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Editorial

The role of inducible nitric oxide synthase in the relaxation of lower esophageal sphincter in septic state

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Expression of inducible nitric oxide synthase in the lower esophageal sphincter of the endotoxemic opossum

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The lower esophageal sphincter (LES) plays a central role in regulating flow across the gastroesophageal junction, and transient LES relaxations are the main mechanism underlying gastroesophageal reflux. Nitric oxide (NO) has been shown to cause relaxation of the LES in various animals and humans.[1,2] NO is produced endogenously from L-arginine by nitric oxide synthase (NOS). Two major classes of NOS isoform have been identified. One class is a constitutive enzyme (cNOS) that is calcium dependent and is responsible for rapid biosynthesis of NO. cNOS is subdivided into two types: nNOS is present mainly in the neural tissue and eNOS is present mainly in the endothelium. The other class is an inducible enzyme (iNOS) that is independent of calcium and is present mainly in epithelia and immune cells such as macrophage.

Under normal physiological [lipopolysaccharide (LPS)-untreated] conditions, in which iNOS induction is minor, cNOS (nNOS and eNOS) is the principal isoform found in the LES.[3] That is, nNOS is localized to nonadrenergic noncholinergic (NANC) nerves in the myenteric plexus and smooth muscle cells of the LES,[4] whereas eNOS is localized to smooth muscle cells.[5] Of these, nNOS rather than eNOS is the enzymatic source of the NO that mediates NANC relaxation of the LES.[6]

It is well known that LPS treatment in vivo induces iNOS, which releases large amounts of NO continuously in many tissues. In addition, a recent study[7] has demonstrated that LPS caused a highly significant increase in the relative expression of iNOS in the LES of the opossum. Furthermore, in the same study,[7] it was shown that LPS caused a dose-dependent fall in the basal tone of the LES. The authors suggested that an LPS-induced fall in the basal tone of the LES may be associated with an increase in iNOS expression by the following evidence. First, LPS caused a selective increase in iNOS protein and mRNA in the LES without significant changes in the expression of other NOS isozymes. Second, observed change in the basal tone in the LES was blocked by the simultaneous administration of the iNOS inhibitor L-canavanine and LPS. In this issue of the *Journal of Gastroenterology*,[8] Park et al. confirmed this result, showing that treatment of opossum with LPS induced a significant increase in expression of iNOS protein and mRNA in LES muscle tissue. Furthermore, the same authors demonstrated previously that LES pressure was significantly decreased in vivo after exposure to LPS, using esophageal manometry in opossum, and that aminoguanidine, a selective inhibitor of iNOS, attenuated this decrease in LES pressure.[9] Taken together, these results show that NO induced by iNOS can actually affect the smooth muscle cells of LES, leading to a decrease in LES pressure in vivo, although the precise localization of iNOS in the LES has not been demonstrated. These studies also suggest that, whatever the source, NO can relax the LES in vivo. A recent study has demonstrated that an abundant amount of NO is formed at the gastroesophageal junction in human by the rapid chemical reaction of nitrite in saliva with acidified gastric juice.[10] NO thus formed in the lumen may also be sufficient to penetrate the epithelium of the gastroesophageal junction and then affect the inner smooth muscle cell of the LES.

Endotoxemia and sepsis are frequently associated with clinical symptoms of abnormal motility of the gastrointestinal tract such as nausea, vomiting, ileus, and diarrhea.[11] Previous studies have suggested that endotoxemia following the administration of LPS leads to an increase in intestinal transit and decrease in gastric emptying. The relaxation of the gastric fundus by NO produced by iNOS is one of the important factors in delaying gastric emptying in the LPS-treated rat.[12] In human, NO derived from iNOS may also contribute to the disturbed gastrointestinal smooth muscle function

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seen in inflammatoy states or sepsis, although how the relaxation of the LES caused by the iNOS-derived NO during sepsis can be relevant to the gastroesophageal reflux remains to be clarified. Interestingly, esophagitis has been reported to be the most frequent cause of upper gastrointestinal bleeding in critically ill patients, some of whom are in sepsis, in an intensive care unit.[13] The mechanism of iNOS induction in sepsis may partly contribute to the development of esophagitis in this patient group.

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