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THEORETICAL ARTICLE

Protective effects of *Helicobacter pylori* against gastroesophageal reflux disease may be due to a neuroimmunological anti-inflammatory mechanism

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There is some evidence that *Helicobacter pylori* infection has a protective effect against gastroesophageal reflux disease (GORD) and its complications such as Barrett's oesophagus and oesophageal adenocarcinoma. In this paper, we propose that a neuroimmunological mechanism is responsible for the protective effect of *H. pylori* on GORD. *H. pylori* infection of the gastric mucosa induces a T helper1-like immune response and production of pro-inflammatory cytokines. These cytokines can inhibit local sympathetic tone, whereas they increase systemic sympathetic tone. Increased sympathetic tone can induce an anti-inflammatory milieu, which in turn can inhibit inflammation in the oesophagus and lower oesophageal sphincter (LOS). Furthermore, *H. pylori* infection may stimulate the cholinergic anti-inflammatory pathway. It has been suggested that reflux-induced oesophageal inflammation plays an important role in the pathogenesis of reflux oesophagitis. Reduction of oesophageal inflammation by increased systemic sympathetic tone and vagal activity may lead to a decrease in reflux-induced oesophageal injury and LOS dysfunction in GORD.
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Gastroesophageal reflux disease (GORD) is a common disease entity in which gastric juice gains access to the oesophagus via an incompetent lower oesophageal sphincter (LOS).[1,2] The presence of refluxed materials induces different grades of oesophageal damage, ranging from low- to high-grade oesophagitis.[2] GORD is a risk factor for oesophageal adenocarcinoma, a rare cancer whose incidence is increasing.[3] The most common factor in the aetiology of GORD is disturbed LOS function. Dysfunction of the LOS occurs via one of several mechanisms, the most common being an increase in the number of transient LOS relaxations, and the second most common being a permanent decrease in LOS pressure.[4]

Oesophageal acid loads seem to be one of the major causes of oesophageal mucosal damage.[2] However, the severity of reflux oesophagitis cannot be accurately predicted simply on the basis of acid exposure, suggesting that other damaging factors or, possibly, impaired mucosal resistance, are also involved in reflux oesophagitis.[2] The importance of mucosal resistance and oxidative stress in the pathogenesis of GORD has been shown.[2,5–7]

Helicobacter pylori infection is recognized to be the most important acquired factor in the aetiology of ulcers of the stomach and duodenum.[8] The type of inflammation induced by *H. pylori* is commonly termed 'chronic active inflammation'. In *H. pylori*-induced inflammation, the antrum is consistently involved, whereas inflammation in the acid-secreting gastric body and fundus is more variable.[9] In spite of some contradictory reports, there is substantial evidence that *H. pylori* infection, especially infection with virulent strains of *H. pylori*, has a protective effect against GORD and its complications such as Barrett's oesophagus and oesophageal adenocarcinoma.[8,10–13]

To date, the mechanisms that have been suggested for the protective effect of *H. pylori* against gastroesophageal reflux include an increase in the production of ammonia, hypochlorhydria associated with gastric atrophy and increased production of protective prostaglandins, change in lifestyle and weight gain and consumption of acid-reducing agents during *H. pylori* infection.[14] In addition, Budzynski *et al.*[15] suggested that *H. pylori*-induced greater autonomic nervous system activity may explain the decrease in the number of gastroesophageal reflux episodes in patients infected with *H. pylori*.

The present paper proposes a neuroimmunological mechanism for the protective effects of *H. pylori* against GORD.

HYPOTHESIS

H. pylori infection of the gastric mucosa induces a T helper1 (Th1)-like immune response and production of the pro-inflammatory cytokines tumour necrosis factor α (TNF-α), interleukin (IL) 1β, IL-6 and IL-8[16] (Figure 1). Any immune challenge that threatens the stability of the internal milieu can be regarded as a stressor, that is

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under certain conditions; an immune response can activate the stress system.

The sympathetic nervous system (SNS) is characterized by a continuous discharge of neural activity, the so-called sympathetic tone. It seems that an inflammatory/immune response to components of *H. pylori* may actually increase sympathetic tone, as other stressors or stimuli do.[17] It has been shown that interferon α, tumour necrosis factor-α, IL-1 (especially IL-1β) and IL-6 can signal the brain to trigger the activation of both SNS and hypothalamus–pituitary–adrenal axis through a complex corticotropin-releasing hormone-dependent pathway.[17] Thus, the SNS, similar to hypothalamus–pituitary–adrenal axis, is involved also in a long feedback loop between lymphoid organs and central nervous system. The afferent limb of this loop seems to be operated by blood-borne cytokines, which activate the central components of the stress system via circulation or through the vagus nerve afferents. The efferent loop consists of the SNS, its projections to different organs and the release of norepinephrine from the sympathetic nerve terminals in these organs.[17] Although the above-mentioned cytokines trigger centrally the sympathetic output, which results in an increase of norepinephrine turn over in several organs, it has been shown that they inhibit SNS activation in the place of administration, so the local effect of these cytokines might be absolutely different.[17] Therefore, the pro-inflammatory cytokines produced by inflammatory response against *H. pylori* can inhibit local sympathetic tone, whereas they increase systemic sympathetic tone[17] (Figure 1). Since antigen-presenting cells carry *H. pylori* antigens to secondary lymphoid tissues, where they activate naive T lymphocytes,[18] there is a Th1-type and pro-inflammatory milieu both at the sites of infection and in the secondary lymphoid tissues to which *H. pylori* antigens are carried. Therefore, during infection by *H. pylori*, there is a reduction in sympathetic tone at the infection site (gastric wall) and in secondary lymphoid tissues, accompanied by an increase in tone elsewhere, including the LOS.

Increased sympathetic tone can induce an anti-inflammatory milieu[17] in the tissues (including the oesophagus and the LOS), with the exception of the sites of *H. pylori* infection and secondary lymphoid tissues through following mechanisms:

There are many indications showing that norepinephrine and epinephrine, inhibit the production of type 1/pro-inflammatory cytokines, such as IL-12, tumour necrosis factor-α and IFN-γ by antigen-presenting cells and Th1 cells through stimulation of the β2-adrenoreceptor–cAMP–protein kinase A pathway, whereas they stimulate the production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β. Also it has been shown that stimulation of SNS can induce regulatory (suppressor) T lymphocytes and attenuate immune responses. Different adrenoreceptors are known as molecules responsible for the induction of regulatory T lymphocytes and increasing the T regulatory (suppressor) vs T helper and T regulatory (suppressor) vs T cytolytic ratios.[19,20] Through above-mentioned mechanisms, endogenous catecholamines may act systemically to cause a selective suppression of pro-inflammatory responses, and result in a dominance of anti-inflammatory responses.[17] Therefore, the systemic increased sympathetic tone can inhibit inflammation in all tissues (including the oesophagus and the LOS), with the exception of the sites of *H. pylori* infection and secondary lymphoid tissues, where there is a decreased sympathetic tone (Figure 1).

It has been suggested that reflux-induced oesophageal inflammation plays an important role in the pathogenesis of reflux oesophagitis. It has been shown that pro-inflammatory cytokines induce neutrophil accumulation and oxygen radical-mediated tissue damage.[21] In addition, recent evidence suggests that pro-inflammatory cytokines, such as IL-1β and IL-6, may be implicated in dysfunction of the LOS, because they reduce oesophageal muscle contractility.[22] Thus, reduction of oesophageal inflammation by *H. pylori*-induced increased systemic sympathetic tone may lead to a decrease in reflux-induced oesophageal injury and LOS dysfunction in GORD (Figure 1). Moreover, *H. pylori*-induced increased sympathetic tone may inhibit the development of a non-pre-existing GORD by means of the following mechanism. Because pro-inflammatory cytokines reduce oesophageal

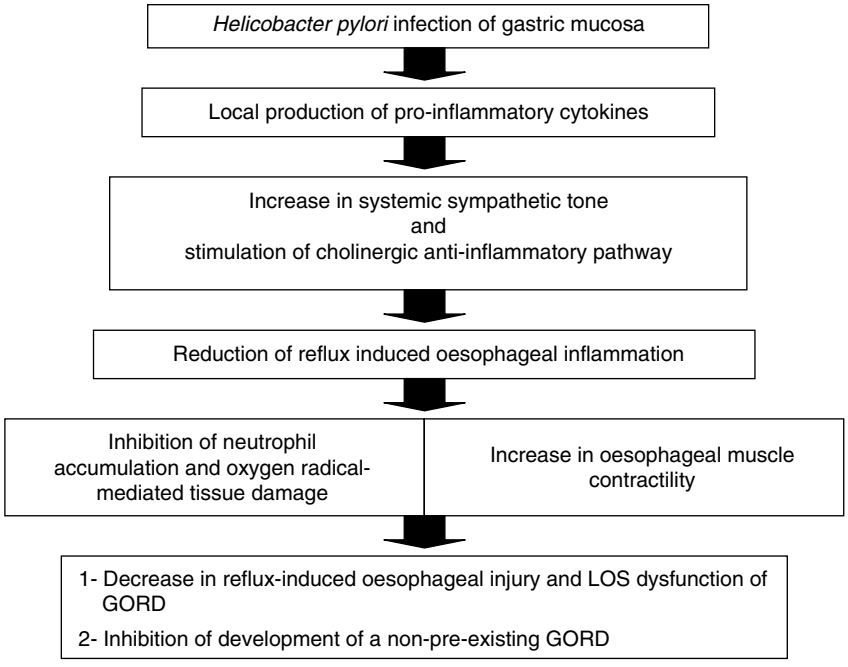

Figure 1 An algorithm which shows the proposed mechanism for the protective effects of *H. pylori* infection against GORD.

muscle contractility, it seems that when the refluxed gastric juice comes into contact with the oesophageal mucosa, induction of a pro-inflammatory process in the oesophageal wall can intensify LOS dysfunction and promote the development of GORD. Inhibiting the induction of the pro-inflammatory process by increasing sympathetic tone may block this positive feedback and prevent the development of GORD. Thus, the rate of GORD development will be lower in persons with *H. pylori* infection than in those without this infection.[11] Furthermore, this could be the mechanism by which slight decreases in sympathetic function in patients with GORD[23] correlate with the pathogenesis of this disease.

In addition to stimulating the SNS, *H. pylori* infection may also stimulate the cholinergic anti-inflammatory pathway. *H. pylori*-derived lipopolysaccharide and *H. pylori*-induced pro-inflammatory cytokines may stimulate vagal sensory neurons (Figure 1), which in turn may stimulate vagal efferent neurons, resulting in a decrease in the production of pro-inflammatory cytokines and inhibition of inflammation in the visceral organs, including the oesophagus[24] (Figure 1). The above-mentioned mechanisms may be responsible for the protection against GORD that results from inhibition of the pro-inflammatory process.

DISCUSSION

According to the suggested hypothesis, the protective effects of *H. pylori* infection against GORD can be attributed to the anti-inflammatory effects exerted by the increase in sympathetic tone and stimulation of the cholinergic anti-inflammatory pathway due to *H. pylori*-induced inflammation.

It has been shown that infection with the more virulent, cytotoxin-associated gene A (*cagA*)-positive strains of *H. pylori* and pro-inflammatory genotypes of the *IL*-1β gene are independently associated with protection against GORD.[25] Both of these factors can be responsible for the induction of a more severe pro-inflammatory immune response against *H. pylori* infection.[25] It has been suggested that the severe gastric inflammation caused by *cagA*-positive strains and pro-inflammatory genotypes of the *IL*-1β gene leads to gastric atrophy, and the resulting hypochlorhydria may protect against GORD.[25] The greater protection against GORD by *cagA*-positive strains of *H. pylori* and pro-inflammatory genotypes of the *IL*-1β gene can also be explained by our proposed hypothesis: the more extensive the pro-inflammatory response to *H. pylori* infection, the stronger the stimulation of the SNS and vagus nerve. Any increase in the activation of the SNS and vagus nerve will lead to more efficient inhibition of the inflammation in the oesophageal wall, resulting in greater protection against GORD. The differences between the different strains of *H. pylori*, as well as differences between different populations in the induction of inflammatory responses against *H. pylori* infection, may explain why some studies have not found *H. pylori* to exert protective effects against GORD.[26–29]

Budzynski *et al*.'s[15] finding that patients infected with *H. pylori* have greater sympathetic and parasympathetic tone than *H. pylori*-negative subjects, and their suggestion that the greater autonomic nervous system activity may explain the protective effects of *H. pylori* infection against GORD, may support this hypothesis.

According to the present hypothesis, *H. pylori* infection may have protective effects against GORD because the pro-inflammatory immune response plays an important role in both diseases. The protective effects of *H. pylori* infection on multiple sclerosis and Crohn's disease (CD)[30–34] two diseases for which pro-inflammatory cytokines have a key role in their pathogenesis,[35,36] may be due to the proposed mechanism. Stimulation of the SNS and the cholinergic anti-inflammatory pathway by *H. pylori* infection may lead to a reduction in the production of pro-inflammatory cytokines and result in alleviation of these autoimmune diseases. The relationships between *H. pylori* infection and GORD, multiple sclerosis and CD, are similar to the relationships between mycobacterial infection and some Th1-type autoimmune diseases, including multiple sclerosis and experimental autoimmune encephalomyelitis (an animal model for multiple sclerosis). Both mycobacterial infection and the above-mentioned autoimmune diseases induce Th1 immune responses and pro-inflammatory cytokines, but it has been shown that mycobacterial infection alleviates the symptoms of these autoimmune diseases.[37–41] We previously hypothesized that the anti-inflammatory effects of mycobacterial infection-induced increased systemic sympathetic tone may explain the modulation of these autoimmune diseases by mycobacterial infection.[37,38] Although, in the present article, we have proposed that our hypothesis could explain the protective effects of *H. pylori* infection against GORD, we believe that it is not the only mechanism and that other mechanisms also play a role.

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