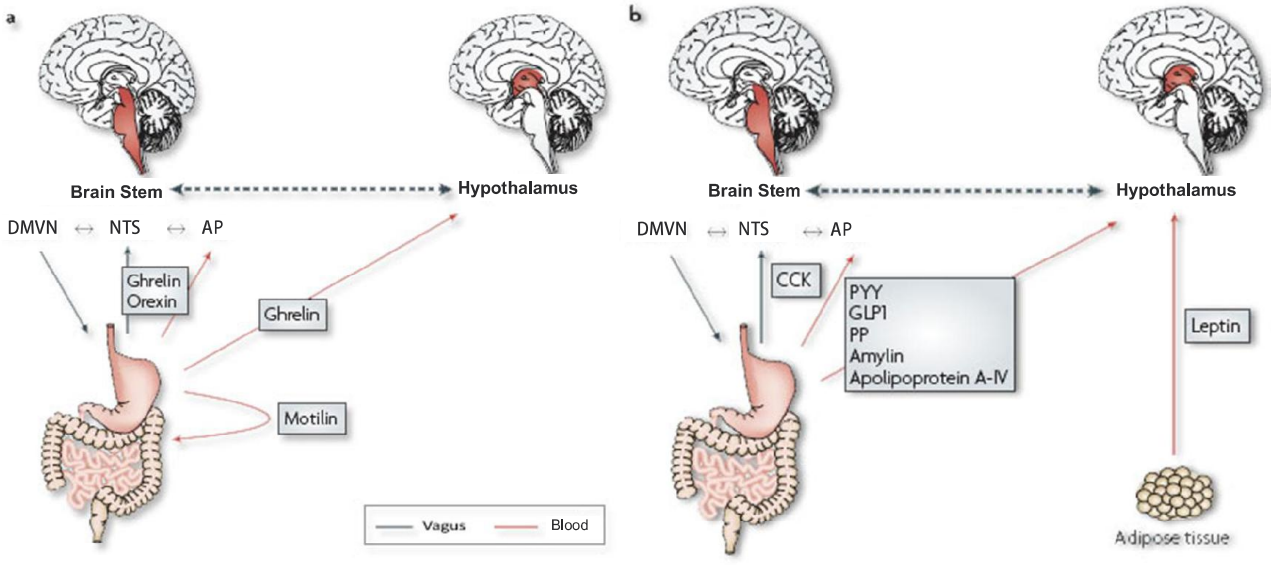

Figure 3. (a) Hormone during fasting and (b) postprandial

Cholecystokinin

CCK hormone, previously called as pancreozimin, is produced by I-cell in small intestine epithelial mucosa and is secreted through duodenum as response to the presence of food, especially to the presence of fat and protein. This hormone regulates postprandial activity.[8,11,26] CCK is a rapid onset hormone and peak level is reached in 15-30 minutes after meal and the level return to the basal level after 3 to 5 hours.[26,27] Similar to gastrin, CCK hormone is also controlled by vagus nerve.[10] CCK in the circulation will bind specifically to CCK1 receptor. Role of CCK includes regulation of gastric acid secretion, bile duct contraction, decrease gastric emptying rate, and also stimulate sense of satiety.[8,26]

Somatostatin

This hormone is produced by specific enteroendocrine cells, which are D-cell in the gaster. The function of this hormone is to inhibit gastric acid secretion, inhibit digestive tract motility, and decrease splanchnic blood flow.[26] Somatostatin is thought to play role in the regulation of digestive tract motoric activity in fasting condition.[22] Several writers associate the severity degree of dyspepsia complaints with the elevation level of gastrin, CCK, and somatostatin.[22] In FD patients, it is obtained that the somatostatin level is higher compared to healthy individuals, though the exact cause of this elevation is not known.[22]

Motilin

Motilin is produced by endocrine cells from duodenal epithelial and is released to the blood periodically and repeatedly, in accordance with migrating motor complex (MMC) activity. Release of this hormone is not influenced by food.[8,26] Together with ghrelin, this hormone regulates digestive tract motoric activity during fasting by increasing the gastric emptying rate, small and large intestine motility. Motilin binds specifically with receptors in smooth muscle cells in the esophagus, gaster, small and large intestine.[26] Although the fasting level of motilin in FD patients is the same with healthy individuals, when motilin is given exogen intravenously, inhibition of accomodation reflex in gastric proximal is larger compared to healthy individuals.[8]

ROLE OF DIGESTIVE TRACT HORMONE IN FUNCTIONAL DYSPEPSIA

From various digestive tract hormones which play role in FD pathophysiology, it seems that only motilin and ghrelin are further developed as new therapy modality in FD through hormonal approach (see Table 1).

Erithromycin, a macrolide class antibiotic, has been long known may increase gastric emptying rate in diabetic patients because it has strong gastrokinetic effect. This is actually caused by erythromycin works in motilin receptor.[3] We have known that motilin is a hormone which increase gastric emptying rate, small and large intestine motility. Other drugs, such as mitemcinal has been reported to increase gastric emptying rate and decrease symptoms of nausea, stomach fullness, and stomachache in FD patients. This could be understood considering that mimtecinal is motilin agonist receptor. However, overstimulation to motilin receptor may induce vomiting.[11] Currently, it is developed a research which give ghrelin receptor agonist TZP-01, in diabetic patients with gastroparesis. The result was reduced dyspepsia symptoms.[8]

Table 1. Motilin and ghrelin receptors agonist as therapy in gastrointestinal disturbance[11]

Hormonal approach	Component	Remarks
Motilin receptor agonist	Mitemcinal (GM-611)	Phase II Was reported may improve symproms in diabetic patients with gastroparesis compared to placebo, given orally
	PF – 045480434 (KOS-2187)	Preclinical Proven effective as a gastric prokinetic agent in study with dogs
	ABT-229	Cancelled Failed to overcome symptoms in type I DM patients with functional dyspepsia
Ghrelin receptor agonist	TZP-101	Phase II A pilot study revealed improvement of gastroparesis symptoms after intravenous administration

DM: diabetes mellitus

CONCLUSION

Digestive tract hormones are known to play role in FD pathophysiology, thus it is not surprising if currently it has been developed new modalities using hormonal approach as therapy in gastrointestinal disturbance.

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