

Review**New Aspects of Gastric Adaptive Relaxation, Reflex after Food Intake for More Food: Involvement of Capsaicin-sensitive Sensory Nerves and Nitric Oxide**

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Abstract

To accommodate the intake of food or liquid, gastric reservoir functions are important as the physiological reflex. There exist two major responses as a reservoir function of the stomach; adaptive and receptive relaxations. Adaptive relaxation is a reflex in which the fundus of the stomach dilates in response to small increases in intragastric pressure when food enters the stomach. Receptive relaxation is a reflex in which the gastric fundus dilates when food passes down the pharynx and the esophagus. The mechanisms of these two types of functional responses are to some extent different, although a nitric oxide (NO)-dependent non-adrenergic, non-cholinergic neural pathway is involved in the both relaxation reflexes. Adaptive relaxation is an intragastric pressure-induced reflex. Stretch of the gastric wall activates the mechanoreceptors in gastric mucosa (Mu), which generate impulses carried by the capsaicin-sensitive afferent sensory neuron. The sensory neuron can synapse on the inhibitory efferent neuron directly or activate it via interneurons of the myenteric plexus. This leads to the release of NO from the nitroergic efferent neuron, which causes relaxation of circular muscle and hence of the fundus. Alternatively, an axon reflex causes the NO release from the sensory neuron, resulting in hexamethonium-resistant gastric relaxation. Receptive relaxation is mediated by vagal motor fibers. In contrast with the pressure-induced adaptive relaxation, ganglionic nicotinic transmission is essential in the vagally-induced relaxation. VIP and CGRP are important neurotransmitters of the inhibitory sensory neuron, which, however, may not mediate both adaptive and receptive relaxations. Disorders of these reservoir functions result in symptoms of early satiety and anorexia, which are the major symptoms of patients with functional dyspepsia.

Key words: adaptive relaxation, receptive relaxation, capsaicin-sensitive sensory nerve, nitric oxide, functional dyspepsia

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Introduction

Reservoir functions in such organs as the stomach and bladder are important for daily life. If these organs had no such functions, we were forced to eat and urinate continuously during whole day and night, hence we could do nothing else. The stomach has variety of functions including reservoir functions. Disorders of the reservoir functions result in symptoms of early satiety and anorexia, which are the major symptoms of patients with functional dyspepsia. There exist two major responses as a reservoir function of the stomach; adaptive and receptive relaxations. These physiological responses are important to accommodate the intake of food and liquid. In this issue, we would like to focus mainly on mechanisms and clinical implication of gastric adaptive relaxation.

Adaptive and Receptive Relaxation as Gastric Reservoir Functions

Adaptive relaxation is a reflex in which the fundus of the stomach dilates in response to small increases in intragastric pressure when food enters the stomach. Receptive relaxation is a reflex in which the gastric fundus dilates when food passes down the pharynx and the esophagus. A variety of gastrointestinal hormones and chemical mediators such as gastrin, histamine¹⁾, serotonin²⁾, vasoactive intestinal peptide (VIP)³⁾, and the vagus^{4,5)} have been shown to mediate these two types of relaxations, which may be induced by a vago-vagal reflex or an axon reflex from sensory nerves, possibly via a nitric oxide (NO)-dependent non-adrenergic, non-cholinergic (NANC) neural pathway when mechanoreceptors are stimulated by stretching of the gastric or esophageal walls^{6,7)}. The mechanisms of these two types of functional responses are to some extent different.

Receptive relaxation is induced by vagal stimulation in an *in vitro* experiment⁸⁾. This vagally-induced relaxation is abolished by tetrodotoxin but not by atropine and guanethidine, or by desensitization to capsaicin⁹⁾, suggesting involvement of NANC nerves other than capsaicin-sensitive sensory nerves in the receptive relaxation. Hexamethonium, an antagonist of ganglionic nicotinic receptors⁸⁾, inhibits this relaxation, indicating mediation of a pathway through the nicotinic ganglion. NO may be a final mediator of the vagally-induced relaxation because *N* ω -nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthesis, strongly inhibits this relaxation and coincubation with L-arginine, a precursor of NO, partially reverses it⁸⁾. As for gastric adaptive relaxation, we will discuss in detail below.

Assessment of Gastric Adaptive Relaxation

Desai *et al.*^{6,7)} at the first time reported the method to detect gastric adaptive relaxation in the experiment using the stomach isolated from guinea-pig *in vitro*. We made a device to record the gastric adaptive relaxation (Fig. 1) according to Desai's reports^{6,7)}. Briefly, the cannulated stomach is placed in a warmed (37°C) organ bath (500 ml) filled with oxygenated Krebs solution. The cannula in the stomach is connected to both a wide reservoir bottle (2

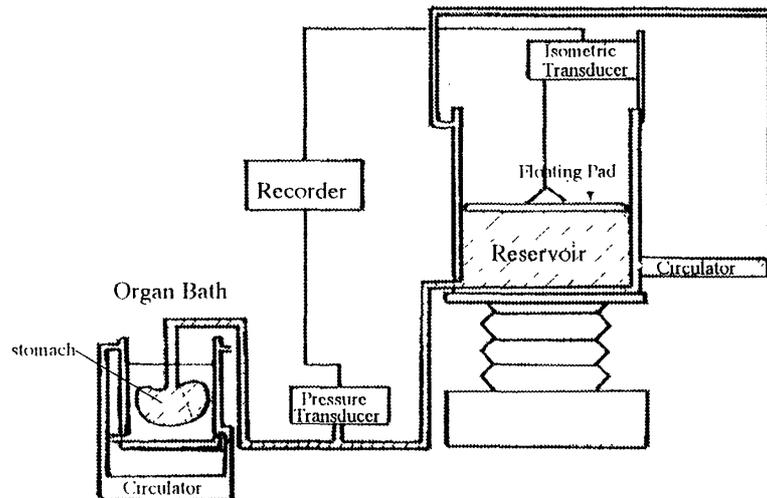


Fig. 1. Diagram of experimental arrangement for assessment of gastric adaptive relaxation.

liters) containing oxygenated Krebs solution and a pressure transducer (DT-XXAD, Viggo-Spectramed, Singapore, Singapore) to monitor the intragastric pressure. The reservoir is mounted on a movable rack and sealed by a floating recorder to record changes in the gastric volume. The gastric volume is measured with a floating recorder attached to an isotonic transducer (type 45347, NEC San-ei, Tokyo, Japan). Serial changes in pressure and volume are recorded on a chart recorder (R-60, Rikadenki, Tokyo, Japan). The reservoir is elevated stepwise (in 1-cm increments) and Krebs solution enters the stomach as the pressure increased. Adaptive relaxation is found as a response wherein the fundus suddenly relaxes at a certain

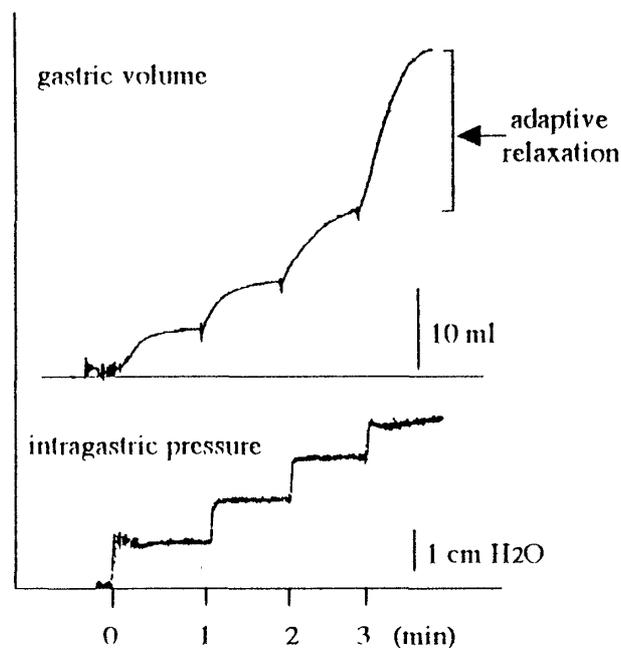


Fig. 2. Original chart of gastric volume obtained by stepwise increments (1 cm H₂O each) of intragastric pressure in an isolated stomach of a guinea pig. Adaptive relaxation is the response wherein the fundus suddenly relaxes and the volume increases sharply (arrow)⁸⁾.

intra-gastric pressure and a large volume of Krebs solution enters the stomach (Fig. 2). This burst-like adaptive response occurred at the intra-gastric pressures of 3.9 ± 0.1 cm H₂O and at the gastric volumes of $30.2 \pm 0.7\%$ of the total gastric volume in our previous study⁸). The increment volume of adaptive relaxation was $29.1 \pm 0.5\%$ of the total gastric volume (n=61). In the same stomach, adaptive relaxation can be obtained repeatedly at the same intra-gastric pressure, and the dilated gastric volume is always fixed, indicating a good reproducibility of results during the experiment.

Jahnberg⁹) has described the method to detect the adaptive relaxation in an *in vivo* experiment with dogs. A flaccid plastic balloon of about 1,000 ml volume is introduced orally into the stomach in the acute experiments on anesthetized dogs and through a gastric fistula in the chronic experiments on conscious dogs. The balloon is connected to the similar equipments described above. At low pressure loads (5-10 cm H₂O or less), a new steady state level of gastric tone is monitored. At higher pressure loads (15-20 cm H₂O), steeper expansion curve is seen as a phenomenon indicating the gastric adaptive relaxation. This method can be used for humans, although it may be discomfort for patients⁹).

Mechanisms of Gastric Adaptive Relaxation

Adaptive relaxation is independent of external innervation and resistant to ganglion blockade, but reflex in origin. NANC nerves are a major component of vagus including afferent sensory fibers, which play important roles in gastrointestinal functions¹⁰). Incubation of the stomach isolated from guinea pig with tetrodotoxin completely eliminates the adaptive relaxation⁶). Therefore, this pressure-induced adaptive relaxation is mediated by nerves, possibly intramural nerves. The adaptive relaxation is completely preserved in the presence of atropine and guanethidine in the same experiment, indicating involvement of NANC nerves. NO, a NANC neurotransmitter substance, may mediate adaptive relaxation because *N*^G-monomethyl-L-arginine and LNNA, both inhibitors of NO synthesis, and methylene blue, an inhibitor of soluble guanylate cyclase, abolish the adaptive relaxation⁶).

The afferent sensory nerves are sensitive to the stimulant and neurotoxic effects of capsaicin, they are collectively termed capsaicin-sensitive sensory nerves. In the stomach, the submucosal arterioles and vessels which regulate mucosal blood flow are densely innervated by capsaicin-sensitive sensory nerves¹¹). In the rat gastric muscle strip, capsaicin exerts two motor effects: contraction induced by cholinergic interneurons via the release of substance P, and relaxation neurally induced by NANC neurons¹²), indicating that the balance of the capsaicin-sensitive sensory nerves regulates gastric motility. As for a reservoir function of the stomach, capsaicin relaxes the isolated stomach taken from guinea pig in the presence of atropine and guanethidine, and the pressure-induced adaptive relaxation is abolished by the desensitization to capsaicin (Fig. 3)⁸). The capsaicin-induced relaxation is inhibited by tetrodotoxin in this *in vitro* experiment, indicating the phenomenon is mediated by the intramural NANC fibers. LNNA inhibits this relaxation and L-arginine reverses the inhibition by LNNA. Sodium nitroprusside, a donor of NO, induces gastric relaxation even after the desensitization to capsaicin. On the other hand, when LNNA is combined with desensitization

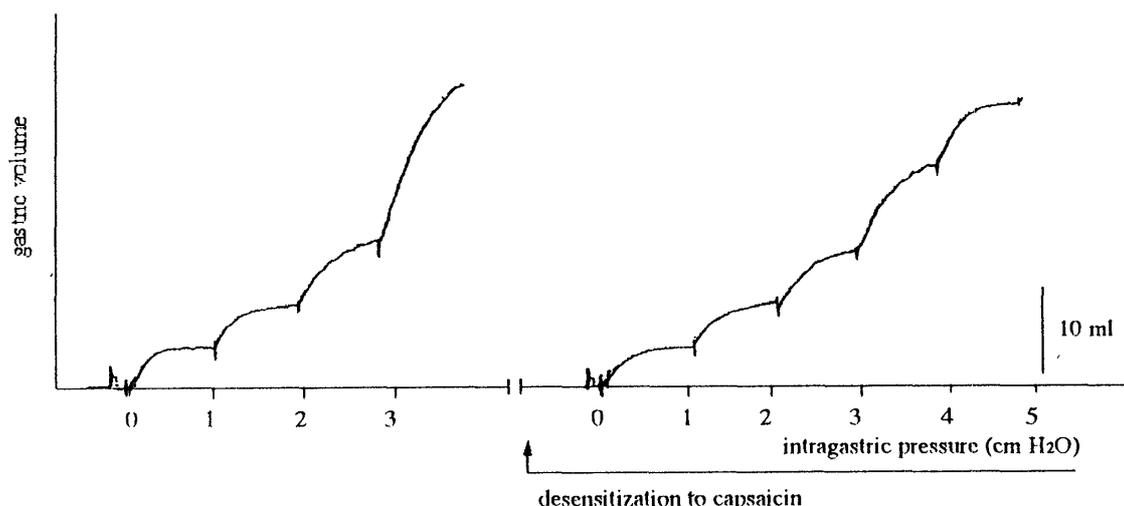


Fig. 3. Effects of desensitization to capsaicin on adaptive relaxation in an isolated stomach from a guinea pig⁸⁾.

to capsaicin, the effect on the adaptive relaxation is not additive. Together with these findings, the release of NO through the stimulation of capsaicin-sensitive sensory nerves may be essential to the adaptive relaxation⁸⁾. The adaptive relaxation is resistant to hexamethonium, suggesting that this pressure-induced reflex is induced by other pathway than through the nicotinic ganglion. Therefore, NO synthesis may be stimulated via an axon-reflex after the activation of mechanoreceptors in gastric mucosa.

The capsaicin-sensitive sensory nerves affect various gastrointestinal functions via the release of calcitonin gene-related peptide (CGRP). Chen and Guth¹⁵⁾ reported that an inhibitor of NO synthesis more strongly attenuated capsaicin-induced dilation of the submucosal arterioles of rat stomach than did CGRP-induced dilation. Therefore, the capsaicin-sensitive sensory nerves mediate NO through CGRP-dependent and -independent pathways. CGRP induces gastric relaxation in guinea pigs¹⁶⁾. Adaptive relaxation is, however, not inhibited by a CGRP receptor antagonist⁸⁾. Therefore, the capsaicin-sensitive sensory nerves may mediate NO through a CGRP-independent pathway in the adaptive relaxation.

VIP is a possible NANC inhibitory mediator in the gastrointestinal tract similar to NO¹⁷⁾. VIP induces gastric relaxation in various kinds of animals¹⁸⁾. However, the mediation of VIP in the adaptive relaxation is less possible, because a VIP antagonist does not inhibit the adaptive relaxation⁸⁾.

Possible mechanisms of adaptive and receptive relaxations of the stomach are summarized in Fig. 4.

Impairment of Gastric Adaptive Relaxation and Functional Dyspepsia

The pathogenesis of dysmotility-like functional dyspepsia cannot be explained by the abnormality of gastric emptying alone^{19,20)}. Disturbances of gastric reservoir functions may cause symptoms of epigastric fullness or early satiety.

Troncon *et al.*²¹⁾ have demonstrated the disturbance of adaptive relaxation in patients with

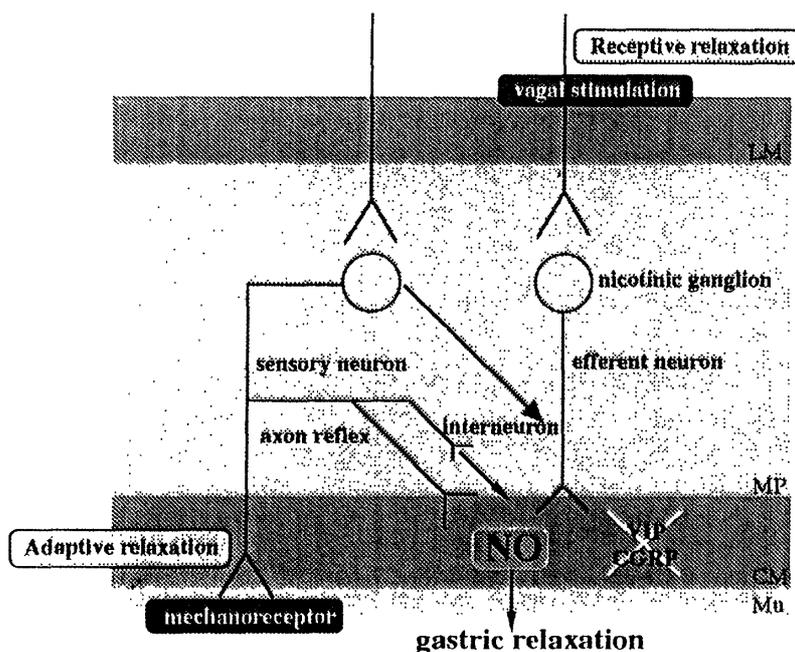


Fig. 4. Possible mechanisms of adaptive and receptive relaxations of the stomach. Adaptive relaxation is an intragastric pressure-induced reflex. Stretch of the gastric wall activates the mechanoreceptors in gastric mucosa (Mu), which generate impulses carried by the sensory neuron. The sensory neuron can synapse on the inhibitory efferent neuron directly or activate it via interneurons of the myenteric plexus (MP). This leads to the release of nitric oxide (NO) from the nitroergic efferent neuron, which causes relaxation of circular muscle (CM) and hence of the fundus. Alternatively, an axon reflex causes the NO release from the sensory neuron, resulting in hexamethonium-resistant gastric relaxation. The neurons involved in the extrinsic reflex responsible for receptive relaxation of the stomach enter the stomach wall as vagal motor fibers. The impulses carried by these fibers activate nitroergic efferent neuron, resulting in the generation of NO. In contrast with the pressure-induced adaptive relaxation, ganglionic nicotinic transmission is essential in the vagally-induced relaxation. VIP and CGRP are important neurotransmitters of inhibitory sensory neuron. However, these substances may not mediate both adaptive and receptive relaxations, because these two types of gastric relaxations are resistant to antagonists of VIP and CGRP. LM, longitudinal muscle.

functional dyspepsia by the serial measurement of intragastric pressure and volume using an intragastric balloon. Therefore, the adaptive relaxation may be related to the pathogenesis of functional dyspepsia. If the adaptive relaxation is disturbed, amounts of food may be forced into the antrum after ingestion and the antrum wall may be extended. Hausken *et al.*^{22,23)} measured the antral area postprandially by ultrasonography. They showed that the antral area was wide in functional dyspepsia patients, and supposed the disturbance of adaptive relaxation in the patients. On the other hand, in another study using the intragastric balloon method, no difference in the intragastric pressure-volume relationship was found between patients with dysmotility-like functional dyspepsia and normal controls²⁴⁾. They hypothesized that abnormalities exist in the sensory threshold for gastric wall dilation such as induction of pain and fullness by a small gastric content in these patients. Thus, there exist various situations in patients with functional dyspepsia.

The concentrations of somatostatin and substance P increase in the gastric mucosa of

patients with ulcer-like functional dyspepsia but not in the mucosa of patients with dysmotility-like dyspepsia. No difference in CGRP concentrations is observed between healthy volunteers and functional dyspepsia patients²⁵). To our knowledge, there is no report concerning the concentrations of VIP and NO in these patients. However, one report shows that donors of NO relax the proximal stomach and decrease postprandial abdominal discomfort in the dyspepsia patients²³). Such a new therapy to improve the gastric reservoir functions should be examined for the functional dyspepsia patients future.

References

- 1) Takasugi S, Ueda T, Kurata Y, Kurata Y, Kodama M, Ezaki H, Fujii K (1982). Neural and humoral factors influence gastric receptive relaxation in dogs. *Jpn J Surg* **12**: 208-213.
- 2) Bugge W, Ribbegren CJ, Gerner T, Haffner J (1989). Serotonin-a possible transmitter for the gastric adaptive relaxation. Interaction with histamine and prostaglandin F_{2α} on pressure responses in the isolated stomach. *Scand J Gastroenterol* **24**: 1079-1083.
- 3) Fahrenkrug J, Haglund U, Jodal M, Lundgren O, Olbe L, de Muckadell OBS (1978). Nervous release of vasoactive intestinal polypeptide in the gastrointestinal tract of cats: possible physiological implications. *J Physiol* **284**: 291-305.
- 4) Abrahamsson H, Jansson G (1969). Elicitation of reflex vagal relaxation of the stomach from pharynx and esophagus in the cat. *Acta Physiol Scand* **77**: 172-178.
- 5) Hartley MN, Mackie CR (1991). Gastric adaptive relaxation and symptoms after vagotomy. *Br J Surg* **78**: 24-27.
- 6) Desai KM, Sessa WC, Vane JR (1991). Involvement of nitric oxide in the reflex relaxation of the stomach to accommodate food or fluid. *Nature Lond* **351**: 477-479.
- 7) Desai KM, Zembowicz A, Sessa WC, Vane JR (1991). Nitroxergic nerves mediate vagally induced relaxation in the isolated stomach of the guinea pig. *Proc Natl Acad Sci USA* **88**: 11490-11494.
- 8) Uno H, Arakawa T, Fukuda T, Higuchi K, Kobayashi K (1997). Involvement of capsaicin-sensitive sensory nerves in gastric adaptive relaxation in isolated guinea-pig stomachs. *Digestion* **58**: 232-239.
- 9) Jahnberg T (1977). Gastric adaptive relaxation. Effects of vagal activation and vagotomy an experimental study in dogs and in man. *Scand J Gastroenterol* **12**: 1-32.
- 10) Mayer EA, Raybould HE (1990). Role of visceral afferent mechanisms in functional bowel disorders. *Gastroenterology* **99**: 1688-1704.
- 11) Tepperman BL, Whittle BJR (1992). Endogenous nitric oxide and sensory neuropeptides interact in the modulation of the rat gastric microcirculation. *Br J Pharmacol* **105**: 171-175.
- 12) Holzer-Petsche U, Seitz H, Lembeck F (1989). Effect of capsaicin on gastric corpus smooth muscle of the rat in vitro. *Eur J Pharmacol* **162**: 29-36.
- 13) Bartho L, Petho G, Antal A, Holzer P, Szolcsanyi J (1987). Two types of relaxation due to capsaicin in the guinea pig isolated ileum. *Neurosci Lett* **81**: 146-150.
- 14) Maggi CA, Santicioli P, Manzini S, Meli A (1986). Capsaicin activates neurogenic non-adrenergic non-cholinergic relaxations of the isolated rat duodenum. *Eur J Pharmacol* **120**: 367-370.
- 15) Chen RYZ, Guth PH (1995). Interaction of endogenous nitric oxide and CGRP in sensory neuron-induced gastric vasodilation. *Am J Physiol* **268** (Gastrointest. Liver Physiol. 31): G791-G796.
- 16) Katsoulis S, Conlon JM (1989). Calcitonin gene-related peptides relax guinea pig and rat

- gastric smooth muscle. *Eur J Pharmacol* **161**: 129-134.
- 17) Burnstock G (1986). The non-adrenergic non-cholinergic nervous system. *Arch Int Pharmacodyn* **280** (suppl): 1-15.
 - 18) Grider JR, Cable MB, Said SI, Makhoul GM (1985). Vasoactive intestinal peptide as a neural mediator of gastric relaxation. *Am J Physiol* **248** (Gastrointest. Liver Physiol. 30): G73-G78.
 - 19) Jian R, Ducrot F, Ruskone A, Chaussade S, Rambaud JC, Modigliani R, Rain JD, Bernier JJ (1989). Symptomatic, radionuclide and therapeutic assessment of chronic idiopathic dyspepsia. *Dig Dis Sci* **34**: 657-664.
 - 20) Waldron B, Cullen PT, Kumar R, Smith D, Jankowski J, Hopwood D, Sutton D, Kennedy N, Campbell FC (1991). Evidence for hypomotility in non-ulcer dyspepsia: a prospective multifactorial study. *Gut* **32**: 246-251.
 - 21) Troncon LEA, Thompson DG, Ahluwalia NK, Barlow J, Heggie L (1995). Relations between upper abdominal symptoms and gastric distension abnormalities in dysmotility like functional dyspepsia and after vagotomy. *Gut* **37**: 17-22.
 - 22) Hausken T, Berstad A (1992). Wide gastric antrum in patients with non-ulcer dyspepsia. Effect of cisapride. *Scand J Gastroenterol* **27**: 427-432.
 - 23) Hausken T, Berstad A (1994). Effect of glyceryl trinitrate on antral motility and symptoms in patients with functional dyspepsia. *Scand J Gastroenterol* **29**: 23-28.
 - 24) Lemann M, Dederding JP, Flourie B, Franchisseur C, Rambaud JC, Jian R (1991). Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia; the irritable stomach syndrome. *Dig Dis Sci* **36**: 1249-1254.
 - 25) Kaneko H, Mitsuma T, Uchida K, Furusawa A, Morise K (1993). Immunoreactive-somatostatin, substance P, and calcitonin gene-related peptide concentrations of the human gastric mucosa in patients with nonulcer dyspepsia and peptic ulcer disease. *Am J Gastroenterol* **88**: 898-904.

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