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EDITORIAL

Neuro-regulation of lower esophageal sphincter function as treatment for gastroesophageal reflux disease

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Abstract

The junction between the esophagus and the stomach is a specialized region, composed of lower esophageal sphincter (LES) and its adjacent anatomical structures, the gastric sling and crural diaphragm. Together these structures work in a coordinated manner to allow ingested food into the stomach while preventing reflux of gastric contents across the esophago-gastric junction (EGJ) into the esophagus. The same zone also permits retrograde passage of air and gastric contents into esophagus during belching and vomiting. The precise coordination required to execute such a complicated task is achieved by a finely-regulated high-pressure zone. This zone keeps the junction between esophagus and stomach continuously closed, but is still able to relax briefly *via* input from inhibitory neurons that are responsible for its innervation. Alterations of the structure and function of the EGJ and the LES may predispose to gastroesophageal reflux disease (GERD).

Key words: Gastroesophageal reflux disease; Lower esophageal sphincter; Esophago-gastric junction

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INTRODUCTION

The junction between the esophagus and the stomach is a specialized region, composed of the lower esophageal sphincter (LES) and its adjacent anatomical structures, the gastric sling and the crural diaphragm. Together these structures work in a coordinated manner to allow ingested food into the stomach while preventing reflux of gastric contents across the esophago-gastric junction (EGJ) into the esophagus. The same zone also permits retrograde passage of air and gastric contents into the esophagus during belching and vomiting. The precise coordination required to execute such complicated tasks is achieved by a finely-regulated high-pressure zone. This zone keeps the junction between esophagus and stomach continuously closed, but is still able to relax briefly via input from inhibitory neurons[1] that are responsible for its innervation. Alterations of the structure and function of the EGJ and the LES may predispose to gastroesophageal reflux disease (GERD) (Table 1).

ANATOMY, INNERVATION AND NEURAL PATHWAYS

At the EGJ, the LES and the crural diaphragm constitute the intrinsic and extrinsic sphincters, respectively. These two sphincters are anatomically superimposed and are anchored to each other by the phreno-esophageal ligament[2]. The LES is a specialized thickened region of the circular muscle layer of the distal esophagus, extending in humans over an axial distance of 2-5 cm. Sensory information from LES to the brain is conveyed by both spinal and vagal sensory afferents[3,4]. The spinal afferents have their cell bodies in the dorsal root ganglia at T1 to L3, and are believed to detect mainly nociceptive stimuli[5]. The vagal afferents, with their cell bodies in nodose ganglia, transmit non-painful sensory information to the brain stem where the central terminations synapse in the nucleus tractus solitarius[1]. The neurons of this nucleus are closely connected to dorsal motor nucleus of vagus nerve. The latter provides the motor innervation to the LES and contains the efferent neurons that can either increase or decrease LES tone by stimulation of inhibitory or excitatory motor neurons in the myenteric plexus of the sphincter[1]. The excitatory myenteric neurons in LES are cholinergic in nature and act to stimulate muscarinic receptors on the smooth muscle[6]. Inhibitory motor neurons to LES are abundant and receive powerful

Table 1 Factors that regulate LES function

Factors that increase tLESRs	Factors that decrease tLESRs
Gastric distention	GABA agonists
Pharyngeal stimulation	Anticholinergics
High-fat meals	Opioid receptor agonists
CCK-A receptor agonists	Nitric oxide synthase inhibitors
	Endoscopic therapy
	Fundoplication

cholinergic nicotinic inputs from vagal efferents[6]. Although the vagal nerve innervates both excitatory and inhibitory myenteric motor neurons, vagal stimulation in experimental models invariably results in LES relaxation[7-9]. On the contrary, splanchnic nerve stimulation relaxes the LES by activating adrenergic neurons, probably *via* nicotinic and non-nicotinic mechanisms of neural transmission, which in turn elicit beta-adrenergic inhibitory effects on the sphincter[10]. The inhibitory myenteric neurons innervating the LES are nitrergic in nature.

MECHANISMS OF GASTRO-ESOPHAGEAL REFLUX

The movement of gastric contents into the esophagus, or gastro-esophageal reflux, is due to a defective sphincter mechanism at the EGJ. An understanding of the two lower esophageal sphincters would lead one to expect weakness in either of the two to cause reflux. Indeed, some patients with reflux disease have a weak lower esophageal sphincter, some have a weak crural diaphragm, and some have both[2]. Reports suggest that it is possible to distinguish between two main mechanisms causing reflux: low basal sphincter pressure leading to free reflux, mostly occurring at night in the supine position, and increased frequency of transient lower esophageal sphincter relaxations with normal or increased resting LES pressure leading to reflux during the day in an upright position[11]. For example, in patients with mild-to-moderate (typically non-erosive) reflux disease, the pressures exerted by the lower esophageal sphincter[12] and the crural diaphragm[13] are normal. In such patients, the mechanism of reflux is due to transient spontaneous and inappropriate sphincter relaxations (tLESRs)[14].

A tLESR is a long period (lasting 10 to 60 s) of simultaneous relaxation of both the intrinsic distal esophageal sphincter and the crural diaphragm[2] representing a neural reflex that is mediated through the brain stem[2]. The efferent pathway for such relaxation is in the vagus nerve, and nitric oxide is the postganglionic neurotransmitter[15]. The mechanism of relaxation of the crural diaphragm is not known. Gastric distention and pharyngeal stimulation are two possible mechanisms by which the afferent stimulus that initiates transient relaxation of the LES may originate[16]. Gastric distention, upright and right lateral decubitus postures, and high-fat meals increase the frequency of such relaxation[16].

Diet

Patients with GERD are usually counseled on lifestyle changes that decrease the incidence of reflux, such as reducing fat in the diet. High dietary fat intake, particularly saturated fat, is associated with an increased risk of GERD symptoms and the likelihood of erosive esophagitis. These associations are independent of energy intake and therefore do not reflect a mere increase in total dietary intake. However, the effects are not completely independent of body mass index and are statistically significant only in overweight individuals. Other findings include a possible protective effect for high-fiber intake relative to GERD symptoms and a non-significant unfavorable trend for total energy intake[17].

An important role for dietary fat in causing temporary episodes of reflux is supported by studies of human volunteers that have shown increased frequency of tLESRs and increased esophageal acid exposure with high-fat consumption in both healthy volunteers[18,19] as well as patients with GERD[20,21]. Several food items have been associated with precipitating reflux symptoms in cross-sectional epidemiological surveys[22]. Previous case control studies reported a significant positive effect of fat intake on the rising rates of GERD and esophageal adenocarcinoma in the general population[23-25]. The fat content of the US food supply has increased 38% between 1909 and 1988[26]. These secular trends are consistent with the notion that high fat intake may be at least partially responsible for rising rates of esophageal adenocarcinoma, which were first observed in the late 1970s[17].

Sleep impairs esophageal acid clearance resulting in a prolongation of esophageal mucosal contact with acid[27]. Therefore avoiding meals two hours before lying down and sleeping with the head of the bed elevated prevents nocturnal acid reflux as nocturnal reflux *portends* a greater risk of erosive esophagitis and other GERD complications. Marked hyperglycemia has been shown to increase the frequency of tLESRs[28] and this may be a factor underlying the high rate of gastroesophageal reflux in patients with diabetes mellitus.

Pharmacologic control of LES

Since tLESRs represent the major mechanism responsible for episodic reflux, patients with GERD without mucosal disease or with mild erosive disease could potentially benefit from anti-tLESR therapy alone. Yet, this therapy could also be of value to treat some more severe forms of erosive esophagitis in combination with acid suppressants.

γ-GABA-b agonists: GABA is the major inhibitory neurotransmitter within the central nervous system, and GABA receptors are present at many sites within the central and peripheral nervous systems. GABA receptors are abundant pre-synaptically on vagal afferents in the dorsal medulla[29] and have been shown to inhibit neurotransmitter release in vagal nuclei[30]. Baclofen, a GABA analog, has recently been shown to be effective in reducing gastro-esophageal reflux[31,32]. Unlike acid suppressing agents, baclofen reduces the frequency of tLESRs and decreases the number of gastro-duodenal reflux episodes[33]. The drug has several advantages over other agents tested to date. It is available in an oral formulation and appears to have no adverse effects on other aspects of esophageal motor function, such as

basal LES pressure or acid clearance[34]. It also increases gastric pH in both GERD patients and controls even after repeated administrations. Since baclofen addresses a different factor in the pathophysiology of GERD, it can be used as add-on therapy in GERD patients with incomplete relief by acid suppression and/or in patients with more severe GERD[35]. However, baclofen has several limitations, including the need for frequent dosing due to its short half-life (3-4 h), and its limited absorption in the lower gastrointestinal tract, which precludes the development of a controlled-release formulation. The drug is nevertheless approved for treatment of spasticity, and its potential utility for the treatment of GERD has been demonstrated in clinical studies[36,37].

Recently, its active stereoisomer R-baclofen, has been incorporated into an experimental prodrug, XP19986. XP19986 overcomes the pharmacokinetic limitations of baclofen; it can be administered in a controlled-release formulation that allows for once- or twice-daily dosing. A recent Phase 1 clinical trial assessed the safety, tolerability and pharmacokinetics of XP19986 dosed once (QD) or twice (BID) daily in healthy adult volunteers. The trial was conducted sequentially in four separate cohorts of 12 subjects, three of whom received placebo per cohort. Following an up-titration period, the first cohort received 30 mg QD of XP19986 for seven days, followed by 30 mg BID for seven days and ending with a down-titration period. Subsequent cohorts received 60 mg and 90 mg QD and BID following a similar protocol. The final group of subjects received 120 mg QD only. Subjects were monitored for adverse events, and blood and urine were sampled to determine pharmacokinetic profiles and bioavailability. The trial demonstrated that repeated QD dosing of XP19986 resulted in sustained levels of R-baclofen in blood over 24-h, which reached steady-state within three days. Repeated BID dosing reduced the steady-state peak-to-trough ratio of R-baclofen by approximately 50% compared to QD dosing. Exposure to R-baclofen increased linearly with dose. This clinical trial also indicated that XP19986 was well tolerated. The most commonly reported adverse events were somnolence, dizziness and nausea that were generally mild in severity and generally increased in incidence compared to placebo with daily doses above 60 mg. In the 120 mg cohort, one subject experienced episodes of slurred speech and tremor, which are reported side effects of baclofen[38].

Cholecystokinin: The cholecystokinin A (CCK-A) receptor subtype is involved in the occurrence of tLESRs induced by gastric distension. Loxiglumide, a CCK-A antagonist, inhibits tLESRs and attenuates the fall in LES pressure following a meal, but has only modest effects on postprandial gastro-esophageal acid reflux[39].

Atropine: As mentioned earlier, the motor innervation to the LES and proximal gastric motor function is under cholinergic control[1]. Distension of the proximal stomach is a major stimulus for triggering tLESRs. Atropine, by acting centrally within the dorsal vagal complex, decreases the rate of tLESRs, despite the fact that it relaxes the proximal stomach and increases the degree of gastric distension under pressure-controlled conditions[40]. Anticholinergic agents are unlikely to have a therapeutic role because of the substantial deleterious effects on acid clearance[41].

Opioid receptor agonists: Opioid nerves have been demonstrated in the myenteric plexus of normal LES in humans[42] and opossum[43]. Morphine inhibits LES relaxation induced by swallowing and by balloon distension of the esophagus[44], thereby increasing residual LES pressure. On this basis, it seems likely that morphine might prevent reflux during tLESRs by rendering them incomplete. In one study[45] of patients with GERD, intravenous morphine inhibited tLESRs by 50%, and this effect was associated with a concomitant decrease in the rate of reflux episodes. Morphine also reduced the rate of tLESRs in normal subjects but by a lesser degree, and there was no decrease in the rate of reflux episodes, perhaps because the control rate was already relatively low. Interestingly, morphine did not appear to affect the residual pressure during tLESRs. The effect of morphine is completely blocked by naloxone, suggesting that it is mediated through μ-receptors. The effect of morphine is presumably central, because the peripherally active opiate loperamide does not influence the rate of tLESRs[46]. The effect of morphine on transient LES relaxations is dependent on the decrease in volume of the proximal stomach. Pharmacological interventions which decrease fundic volume should result in control of transient LES relaxation-mediated gastro-esophageal reflux[47]. Unwanted effects, such as addiction and constipation, are major barriers to the use of opioids[34].

Nitric oxide synthase inhibitors: Nitric oxide is the major post-ganglionic inhibitory neurotransmitter to the LES[34]. Nitrergic neurons are also present in the dorsal motor nucleus of the vagus, the source of pre-ganglionic motor neurons to the LES, and recent evidence suggests that there may be a novel nitrergic, pre-ganglionic, vagal pathway involved in LES relaxation[48]. It seems logical therefore, that blockade of nitric oxide synthesis might inhibit tLESRs. Indeed, in one study[49] the nitric oxide synthase inhibitor, NG-nitro-L-arginine-methyl ester (L-NAME), inhibited the rate of tLESRs, and this effect was reversed by L-arginine but not D-arginine. Other studies have found that, in normal humans, NG-monomethyl-L-arginine (L-NMMA) inhibited tLESRs induced by gastric distension by more than 75%[50], but reduced meal-induced tLESRs by only 25%[51]. Chronic administration of nitric oxide substrate, L-arginine, prolongs the postprandial increase in tLESRs[52].

The therapeutic potential of nitric oxide inhibition remains to be determined. At present, no orally effective agents exist. Inhibition of nitric oxide is associated with effects on motility in other areas of the gastrointestinal tract as well as in the cardiovascular system, urinary bladder, and respiratory tract. Unless specific and well-targeted antagonists of neuronal nitric oxide synthesis can be developed, unwanted side effects are likely to preclude this pharmacologic approach to the treatment of GERD[34].

Endoscopic methods that regulate LES function

Endoscopic endo-luminal anti-reflux approaches have

been recently introduced aiming to prevent acid reflux by construction of a functional or controlled barrier in the LES zone[53]. These endoscopic therapies offer the potential for significant symptomatic improvement while obviating many of the potential drawbacks associated with long-term medical therapy with acid suppressive or neutralizing medications, or the complications and side effects of anti-reflux surgery. These techniques include the delivery of radiofrequency energy to the EGJ (Stretta), injection of bulking agents (Enteryx), implantation of a bioprostheses into the LES (Gatekeeper), and suture plication of the proximal fundic folds (EndoCinch, NDOplicator)[54]. All these approaches are less invasive than antireflux surgery, and are performed in the outpatient setting. However, only limited data are available on their respective mechanisms of action[55]. Stretta increases the barrier between the stomach and the esophagus by either collagen deposition or disruption of vagally-mediated tLESRs[56]. The decrease in transient LES relaxation is presumably caused by either altering the mechanics of the cardia or interrupting afferent nerve transmission to the brainstem control mechanisms. Human and animal studies suggest that radiofrequency energy may decrease GERD symptoms[57] by decreasing the frequency of transient LES relaxations associated with reflux episodes, increasing the intra-gastric pressure needed to induce reflux, and hastening gastric emptying[58-61]. Another potential mechanism of the improved symptoms is decreased visceral sensitivity, as witnessed by the observation that the time needed to report symptoms during esophageal acid perfusion was significantly longer 6 mo after Stretta compared with baseline[62]. Although neurolysis with impairment of sensory afferent pathways is indeed a potential mechanism, other factors may include esophageal exposure to hydrogen ions, mucosal permeability, number and activation state of acid-sensitive nerve endings, and central processing of incoming sensory information. Radiofrequency energy delivery may influence several of these mechanisms as well as the compliance of the EGJ, increasing the resistance of the LES to a distending pressure[58] and decreasing the volume of refluxate during LES relaxations[57].

A variety of injectable agents have been studied for bulking the gastroesophageal junction, including Plexiglas microspheres, ethylene vinyl alcohol co-polymer (Enteryx), and hydrogel prosthesis (Gatekeeper). It is hypothesized that Enteryx leads to an increased barrier to reflux, whereas the hydrogel prosthesis may exert its effect by decreasing the aperture through which refluxate may flow, thus resulting in less proximal migration of the refluxate. Endoscopic plication is hypothesized to impede reflux by approximating tissue at or below the EGJ. The resulting effect of all these endoscopic techniques on LES pressure and 24-h intra-esophageal pH profiles is modest and complete normalization of acid exposure is uncommon. Nevertheless, all these techniques reduce GERD symptoms, improve quality of life, and decrease esophageal acid exposure and the need for anti-secretory medications[63,64].

Surgery

Laparoscopic fundoplication (LF) tightens the EGJ through a set of suture placations, resulting in significant increases in LES resting and post-deglutition relaxation pressures in both left lateral and upright positions and after gastric distention[65]. Post-fundoplication patients exhibit a diminished rate of tLESRs both at rest and during isobaric gastric distension compared with both normal controls and GERD subjects. Further, tLESRs in fundoplication patients are characterized by a higher residual pressure and a lower efficacy of facilitating gastric venting[66]. The reduction of tLESRs after a successful LF, is possibly due to disruption of the efferent vagal pathways to the LES. An adequate dissection of the EGJ alone prior to the actual fundoplication is sufficient to significantly disrupt the efferent pathway of this neural reflex, which may underscore the importance of performing a circumferential mobilization of the EGJ in all patients. Moreover, the wrap itself appears to further inhibit efferent neural impulses to the LES, thereby decreasing tLESRs[67].

Although the receptive field for triggering tLESRs is not completely clear[66], mechanoreceptors in the region of the gastric cardia are commonly implicated[16,68]. On the basis of studies in ferrets[69], two types of mechanoreceptors have been proposed: receptors in series with smooth muscle fibers, responding to wall tension variation, and receptors in parallel with smooth muscle fibers, responding to elongation of the gastric wall. Both types of receptors are activated during gastric distension[70,71]. However, after fundoplication the gastric cardia is situated within the fundic wrap, and has a reduced ability to stretch or elongate[72]. Thus an identical and constant distension stimulus likely leads to a diminished cardiac cross-sectional area compared with what would be observed if the same stimulus were applied in normal or GERD subjects. Reduced cross-sectional area would, in turn, result in decreased wall tension and elongation, thereby reducing the activation of both types of receptors potentially responsible for triggering tLESRs. Furthermore, because tLESR elicitation and gastric receptive relaxation are both mediated by the vagal nerve and since gastric accommodation is not affected by fundoplication[73], it is tempting to speculate that the vagal afferent field for triggering tLESRs is either independent of, or contained within a larger area responsible for elicitation of gastric receptive relaxation and that only the first is substantially reduced by fundoplication[66].

Postprandial epigastric fullness and bloating appear in 10%-80% of patients after Nissen fundoplication[74,75], and an inability to relieve this discomfort by belching is frequently reported[76]. Beyond the reduction in the number of tLESRs, a significant reduction of the percentage of tLESRs associated with a common cavity phenomenon is also found in fundoplication patients[77], and this potentially explains the frequently reported symptoms related to increased amounts of intestinal gas[66].

CONCLUSION

Given the increasing prevalence of GERD the efforts to regulate the EGJ and the LES continue along many fronts, pharmacologic, endoscopic, or surgical. Promising new ways to favorably alter the structure and function of the

EGJ and to reduce tLESRs may eventually replace acid suppression as the primary treatment of GERD or be used as adjunctive therapies.

REFERENCES

1 **Boeckxstaens GE**. The lower oesophageal sphincter. *Neurogastroenterol Motil* 2005; **17** Suppl 1: 13-21
2 **Mittal RK**, Balaban DH. The esophagogastric junction. *N Engl J Med* 1997; **336**: 924-932
3 **Hornby PJ**, Abrahams TP, Partosoedarso ER. Central mechanisms of lower esophageal sphincter control. *Gastroenterol Clin North Am* 2002; **31**: S11-S20, v-vi
4 **Goyal RK**, Padmanabhan R, Sang Q. Neural circuits in swallowing and abdominal vagal afferent-mediated lower esophageal sphincter relaxation. *Am J Med* 2001; **111** Suppl 8A: 95S-105S
5 **Collman PI**, Tremblay L, Diamant NE. The distribution of spinal and vagal sensory neurons that innervate the esophagus of the cat. *Gastroenterology* 1992; **103**: 817-822
6 **Yuan S**, Costa M, Brookes SJ. Neuronal pathways and transmission to the lower esophageal sphincter of the guinea Pig. *Gastroenterology* 1998; **115**: 661-671
7 **Paterson WG**, Anderson MA, Anand N. Pharmacological characterization of lower esophageal sphincter relaxation induced by swallowing, vagal efferent nerve stimulation, and esophageal distention. *Can J Physiol Pharmacol* 1992; **70**: 1011-1015
8 **Sivarao DV**, Mashimo HL, Thatte HS, Goyal RK. Lower esophageal sphincter is achalasic in nNOS(-/-) and hypotensive in W/W(v) mutant mice. *Gastroenterology* 2001; **121**: 34-42
9 **Yamato S**, Saha JK, Goyal RK. Role of nitric oxide in lower esophageal sphincter relaxation to swallowing. *Life Sci* 1992; **50**: 1263-1272
10 **Blackshaw LA**, Haupt JA, Omari T, Dent J. Vagal and sympathetic influences on the ferret lower oesophageal sphincter. *J Auton Nerv Syst* 1997; **66**: 179-188
11 **Meining A**, Fackler A, Tzavella K, Storr M, Allescher HD, Klauser A, Heldwein W. Lower esophageal sphincter pressure in patients with gastroesophageal reflux diseases and posture and time patterns. *Dis Esophagus* 2004; **17**: 155-158
12 **Dent J**, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux. *Gut* 1988; **29**: 1020-1028
13 **Mittal RK**, Chowdhry NK, Liu J. Is the sphincter function of crural diaphragm impaired in patients with reflux esophagitis? *Gastroenterology* 1995; **108** Suppl 1: A168
14 **Katzka DA**, Sidhu M, Castell DO. Hypertensive lower esophageal sphincter pressures and gastroesophageal reflux: an apparent paradox that is not unusual. *Am J Gastroenterol* 1995; **90**: 280-284
15 **Boulant J**, Mathieu S, D'Amato M, Abergel A, Dapoigny M, Bommelaer G. Cholecystokinin in transient lower oesophageal sphincter relaxation due to gastric distension in humans. *Gut* 1997; **40**: 575-581
16 **Mittal RK**, Holloway RH, Penagini R, Blackshaw LA, Dent J. Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995; **109**: 601-610
17 **El-Serag HB**, Satia J A, Rabeneck L. Dietary intake and the risk of gastro-oesophageal reflux disease: a cross sectional study in volunteers. *Gut* 2005; **54**: 11-17
18 **Becker DJ**, Sinclair J, Castell DO, Wu WC. A comparison of high and low fat meals on postprandial esophageal acid exposure. *Am J Gastroenterol* 1989; **84**: 782-786
19 **Hills JM**, Aaronson PI. The mechanism of action of peppermint oil on gastrointestinal smooth muscle. An analysis using patch clamp electrophysiology and isolated tissue pharmacology in rabbit and guinea pig. *Gastroenterology* 1991; **101**: 55-65
20 **Nebel OT**, Castell DO. Lower esophageal sphincter pressure changes after food ingestion. *Gastroenterology* 1972; **63**: 778-783
21 **Murphy DW**, Castell DO. Chocolate and heartburn: evidence of increased esophageal acid exposure after chocolate ingestion. *Am J Gastroenterol* 1988; **83**: 633-636
22 **Nebel OT**, Fornes MF, Castell DO. Symptomatic gastroesophageal reflux: incidence and precipitating factors. *Am J Dig Dis* 1976; **21**: 953-956
23 **Vaughan TL**, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995; **4**: 85-92
24 **Mayne ST**, Risch HA, Dubrow R, Chow WH, Gammon MD, Vaughan TL, Farrow DC, Schoenberg JB, Stanford JL, Ahsan H, West AB, Rotterdam H, Blot WJ, Fraumeni JF Jr. Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 1055-1062
25 **Brown LM**, Swanson CA, Gridley G, Swanson GM, Schoenberg JB, Greenberg RS, Silverman DT, Pottern LM, Hayes RB, Schwartz AG. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995; **87**: 104-109
26 **Raper NR**, Zizza C, Rourke J. Nutrient content of the US food supply, 1909–1988. Home Economics Research Report No. 50. Washington, DC: United States Department of Agriculture, 1992
27 **Orr WC**. Night-time gastro-oesophageal reflux disease: prevalence, hazards, and management. *Eur J Gastroenterol Hepatol* 2005; **17**: 113-120
28 **Zhang Q**, Horowitz M, Rigda R, Rayner C, Worynski A, Holloway RH. Effect of hyperglycemia on triggering of transient lower esophageal sphincter relaxations. *Am J Physiol Gastrointest Liver Physiol* 2004; **286**: G797-G803
29 **Bowery NG**, Pratt GD. GABAB receptors as targets for drug action. *Arzneimittelforschung* 1992; **42**: 215-223
30 **Brooks PA**, Glaum SR, Miller RJ, Spyer KM. The actions of baclofen on neurones and synaptic transmission in the nucleus tractus solitarii of the rat in vitro. *J Physiol* 1992; **457**: 115-129
31 **Koek GH**, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. *Gut* 2003; **52**: 1397-1402
32 **Ciccaglione AF**, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 hour pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. *Gut* 2003; **52**: 464-470
33 **Zhang Q**, Lehmann A, Rigda R, Dent J, Holloway RH. Control of transient lower oesophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in patients with gastro-oesophageal reflux disease. *Gut* 2002; **50**: 19-24
34 **Holloway RH**. Systemic pharmacomodulation of transient lower esophageal sphincter relaxations. *Am J Med* 2001; **111** Suppl 8A: 178S-185S
35 **Koek GH,** Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastro-oesophageal reflux refractory to proton pump inhibitors. *Gut* 2003; **52**: 1397-1402
36 **Cange L**, Johnsson E, Rydholm H, Lehmann A, Finizia C, Lundell L, Ruth M. Baclofen-mediated gastro-oesophageal acid reflux control in patients with established reflux disease. *Aliment Pharmacol Ther* 2002; **16**: 869-873
37 **Vela MF**, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. *Aliment Pharmacol Ther* 2003; **17**: 243-251
38 **Castell DO**, Hirota W K, Gerson L B, Reilley S F, Hila A, Agrawal A, Lal R, Huff F J. XP19986 decreases reflux and is well tolerated in GERD patients. *Gastroenterology* 2007; **132**: A486
39 **Trudgill NJ**, Hussain FN, Moustafa M, Ajjan R, D'Amato M, Riley SA. The effect of cholecystokinin antagonism on postprandial lower oesophageal sphincter function in asymptomatic volunteers and patients with reflux disease. *Aliment Pharmacol Ther* 2001; **15**: 1357-1364
40 **Lidums I**, Hebbard GS, Holloway RH. Effect of atropine on proximal gastric motor and sensory function in normal subjects. *Gut* 2000; **47**: 30-36
41 **Koerselman J**, Pursnani KG, Peghini P, Mohiuddin MA,

Katzka D, Akkermans LM, Castell DO. Different effects of an oral anticholinergic drug on gastroesophageal reflux in upright and supine position in normal, ambulant subjects: a pilot study. *Am J Gastroenterol* 1999; **94**: 925-930
42 **Wattchow DA**, Furness JB, Costa M, O'Brien PE, Peacock M. Distributions of neuropeptides in the human esophagus. *Gastroenterology* 1987; **93**: 1363-1371
43 **Rattan S**, Goyal RK. Identification and localization of opioid receptors in the opossum lower esophageal sphincter. *J Pharmacol Exp Ther* 1983; **224**: 391-397
44 **Penagini R**, Picone A, Bianchi PA. Effect of morphine and naloxone on motor response of the human esophagus to swallowing and distension. *Am J Physiol* 1996; **271**: G675-G680
45 **Penagini R**, Bianchi PA. Effect of morphine on gastroesophageal reflux and transient lower esophageal sphincter relaxation. *Gastroenterology* 1997; **113**: 409-414
46 **Allocca M**, Mangano M, Colombo P, Penagini R. Effect of loperamide on gastro-oesophageal reflux. *Scand J Gastroenterol* 2003; **38**: 343-346
47 **Penagini R**, Allocca M, Cantu P, Mangano M, Savojardo D, Carmagnola S, Bianchi PA. Relationship between motor function of the proximal stomach and transient lower oesophageal sphincter relaxation after morphine. *Gut* 2004; **53**: 1227-1231
48 **Hornby PJ**. How are transient lower esophageal sphincter relaxations triggered? In: Giuli R, Galmiche JP, Jamieson GG, Scarpignato C. The Esophagogastric Junction. Paris: John Libbey, Eurotext, 1998: 62–72
49 **Boulant J**, Fioramonti J, Dapoigny M, Bommelaer G, Bueno L. Cholecystokinin and nitric oxide in transient lower esophageal sphincter relaxation to gastric distention in dogs. *Gastroenterology* 1994; **107**: 1059-1066
50 **Hirsch DP**, Holloway RH, Tytgat GN, Boeckxstaens GE. Involvement of nitric oxide in human transient lower esophageal sphincter relaxations and esophageal primary peristalsis. *Gastroenterology* 1998; **115**: 1374-1380
51 **Hirsch DP**, Tiel-Van Buul MM, Tytgat GN, Boeckxstaens GE. Effect of L-NMMA on postprandial transient lower esophageal sphincter relaxations in healthy volunteers. *Dig Dis Sci* 2000; **45**: 2069-2075
52 **Luiking YC**, Weusten BL, Portincasa P, Van Der Meer R, Smout AJ, Akkermans LM. Effects of long-term oral L-arginine on esophageal motility and gallbladder dynamics in healthy humans. *Am J Physiol* 1998; **274**: G984-G991
53 **Zhi XT**, Kavic SM, Park AE. Management of gastroesophageal reflux disease: medications, surgery, or endoscopic therapy? (Current status and trends). *J Long Term Eff Med Implants* 2005; **15**: 375-388
54 **Portale G**, Filipi CJ, Peters JH. A current assessment of endoluminal approaches to the treatment of gastroesophageal reflux disease. *Surg Innov* 2004; **11**: 225-234
55 **Falk GW**, Fennerty MB, Rothstein RI. AGA Institute technical review on the use of endoscopic therapy for gastroesophageal reflux disease. *Gastroenterology* 2006; **131**: 1315-1336
56 **Triadafilopoulos G**, Utley DS. Temperature-controlled radiofrequency energy delivery for gastroesophageal reflux disease: the Stretta procedure. *J Laparoendosc Adv Surg Tech A* 2001; **11**: 333-339
57 **Cipolletta L**, Rotondano G, Dughera L, Repici A, Bianco MA, De Angelis C, Vingiani AM, Battaglia E. Delivery of radiofrequency energy to the gastroesophageal junction (Stretta procedure) for the treatment of gastroesophageal reflux disease. *Surg Endosc* 2005; **19**: 849-853
58 **Kim MS**, Holloway RH, Dent J, Utley DS. Radiofrequency energy delivery to the gastric cardia inhibits triggering of transient lower esophageal sphincter relaxation and gastroesophageal reflux in dogs. *Gastrointest Endosc* 2003; **57**: 17-22
59 **Tam WC,** Schoeman MN, Zhang Q, Dent J, Rigda R, Utley D, Holloway RH. Delivery of radiofrequency energy to the lower oesophageal sphincter and gastric cardia inhibits transient lower oesophageal sphincter relaxations and gastro-oesophageal reflux in patients with reflux disease. *Gut* 2003; **52**: 479-485
60 **Triadafilopoulos G**, DiBaise JK, Nostrant TT, Stollman NH, Anderson PK, Wolfe MM, Rothstein RI, Wo JM, Corley DA, Patti MG, Antignano LV, Goff JS, Edmundowicz SA, Castell DO, Rabine JC, Kim MS, Utley DS. The Stretta procedure for the treatment of GERD: 6 and 12 month follow-up of the U.S. open label trial. *Gastrointest Endosc* 2002; **55**: 149-156
61 **Utley DS**, Kim M, Vierra MA, Triadafilopoulos G. Augmentation of lower esophageal sphincter pressure and gastric yield pressure after radiofrequency energy delivery to the gastroesophageal junction: a porcine model. *Gastrointest Endosc* 2000; **52**: 81-86
62 **Arts J**, Sifrim D, Rutgeerts P, Lerut A, Janssens J, Tack J. Influence of radiofrequency energy delivery at the gastroesophageal junction (the Stretta procedure) on symptoms, acid exposure, and esophageal sensitivity to acid perfusion in gastroesophagal reflux disease. *Dig Dis Sci* 2007; **52**: 2170-2177
63 **Portale G**, Filipi CJ, Peters JH. A current assessment of endoluminal approaches to the treatment of gastroesophageal reflux disease. *Surg Innov* 2004; **11**: 225-234
64 **Arts J**, Tack J, Galmiche JP. Endoscopic antireflux procedures. *Gut* 2004; **53**: 1207-1214
65 **Chrysos E**, Athanasakis E, Pechlivanides G, Tzortzinis A, Mantides A, Xynos E. The effect of total and anterior partial fundoplication on antireflux mechanisms of the gastroesophageal junction. *Am J Surg* 2004; **188**: 39-44
66 **Scheffer RC**, Tatum RP, Shi G, Akkermans LM, Joehl RJ, Kahrilas PJ. Reduced tLESR elicitation in response to gastric distension in fundoplication patients. *Am J Physiol Gastrointest Liver Physiol* 2003; **284**: G815-G820
67 **Sarani B**, Chan T, Wise R, Evans S. Nissen fundoplication has a vagolytic effect on the lower esophageal sphincter. *Surg Endosc* 2003; **17**: 1206-1211
68 **Franzi SJ**, Martin CJ, Cox MR, Dent J. Response of canine lower esophageal sphincter to gastric distension. *Am J Physiol* 1990; **259**: G380-G385
69 **Blackshaw LA**, Grundy D, Scratcherd T. Vagal afferent discharge from gastric mechanoreceptors during contraction and relaxation of the ferret corpus. *J Auton Nerv Syst* 1987; **18**: 19-24
70 **Piessevaux H**, Tack J, Wilmer A, Coulie B, Geubel A, Janssens J. Perception of changes in wall tension of the proximal stomach in humans. *Gut* 2001; **49**: 203-208
71 **Tack J**, Sifrim D. A little rest and relaxation. *Gut* 2000; **47**: 11-12
72 **Wijnhoven BP**, Salet GA, Roelofs JM, Smout AJ, Akkermans LM, Gooszen HG. Function of the proximal stomach after Nissen fundoplication. *Br J Surg* 1998; **85**: 267-271
73 **Vu MK**, Straathof JW, v d Schaar PJ, Arndt JW, Ringers J, Lamers CB, Masclee AA. Motor and sensory function of the proximal stomach in reflux disease and after laparoscopic Nissen fundoplication. *Am J Gastroenterol* 1999; **94**: 1481-1489
74 **Negre JB**. Post-fundoplication symptoms. Do they restrict the success of Nissen fundoplication? *Ann Surg* 1983; **198**: 698-700
75 **Stipa S**, Fegiz G, Iascone C, Paolini A, Moraldi A, de Marchi C, Chieco PA. Belsey and Nissen operations for gastroesophageal reflux. *Ann Surg* 1989; **210**: 583-589
76 **Lundell L**, Myers JC, Jamieson GG. The effect of antireflux operations on lower oesophageal sphincter tone and postprandial symptoms. *Scand J Gastroenterol* 1993; **28**: 725-731
77 **Wyman JB**, Dent J, Heddle R, Dodds WJ, Toouli J, Downton J. Control of belching by the lower oesophageal sphincter. *Gut* 1990; **31**: 639-646

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