ROLE OF VAGAL NERVE IN DEFENCE MECHANISMS AGAINST NSAID-INDUCED GASTROINTESTINAL MUCOSAL DAMAGE

G. MÓZSIK, O.M.E. ABDEL-SALAM, B. BÓDIS, O. KARÁDI, L. NAGY and J. SZOLCSÁNYI
First Department of Medicine and Department of Pharmacology, Medical University of Pécs, H-7643, Pécs, Hungary

ABSTRACT

Many papers suggested only an aggressive role of the vagus nerve on the gastrointestinal (GI) mucosa; however, the essential role of the vagus nerve was proven in GI mucosal defence against different chemicals, e.g. ethanol, HCl, non-steroidal anti-inflammatory drugs (NSAIDs). In order to evaluate the role of the vagus nerve in the development of GI mucosal damage evoked in the rat by the administration of NSAIDs, the present studies were designed to: (1) compare the changes in the NSAID-induced GI mucosal damage after acute surgical and chemical (atropine treatment) vagotomy; (2) investigate the effect of sensory nerve stimulation and chemical deafferentation on the NSAID-induced gastric mucosal damage; (3) evaluate the cytoprotective action of prostacyclin under the above experimental conditions; (4) study the effect of surgical vagotomy on the gastroprotection induced by different drugs.

Gastric mucosal damage was produced by intragastrically (acidified salicylates) or systemically (indomethacin) applied NSAIDs, while the small intestinal and large bowel mucosal injury was produced by systemic indomethacin application.

Results. (1) acute surgical vagotomy aggravated, whereas, chemical vagotomy prevented the GI mucosal damage produced by topically and systemically applied NSAIDs; (2) indomethacin produced significantly more damage in the small intestine than in the large bowel and stomach (order is small intestine > stomach > proximal colon) which is aggravated by acute surgical vagotomy in all these areas of the GI tract; (3) stimulation of capsaicin-sensitive sensory nerves with the capsaicin analogue resiniferatoxin protected against gastric mucosal damage by acidified salicylates and indomethacin; (4) chemical deafferentation enhanced the aspirin-induced gastric mucosal injury, while it did not interfere with the prostacyclin-induced gastric cytoprotection; (5) the mucosal protective effects of PGI2, atropine, cimetidine, sucralfate and scavengers (β-carotene) disappeared after acute surgical vagotomy.

Keywords: atropine, capsaicin-sensitive sensory nerves, gastric acid secretion, GI mucosa, H+ back-diffusion, mucosal PG2 and PGI2, mucosal biochemistry, NSAIDs, surgical vagotomy

INTRODUCTION
It is generally believed that the gastric mucosal damage is the result of the impaired balance between aggressive luminal factors and mucosal defence mechanisms. This can be clearly seen in different clinical circumstances such as Zollinger–Ellison syndrome, the use of NSAIDs and other mucosal damaging compounds. A role of the vagus nerve has been suggested in the development of gastric acid hypersecretion which in turn
suggested an aggressive role for the vagus nerve in the development of gastric mucosal injury. The observations in different experimental models also indicated that chemical vagotomy (atropine treatment) prevents or decreases the gastric mucosal damage due to vagal hyperactivity. Therefore, for long time, therapy of peptic ulcer disease aimed to reduce the so-called 'aggressive side' of the balance mainly HCl and pepsin secretion with antacids, antisecretory agents (anticholinergics, H₂-receptor antagonists) or with surgical vagotomy.

The role of the vagus nerve was proved in the development of the prostacyclin (PGI₂)-induced gastric mucosal protection in 1982, when we indicated that PGI₂-induced gastric cytoprotection was detectable in rats with intact vagus nerve; however, it disappeared after surgical vagotomy [1]. Similar data were obtained with regard to adaptive cytoprotection by Miller (1983) [2]. Observations made later indicated the same results in the different experimental circumstances after surgical vagotomy [3]. Recently, we demonstrated that the gastroprotective effects of PGI₂, atropine and cimetidine (both in cytoprotective and antisecretory doses) are not evident in surgically

(Peripheral mechanisms only)

CNS

Surgical vagotomy

Afferent nerves (CSSN)
1. Stimulation
2. Desensitization

Receptors
(Chemical vagotomy)

Stomach
Small intestine
Large bowel

Ach, pentagastrin, histamine

CSSN = capsaicin-sensitive sensory nerves

Figure 1. Schematic representation of the role of the vagus nerve in gastrointestinal mucosal damage and protection