Toward a better understanding of the role of *Helicobacter pylori* infection as a cause of dyspepsia

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ARTICLE

Bercik P, De Giorgio R, Blennerhassett P, Verdu EF, Barbara G, Collins SM. Immune-mediated neural dysfunction in a murine model of chronic *Helicobacter pylori* infection. *Gastroenterology* 2002;123:1205-15.

SUMMARY

The relationship between gastric inflammation caused by *Helicobacter pylori* infection and symptoms of dyspepsia remains controversial (1). Using a murine model of gastric infection, Bercik et al provide new insights into the mechanism underlying such interactions. Gastric sections from Balb/c mice infected with *H pylori*, strain SS-1, were used for both histological evaluation and studies of neuromuscular physiology. Acute infection (two weeks) caused an antral-predominant polymorphonuclear cell infiltrate that was superceded by a corpus-predominant mononuclear and macrophage infiltrate in chronic infection (three to 16 months).

Contractility in excised antral muscle strips was measured following administration of either carbachol or potassium chloride or muscle electric field stimulation. Acute infection increased carbachol- and potassium chloride-stimulated contractility, which returned to normal during chronic infection. Neural electric field stimulation induced a greater degree of muscle relaxation during chronic infection compared with uninfected controls. As antral muscle is under tonic neural inhibitory control, the authors noted that this enhanced relaxation suggests the presence of increased neural inhibition, decreased neural excitation or both.

The release of acetylcholine was diminished in response to neural electric field stimulation during chronic *H pylori* infection, whereas potassium chloride-stimulated acetylcholine release was enhanced. These findings led the authors to suggest that abnormal neural function is due to altered acetylcholine release rather than impaired acetylcholine synthesis or storage.

Immunostaining of gastric sections showed increased density, but no change in the distribution, of substance P, calcitonin gene-related peptide and vasoactive intestinal peptide nerve fibres in chronically infected mice. Substance P and calcitonin gene-related peptide, but not vasoactive intestinal peptide, containing nerve fibre densities also were increased in the spinal cord following chronic gastric infection.

Severe combined immunodeficiency (SCID) mice, which lack both B and T lymphocytes, were colonized with a moderate to high bacterial load, but did not demonstrate cholinergic nerve dysfunction, suggesting that the host immune response is important in producing neuromuscular dysfunction. Following *H pylori* eradication, using standard triple therapy, mucosal inflammation was reduced and this was accompanied by a return of neuromuscular parameters towards control values.

COMMENTS

Dyspepsia is a prevalent symptom affecting millions of Canadians (2). The underlying cause of symptoms is not known, but a variety of pathogenic factors have been postulated. These include gastric dysmotility, visceral hypersensitivity, psychological factors and, more recently, *H pylori* infection. It has been proposed that a bacterial infection causes neuromuscular alterations that manifest as functional lower gastrointestinal tract symptoms (so-called irritable bowel syndrome) (3). However, the precise role of *H pylori* infection and resulting gastric mucosal inflammation in nonulcer dyspepsia remains controversial. Three meta-analyses that addressed the relationship between *H pylori* infection and dyspepsia yielded conflicting results (4-6). Moreover, gastric motor function abnormalities are not consistently demonstrated in dyspeptic patients with *H pylori* infection (7,8).

Both human and animal studies demonstrate a link between mucosal inflammation and changes in sensory-motor function in the small intestine and colon (9). However, little attention had previously been given to the stomach (10). Bercik et al demonstrated altered neuromuscular function in the stomach and changes in spinal neuropeptide expression associated with chronic inflammation induced by *H pylori* infection in mice. These changes were largely reversed two months after eradication of *H pylori*. The observation that gastric and spinal substance P and calcitonin gene-related peptide immunoreactivity levels only partially returned to normal could explain why clinical trials do not always show that symptoms respond to *H pylori* eradication.

Host immune responses appear to be essential to initiating neuromuscular dysfunction in chronic *H pylori* infection. For example, acetylcholine release correlates with the degree of mononuclear infiltration in Balb/c mice. In contrast, there is an absence of acetylcholine release in *H pylori*-infected SCID mice despite moderate to high levels of bacterial colonization. *H pylori* infection leads to the release of chemokines and

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cytokines by epithelial cells and subsequent recruitment of immune cells (11). Evidence that pro-inflammatory cytokines, such as interleukin (IL)-1 β and IL-6, suppress acetylcholine release from nerve terminals (12), suggests a possible mechanism for the observations of Bercik et al. In addition, because the cells of the enteric nervous system lie in close proximity to immune cells, inflammatory mediators released during infection, such as bradykinin and prostanoids, could mediate neuropeptide release, thereby sensitizing afferent nerve endings, in turn resulting in abnormal sensory perception (10). Visceral hyperalgesia, or increased perception to noxious stimuli, is frequently observed in subjects with dyspepsia (13,14). Bercik et al demonstrated that *H. pylori* causes an increase in the densities of gastric and spinal nerve fibres containing substance P and calcitonin gene-related peptide, which are important in mediating visceral hyperalgesia. The mechanisms underlying these

observations, however, still remain to be elucidated. It is possible that neurotrophins like nerve growth factor may play a role in promoting nerve growth in inflammatory states (15).

Future studies in animals should employ specific targeted gene knockouts (eg, IL-6), modulation of neurotransmitter and cytokine signaling pathways with highly specific pharmacological agonists and antagonists, and infection of animals with *H. pylori* strains lacking specific putative virulence factors (eg, Cag A, Cag E, and Vac A) to clearly delineate the role of both bacterial and host factors in gastric dysmotility and dyspepsia in the absence of mucosal ulceration.

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