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Editorial

Can Acute Stress Cause Esophageal Hypersensitivity in Healthy Individuals?

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Article: Intravenous corticotropin releasing hormone administration increases esophageal electrical sensitivity in healthy individuals
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Stress exacerbates heartburn symptoms in gastroesophageal reflux disease (GERD) patients and also affects visceral sensitivity.[1] The mechanism of visceral hypersensitivity in functional gastrointestinal disorders and functional heartburn remains unclear. However, the involvement of stress in relation to esophageal sensitivity has been reported.[1,2] Fass et al[3] demonstrated that GERD patients who were exposed to acute auditory stress experienced increased levels of heartburn induced by intraesophageal acid perfusion, and the stress from disturbed sleep has also been shown to cause similar esophageal hypersensitivity.

In the revised Rome IV criteria, functional esophageal disorders include functional chest pain, functional heartburn, reflux hypersensitivity, globus, and functional dysphagia.[4] The Rome IV adopts a more rigorous definition of GERD. GERD patients are subgrouped as erosive esophagitis, non-erosive reflux disease (NERD), reflux hypersensitivity, and functional heartburn.[4] The pathophysiology of erosive esophagitis and NERD is the result of pathologic acid exposure in contrast to the functional disorders that are related to esophageal hypersensitivity. Esophageal hypersensitivity is one of the important mechanisms in GERD patients who are refractory to acid-suppressive therapy.[5] There is an association between distal esophageal acid exposure and esophageal hypersensitivity among the reflux-related disorders.

Esophageal pain can be induced by mechanical distension, chemical stimuli, and others. A high percentage of patients with functional chest pain reported pain after balloon distension of the esophagus.[6] Enhanced chemosensitivity in functional heartburn patients has also been reported.[7] Factors that influence visceral hypersensitivity in the esophagus, include stress, mucosal integrity, and microinflammation in the esophagus, though the mechanisms by which visceral hypersensitivity of the esophagus occurs are incompletely understood.[1]

Corticotropin-releasing hormone (CRH) plays a key role in the acute regulation of stress- and anxiety-related behaviors and in the regulation of endocrine responses during chronic stress via activation of the hypothalamic-pituitary-adrenal axis. Peripheral CRH is a key mediator of the gut stress response, and has been shown to influence visceral hypersensitivity in humans.[8] Stress affects esophageal motility. A previous study demonstrated that intravenous CRH administration enhanced esophageal sensitivity to mechani-

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cal distension, increased esophageal contractility, and decreased LES relaxation, therefore improving esophageal bolus clearance.[8] The changes after CRH administration in esophageal contractile properties may be associated with the increased sensitivity to balloon distention after CRH.

Stress is able to alter esophageal sensitivity. In this issue of the *Journal of Neurogastroenterology and Motility*, Yamasaki et al[9] demonstrated CRH administration increased esophageal electrical sensitivity in normal subjects, emphasizing the important role of stress in esophageal sensitivity. The results of this study were meaningful in studying the mechanisms of esophageal functional pain in refractory GERD or functional heartburn.

There is increasing evidence that esophageal hypersensitivity in patients with proton proton pump inhibitor (PPI)-refractory GERD symptoms is of a multisensory nature. Many solutions are suggested as the next therapeutic or diagnostic option in PPI-refractory NERD patients. Some of these patients proved to have functional heartburn and reflux hypersensitivity. Esophageal hypersensitivity will be a new therapeutic target in addition to PPIs for those patients.

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