Brain meets gut: gastroesophageal reflux

Ronald F. Pfeiffer, M.D.
Department of Neurology, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Address correspondence and reprint requests to Ronald Pfeiffer, M.D., Department of Neurology, University of Tennessee, Memphis, 855 Monroe Ave., Room 415, Memphis, TN 38163-4901, USA.
Tel: 901 448-6661; Fax 901 448-7440
rpfeiffer@utmem.edu

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The first reflex for a neurologist is to assume that the word “reflux” is simply misspelled and to attach to it adjectives such as patellar or palmental, rather than gastroesophageal. The worlds of the neurologist and the gastroenterologist, however, are more closely intertwined than is commonly realized, as is readily evident when the pathophysiologic basis of gastroesophageal reflux is investigated.

Gastroesophageal reflux disease is an extremely common phenomenon that affects at least 20% of the population [1] and probably much more, because many persons who have gastroesophageal reflux disease are misdiagnosed because they experience symptoms other than “heartburn,” such as noncardiac chest pain, cough, hoarseness, and even asthma [1]. The concept of nonerosive reflux disease, in which acid in the esophagus may produce symptoms of esophagitis without visible esophageal injury [1], extends the concept of reflux-mediated dysfunction still further.

It is accepted that tonic contraction of the lower esophageal sphincter is primarily responsible for preventing reflux of acidic gastric components into the esophagus [2], but evidence suggests that the crural diaphragm may also play an important role [3]. It has been shown that decreased lower esophageal sphincter pressure alone does not result in reflux, but that relaxation of both the lower esophageal sphincter and the crural diaphragm are necessary for reflux to occur [4]. Lower esophageal sphincter relaxation occurs with swallowing, but it also occurs with gastric distension, apparently by means of a different neural circuit [5]. Distension of gastric mechanoreceptors triggers what has been termed transient lower esophageal sphincter relaxation (TLESR), and this is the almost exclusive mechanism for gastroesophageal reflux in healthy persons [6,7]. In persons with gastroesophageal reflux disease, the picture is less homogeneous, but TLESR still accounts for 65% of reflux events [7].

What, then, controls lower esophageal sphincter tone, and by what mechanism is TLESR carried out? Control of lower esophageal sphincter function may involve muscular [8] and hormonal [9] factors, but neuronal regulation of the lower esophageal sphincter seems to be of primary importance [10]. The enteric nervous system is most probably the final common pathway for regulation of lower esophageal sphincter function, but it integrates signals from the central nervous system. Although central nervous system control of lower esophageal sphincter function involves sympathetic and parasympathetic input both, most attention has centered on the parasympathetic component.

Afferent fibers from the distal esophagus and lower esophageal sphincter ascend to the nucleus tractus solitarius, whereas efferent fibers travel to the lower esophageal sphincter from the dorsal motor nucleus of the vagus complex. Two distinct sites in the dorsal motor nucleus of the vagus complex seem to be important for lower esophageal sphincter function: one site, rostral to the obex, is responsible for increasing lower esophageal sphincter pressure; the other, caudal to the obex, signals the lower esophageal sphincter to relax [11,12].

A considerable amount of data has accumulated on the neurochemical basis of this anatomic circuitry. Preganglionic vagal motor output is cholinergic; these neurons, then, stimulate either excitatory postganglionic motor neurons that evoke muscarinic-mediated lower esophageal sphincter contraction [12] or inhibitory motor neurons that evoke either nitric oxide– [13,14] or vasoactive intestinal polypeptide–related [12] lower esophageal sphincter relaxation. This contingent of neurotransmitters opens the door for an array of potential neuropharmacologic approaches to manipulation of lower esophageal sphincter function.

In gastroesophageal reflux disease, evidence seems to indicate that the primary problem is not within the lower esophageal sphincter itself, but with the neural regulation of lower esophageal sphincter function. Moreover, vagal nerve–mediated dysfunction in gastroesophageal reflux disease is not caused simply by local, acid-instigated damage to
nerve endings at the lower esophageal sphincter level, but by dysfunction at a more central level because a significant proportion, perhaps up to 40%, of persons with gastroesophageal reflux disease, also displays abnormal cardiovascular function [8,15].

Campos et al. [16] propose that control of lower esophageal sphincter function and reflux may not be mediated solely through parasympathetic pathways, and they suggest a role for sympathetic involvement [16]. Sympathetic innervation of the lower esophageal sphincter occurs primarily by means of splanchnic pathways [12]. Blackshaw et al. [17] showed that splanchnic stimulation reduces lower esophageal sphincter pressure, but a more recent report by Staunton et al. [18] from the same laboratory indicated that splanchnic pathways do not seem to be important in the triggering of TLESR by gastric distension, possibly because they have a higher threshold than do gastric vagal mechanoreceptors. The suggestion by Campos et al. [16] that diminished sympathetic activity may be related to more severe gastroesophageal reflux is interesting.

Other reports [19,20] have provided evidence for the involvement of additional neurotransmitters in the regulation of lower esophageal sphincter pressure. Baclofen, a γ-aminobutyric acid B receptor agonist, reduces both TLESR and gastroesophageal reflux. Whether this effect is mediated by means of gastric mechanoreceptors [20] or at a brain stem level [19] is not certain. A role has also been proposed for cholecystokinin A in the reflex pathway that mediates TLESR induced by gastric distension [21,22].

What does this mean for practicing clinicians? The idea that gastroesophageal reflux disease may be a neurologic problem, perhaps even caused by central nervous system dysfunction at a brain stem level, will be a surprising revelation. More important, the expanding and amazing array of neurotransmitters apparently involved in regulation of lower esophageal sphincter function potentially opens the door for new and more effective treatment approaches for this very common neurogastroenterologic problem.

References