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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Is the Lower Esophageal Sphincter Tone Related to a Gas?

Sphincters are placed at critical locations in the gastrointestinal tract, where they separate adjoining regions with distinct functions (eg, the lower esophageal sphincter [LES] between the esophagus and stomach). Sphincters are generally 2-way valves and control the direction of movement of luminal contents. Under resting conditions, sphincters maintain tonic closure for compartmentalization, as in the case of the LES, which prevents movement of gastric contents into the esophagus (reflux). With swallowing, the LES opens briefly for esophageal emptying into the stomach. The LES also can open to allow gastric contents to enter the esophagus, as happens with belching and vomiting. Understanding what maintains tonic closure and what causes opening of the sphincters is of fundamental importance from a basic physiology point of view as well as a disease perspective. For example, low LES tone or intermittent transient LES relaxation leads to reflux disease, while failure of LES relaxation leads to achalasia esophagus and possibly other esophageal motor disorders. Generally, sphincters are thought of as muscle cells organized as rings, although recent studies from our laboratory have shown that the LES muscle fibers are organized in the shape of a "purse string"; the muscle fibers from the ventral and dorsal surface of the esophagus cross the midline at the angle of HIS and continue into the stomach as sling fibers or the inner oblique muscle layer of the stomach.[1]

Contraction in skeletal muscle is the result of neural drive and neurotransmitter release (acetylcholine) at the neuromuscular junction. The LES, however, is smooth muscle and its tone, although modulated by endocrine, paracrine, and neural influences, largely is owing to unique myogenic properties intrinsic to the muscle, such that isolated muscle strips in a muscle bath maintain tone even in the absence of all nerve activity and endocrine stimuli. The genesis of intrinsic myogenic tone has intrigued many investigators. Earlier studies have suggested that the source of intracellular calcium (crucial for muscle contraction) is different for esophagus and the LES, being extracellular for esophagus and intracellular (endoplasmic reticulum) for the LES. There also are differences in calmodulin, myosin light chain kinase, and caldesmon, which are lower in the LES compared with the esophagus.[2] Recent studies also have shown differences in the RhoA/ROCK pathway in phasic vs tonic muscles.[3] The critical intracellular step in the contraction of smooth muscle is the phosphorylation of myosin light chain (MLC) through the kinase MLC, which induces contraction. MLC then is dephosphorylated by MLC phosphatase, resulting in muscle relaxation. The critical difference between a phasic and tonic muscle is that RhoA/ROCK machinery is more active in the tonic muscles, similar to the internal anal sphincter and LES. The activation of RhoA/ROCK by intracellular calcium (also known as calcium sensitization) leads to inhibition of MLC phosphatase, resulting in a sustained increase of phosphorylated MLC, which induces a sustained or tonic contraction. Known extracellular signals that activate RhoA/ROCK are products of the renin angiotensin system (angiotensin 2) and the arachidonic acid pathway (thromboxane A_2 and prostaglandin $F_2\alpha$).[4] A product of inflammation, platelet activating factor, is also a major regulator of LES tone.[5]

Xiaopeng Bai et al[6] studied hydrogen sulfide (H_2S), possibly an important physiological neurotransmitter in the gastrointestinal tract, in the maintenance of LES tone. Isometric contraction (force) in the circular smooth muscle strips of porcine LES were recorded while cytosolic Ca^2+ concentration ($[Ca^2+]i$) in fura-2–loaded strips was measured simultaneously with a front-surface fluorimeter. The effects of inhibiting H_2S-generating enzymes (cystathionine-β-synthase [CBS], cystathionine-γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase [3MST]) on LES function was studied. The investigators found that the myogenic LES basal tone was inhibited by aminooxyacetic acid (AOA, a CBS inhibitor) and L-aspartic acid (L-Asp, a 3MST inhibitor), but not by DL-propargylglycine (a cystathionine-γ-lyase inhibitor). The inhibitory effects of AOA and L-Asp are additive. Immunohistochemistry showed that CBS and 3MST, but not CSE, were expressed in the circular and longitudinal muscles of the LES. The inhibitory effects of H_2S blockade were accompanied by a decrease in$[Ca^2+]i$ and an increase in extracellular Na^+, suggesting involvement of the Na^+/Ca^{2+} exchanger (NCX). The reduction in the [Ca2+]i level by H_2S inhibition was augmented significantly in the antral smooth muscle sheets of NCX transgenic mice compared with wild-type mice. These studies suggest that H_2S, which is endogenously present in the muscle, acts via NCX to maintain basal [Ca2+]i, which is partly responsible for LES myogenic tone.

There were several limitations to this study. If one presumes that H_2S indeed is responsible for maintenance of LES tone, it is not clear why, sodium hydrogen sulfide (NaHS) induced a biphasic response, an initial relaxation followed by contraction. It also is not clear why biphasic responses were not seen with enzyme inhibitors and why L-cystin did not reverse the effects seen when 1 mmol/L AOA and 3 mmol/L L-Asp were applied simultaneously. The intracellular calcium and LES muscle force curves show a greater reduction in calcium compared with the force, but it is not clear why. These studies also showed only a 30% reduction in LES tone with inhibitors of H_2S, suggesting that it does not account for the entire myogenic tone. Finally, factors that stimulate and inhibit intracellular H_2S production require further investigation.

In summary, the investigators need to be congratulated for studying a completely novel pathway for the maintenance of LES tone. It is clear that more work is in order.

Disorders of the LES are major motility disorders and it is possible that H_2S-generating enzymes are potential therapeutic targets in their treatment.

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Conflicts of interest
The author discloses no conflicts.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2017.12.006