ROLE OF HISTAMINE IN REGULATION OF BLOOD FLOW IN THE INJURED GASTRIC MUCOSA OF THE CAT

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Superficial mucosal damage caused by a mild irritant (2 M NaCl) results in release of histamine and probably prostaglandins giving increased GMBF. This hyperemic response contributes to protect the mucosa during the early phase of repair after damage by supplying the mucosa with bicarbonate and by eliminating back diffusing acid and other toxic substances such as ethanol. We conclude that histamine plays an important role in the blood flow regulation in the stomach.

Key words: histamine, histidine decarboxylase, mast cells, gastric blood flow

Histamine-producing cells in the gastric mucosa

Histamine is present in high concentration in the gastric mucosa of all mammals studied (1). Gastric histamine resides in three main pools — mast cells, enterochromaffin-like (ECL) cells, and neurones (2). In several species such as the mouse, rat, and hamster histamine is found mainly in ECL cells, while in the cat, dog, pig and man histamine is stored predominantly in mucosal mast cells (1).

The mucosal mast cells have low levels of histidine decarboxylase (HDC), which means that their histamine stores are replenished slowly. Furthermore, mucosal mast cells have never been shown to respond with histamine release to any physiological stimulus known to induce acid secretion (3). Lacy et al. (4) have recently demonstrated two morphologically different types of mucosal mast cells in the rat gastric mucosa that congregated in 3 locations: serosa, basal mucosa, and luminal mucosa closely apposed to capillaries near the gastric lumen between adjacent foveolae.

Recently it has been shown that mast cells, known to be an important part of the immune system (5), are closely apposed to nerve endings in the gastric mucosa (6). Mast cell degranulation can be induced by conditioned stimuli (7), and in addition histamine may have an important role as a modulator of the immune response (8).

On the other hand, the ECL cells are rich in histidine decarboxylase (9) and located in the chief cell rich region, in the basal third of the gastric mucosa, whereas the parietal cells predominate the middle third (10).

Much evidence would seem to support the view that the histamine in ECL cells represents the histamine released to activate the H₂ receptor of the parietal cell (11). Histochemical studies in the rat shown that both endogenous and exogenous gastrin induce histamine release, and the biochemical changes are localized to the ECL cells (12, 13).

Histamine-immunoreactive neurones and a few histamine immunoreactive fibers have been observed in the myenteric plexus of the stomach wall, although histaminergic nerve fibers have not been detected in the gastric mucosa.

Histamine released by superficial as well as deep injury to the gastric mucosa probably originates from the mast cells in the superficial part of the mucosa (14, 15).

Vascular response to histamine in normal gastric mucosa

The mechanism of increased gastric mucosal blood flow during pentagastrin- and histamine-stimulated acid secretion is incompletely understood. Jacobsen et al. (16) demonstrated a relationship between gastric mucosal blood flow and acid secretion in dogs and an increase in blood flow with increasing doses of histamine. Main and Whittle (17) reported that two types of histamine receptors are present in the gastric mucosa: H₁ receptors concerned with vasodilatation and H₂ receptors concerned with acid secretion. However, Guth et al (18) showed that both types of receptors are involved in the blood flow response to histamine in the gastric mucosa. Gerkens et al. (19) found that i.v. administration of pentagastrin in dogs increased gastric mucosal blood flow (GMBF), and this effect could be totally blocked by H₁- and H₂-receptor antagonists. He suggested that the vascular effect of pentagastrin was due to histamine release. Skarstein et al (20) showed that pentagastrin caused increased blood flow in the acid producing part of the stomach, but not in the antrum. Gerber et al. (21) recently found that the gastric blood flow changes caused by pentagastrin in dogs roughly paralleled the amount of histamine released. Gerkens et al. (19) and Gerber et al. (22) reported that the increase in GMBF induced by histamine or pentagastrin is partly mediated by
endogenous prostaglandins. When histamine stimulates the parietal cell to secret acid, prostaglandins (19) and adenosine (23, 24) are concomitantly released giving vasodilatation. This release is probably not related to histamine binding to H₂ receptor directly since omeprazole is just as effective as H₂ blocker in inhibiting the histamine stimulated increase in GMBF (25). Hide et al. (26) have shown that H₁ receptors are concentrated in the endothelial cells. Histamine H₁ receptor stimulation of endothelial cells is also accompanied by the synthesis of potent vasodilators such as prostacyclin (27, 28) and nitric oxide (29).

Recent studies (30, 31) indicate that histamine H₃ receptor may be involved in the control of gastric acid secretion where H₃ receptor stimulation induces significant inhibition of stimulated acid secretion. However, the physiological significance of H₃ receptors in the gastric mucosa is still uncertain.

An important action of histamine in the gastric mucosa is the ability to increase vascular permeability. H₁ receptors are clearly important for this response as H₁ antagonists strongly block this action of histamine. Increased permeability results mainly from action of histamine on postcapillary venules where histamine causes endothelial cells to contract and separate at their boundaries and thus to expose the basement membrane, which is freely permeable to plasma protein and fluid (32, 33). This action is an important factor in the mucosal defence system by increasing transcapillary movement of fluid and macromolecules. However, much larger local concentrations of histamine are needed to initiate permeability changes than to initiate an acid secretory response (34).

The hyperemic response to superficial injury of the gastric mucosa

It is well established that the gastric mucosa may respond to injury by increased blood flow. However, if the injury is severe, there may be areas with vascular damage and reduced or no blood flow. Mucosal blood flow during the phase of repair after damage must therefore be markedly influenced by the degree of mucosal injury.

Sørbye et al. have recently found that the GMBF remained elevated for at least 12 h after superficial mucosal injury caused by 4.5 M NaCl in rats (unpublished results from our laboratory). For several years we have used an experimental model with anesthetized cats, where the stomach is perfused with saline at pH 1.0 or 7.4 and the GMBF is measured by radioactive microspheres. We have found (35, 36) that 2 M NaCl causes superficial mucosal damage which is followed by a hyperemic response that occur independent of gastric luminal pH. During gastric perfusion at neutral luminal pH GMBF declines to baseline level 30—60 min after removal of the hypertonic saline. On
the other hand the blood flow remains elevated for at least 90 min during luminal perfusion of pH 1.0. Gronbech et al. (36) showed that when the hyperemic response to 2 M NaCl was inhibited by partial clamping of the celiac artery, and the stomach was perfused at pH 1.0, a marked back diffusion of $H^+$ occurred and extensive mucosal lesions developed. Restitution of the gastric mucosal surface epithelium occurred within 90 min. The study showed that the restituting mucosa is very resistant to back diffusion of $H^+$, as long as the mucosal blood circulation is intact, and that the increase in blood flow observed during the healing period is very important for repair of the mucosa.

Robert et al. (37) showed that the resistance of the rat gastric mucosa to various necrotizing agents increased when the mucosa was pretreated with a mild irritant. This phenomena called adaptive cytoprotection, has evoked much interest in recent years. Svanes et al. (38) have shown that adaptive protection of the gastric mucosa is related to increased mucosal blood flow caused by mild irritants, and that there is a strong inverse correlation between mucosal blood flow and the degree of ethanol-induced mucosal damage in cats. Gislason et al. (39) found that high mucosal blood flow caused by a mild irritant (2 M NaCl), contributes to eliminate ethanol diffusing from the stomach into the mucosa so that the concentration of ethanol in the mucosa remains below a level that causes injury.

Recently several reports have been published concerning mediators involved in the hyperemic response to mucosal damage. Evidence has been provided that calcitonin gene-related peptide (CGRP) mediates the hyperemic response to acid back diffusion in rats (40). Prostaglandins (41), and nitric oxide (42) may also contribute to the hyperemia. However, the results are conflicting.

The old studies of Davenport (43) and Johnson and Overholt (44) showed that acid diffusing into the gastric mucosa of dogs through a broken barrier liberates histamine.

Bruggeman et al. (45) showed that the vasodilatation occurring after breaking the gastric mucosal barrier with salicylic acid was mediated largely by histamine and depended on back diffusion of acid. We have recently studied the role of histamine and CGRP in the hyperemic response (46) using the experimental cat model described above. Blood flow in the celiac artery and portal vein was measured by Transonic Flowmetry. The concentrations of histamine and CGRP in portal vein blood, as measured by radioimmunoassay, were determined before, under and after mucosal damage. Mucosal blood flow as well as concentrations of histamine and CGRP increased during mucosal exposure to hypertonic NaCl. All three parameters returned towards control levels within 30 min of gastric perfusion at pH 7.4. When the stomach was perfused at pH 1.0 after mucosal damage, the mucosal blood flow and histamine concentration in portal blood remained elevated while the CGRP
Fig. 1. Changes in corpus mucosal blood flow (GMBF) and the amount of histamine and CGRP released to portal vein blood, caused by mucosal exposure to 2 M NaCl, followed by gastric luminal perfusion at pH 1. The intragastric solutions used are indicated in the top panel. Mean values ± SEM; n = 8 for all values.

concentration returned to control level during the first 30 min of restitution (Fig. 1).

Pretreatment with H₁- and H₂-blockers partly inhibited the hyperemic response at pH 1. When the injured mucosa was perfused at pH 7.4, a slight H⁺ secretion was observed (about 0.4 μmol/min) while a marked acid back diffusion occurred during perfusion at pH 1.0 (about 65 μmol/min). Increased release of histamine from the gastric mucosa and increased GMBF were significantly related to increased back diffusion of acid through the superficially damaged gastric mucosa.

The present study shows that histamine is an important mediator of the hyperemia associated with acid back diffusion into injured gastric mucosa of cats. On the other hand this hyperemia was not related to the release of CGRP.

REFERENCES


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