

Mechanism of Heartburn Symptom Generation

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Although assessment of symptoms is a part of the foundation of clinical medicine, the mechanisms of symptom manifestation have not been adequately elucidated. Heartburn is known as a typical symptom for GERD, and one of most frequently encountered visceral symptoms in clinical setting. In the past, it was thought that the symptoms of heartburn were perceived by the reflux esophagitis (RE) patient through a mechanism in which acid and pepsin penetrated the esophageal mucosa through visible breaks in it, noxious stimuli from those materials spread in the mucosa and directly activated nociceptive receptors in deep layers of the mucosa, and the resulting signals were transmitted to the central nervous system (conventional acid penetration theory). For this mechanism to explain the symptoms, injury to the barrier represented by the surface of the esophageal mucosa must allow the acid or other noxious stimuli to easily penetrate the deep layers of the mucosa. In addition, dilated intercellular spaces (DIS) in esophageal mucosa are a characteristic finding in GERD patients, which allows the noxious stimuli to spread widely and rapidly in the mucosa and easily reach the corresponding nociceptive receptors.

However, it is clear that this acid penetration theory alone cannot possibly explain the mechanism of heartburn. The most obvious contradictory evidence is the existence of patients with NERD. The heartburn symptoms of NERD patients are as severe as those of patients with erosive reflux disease (RE), but their intra-esophageal acid exposure time is significantly less than that of RE patients. Since endoscopically visible mucosal breaks are absent in NERD patients, it seems unlikely that acid penetrates their esophageal mucosa. Furthermore, in the experimental animals, the intercellular spaces are dilated in the deep layers of the esophageal mucosa and they are not observed on the esophageal surface. Considering that DIS are seen in deep layers of the esophageal mucosa and in NERD patients with little acid reflux, it may be necessary to approach the causes of heartburn symptoms from a new conceptual framework. That is, the activation of nociceptive receptors by noxious stimuli may be indirect. Indeed, using a rat model of reflux esophagitis, researchers have shown that rather than acid directly damaging esophageal mucosal epithelium, such damage was mediated by a neuroimmunological mechanism involving secretion of IL8 and IL1 β from the esophageal mucosal epithelium. In addition, we have reported recently that PGE2 is a pivotal mediator for heartburn. Rather than being caused by penetration of acid, heartburn symptoms may result from indirect activation of nociceptive receptors by some other mechanisms. In my talk, I will present mechanism of heartburn symptom generation based on this viewpoint.