Cytoprotective Action of Histamine against 0.6 N HCl-Induced Gastric Mucosal Injury in Rats; Comparative Study with Adaptive Cytoprotection Induced by Exogenous Acid

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Accepted April 8, 1987

Abstract—We examined the effects of histamine 2HCl (a stimulator of endogenous acid production) and exogenous acid on transmucosal potential difference (PD) and pH of anesthetized rat stomachs, in order to investigate the mechanism underlying the protective action of histamine against 0.6 N HCl-induced gastric mucosal injury in conscious rats. Subcutaneously administered histamine (3–20 mg/kg) dose-dependently produced a decrease in the PD and pH, and it reduced the severity of gastric mucosal injury caused by 0.6 N HCl. Both indomethacin (5 mg/kg, s.c.) and cimetidine (100 mg/kg, s.c.) completely reversed the protection afforded by histamine (20 mg/kg), although the decreased PD and pH responses were unaffected or inhibited, respectively, by indomethacin or cimetidine. Protective action of histamine was also partially mitigated by omeprazole (30 mg/kg, s.c.) which completely abolished histamine-induced acid secretion. On the other hand, exposure of the stomach for 10 min to exogenous acid (0.1–0.35 N HCl) caused a PD reduction and an increase of pH, in a concentration-related manner. The injury caused by 0.6 N HCl was prevented by prior exposure to these low concentrations of HCl, and the degrees of inhibition were associated with the concentration of HCl and the magnitude of PD reduction caused by HCl. The pretreatment with indomethacin, but not cimetidine or omeprazole, significantly antagonized the increased pH and mucosal protection induced by 0.35 N HCl. These results suggest that histamine protected the gastric mucosa against 0.6 N HCl-induced injury by two different ways, mediated with endogenous prostaglandins, (a) mainly through stimulation of H2-receptors and (b) partly through adaptive cytoprotection induced by acid.

Robert et al. (1) have shown that dilute hydrochloric acid (HCl) protects the gastric mucosa against necrotic injury caused by strong irritants through adaptive cytoprotection, mediated with endogenous prostaglandins (PGs). Since it has been known that stimulation of gastric acid secretion is accompanied by an increased formation of endogenous PGs, probably as the result of a feedback mechanism for excess amount of acid production (2–4), gastric secretagogues may exert cytoprotection similar to PGs. In fact, Kobayashi and coworkers (5, 6) and Isobe et al. (7) reported that both histamine and tetragastrin showed cytoprotection mediated with PGs in the rat gastric mucosa. However, it remains unknown whether the protection may result solely from the adaptive cytoprotection induced by acid secreted in the lumen or may be ascribed to other mechanisms which are not associated with acid secretion.

We previously reported that mild irritants produced both PD reduction and increase of pH of the rat stomach and suggested a causal relationship between these changes
and adaptive cytoprotection induced by mild irritants (8–10). Thus, determination of gastric PD and pH may give some information about the involvement of adaptive cytoprotection in the mechanism of mucosal protection afforded by gastric secretagogues.

In the present study, we therefore examined the effects of histamine (a stimulator of endogenous acid) and exogenous acid on PD and pH in anesthetized rat stomachs, and correlated these effects with their protective action against 0.6 N HCl-induced gastric mucosal injury in conscious rats.

**Materials and Methods**

Male Donryu rats (200–230 g), kept in individual cages with raised mesh bottoms, were deprived of food but allowed free access to tap water for 24 hr prior to the experiments. Each study was carried out using 4 to 8 rats per group.

**Determination of PD and pH:** Simultaneous measurement of PD and pH was performed in anesthetized rats with intraperitoneally administered urethane (Nakarai, 1.25 g/kg), according to a previously published method (11). Briefly, the stomach was perfused at a flow rate of 1 ml/min with saline (154 mM NaCl) that was gassed with 100% O₂, heated at 37°C, and kept in a reservoir. The pH of fluid emerging from the stomach was measured using a pH glass electrode of the flow type (Horiba, Model 6901-25T), and the PD was determined using two agar bridges, one positioned in the stomach and the other in the abdominal cavity. Changes in both PD and pH were continuously monitored on a Hitachi two channel recorder (Model 056). In the first study, approximately 1 hr after both PD and pH had stabilized, histamine 2HCI (Nakarai) was given subcutaneously at doses of 3, 10 and 20 mg/kg in a volume of 0.5 ml per 100 g of body wt., and both parameters were recorded for 2 hr thereafter. In some cases, indomethacin (Sigma, 5 mg/kg), cimetidine (Sigma, 100 mg/kg) or omeprazole (Hässle, 30 mg/kg) was given subcutaneously 30 min before histamine treatment. In the second study, the effects of dilute HCl on PD and pH were examined. Approximately 1 hr after both PD and pH had stabilized, the perfusion system was interrupted, and the solution in the stomach was withdrawn. The stomach was then exposed for 10 min to 2 ml of various concentrations of HCl (0.1, 0.15, 0.25 and 0.35 N). After application of HCl, the stomach was rinsed with saline, another 2 ml of saline was instilled, and the perfusion system resumed. Monitoring of pH was also interrupted for 10 min while the stomach was exposed to HCl, whereas the PD was continuously measured throughout a 2 hr test period. Control stomachs were exposed to saline for 10 min. In some cases, indomethacin (5 mg/kg), cimetidine (100 mg/kg) or omeprazole (30 mg/kg) was given subcutaneously 30 min before exposure of the stomach to 0.35 N HCl.

**Induction of gastric mucosal injury by 0.6 N HCl:** The mucosal protective action of histamine and exogenous acid was examined in conscious rats using a 0.6 N HCl-induced gastric lesion model. The animals were given 1 ml of 0.6 N HCl orally by esophageal intubation, and they were killed 1 hr later. The stomachs were removed, inflated by injecting 12 ml of 2% formalin, immersed in 2% formalin for 10 min, and opened along the greater curvature. The stomachs were then examined for lesions under a dissecting microscope with a square grid (×10), and the sum of the areas (mm²) of macroscopically visible lesions was used as a lesion index. The person measuring the lesions did not know the treatment given to the animals. In the first study, histamine (3, 10 and 20 mg/kg) was given subcutaneously 1 hr before administration of 0.6 N HCl. In some cases, indomethacin (5 mg/kg), cimetidine (100 mg/kg) or omeprazole (30 mg/kg) was given subcutaneously 30 min before administration of histamine (20 mg/kg). In the second study, one ml of exogenous acid (0.1, 0.15, 0.25 and 0.35 N HCl) was given orally by esophageal intubation 30 min before administration of 0.6 N HCl. In some cases, indomethacin (5 mg/kg), cimetidine (100 mg/kg) or omeprazole (30 mg/kg) was given subcutaneously 30 min before administration of 0.35 N HCl. In each study, control animals received the vehicle alone.

**Determination of acid secretion:** The effects of indomethacin, cimetidine and
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omeprazole on histamine-stimulated acid secretion were investigated in anesthetized rats, according to a previous paper (12). Determination of acid secretion was performed by introduction of an automatic titrator (Hiranuma Comtite-7) in the perfusion system described for measurement of PD and pH. The titration was made at luminal pH 7.4, using a pH-stat method and by adding 100 mM NaOH to the reservoir. Approximately 1 hr after the basal acid secretion had stabilized, histamine (20 mg/kg) was given subcutaneously, and acid secretion was measured for 2 hr thereafter. Indomethacin (5 mg/kg), cimetidine (100 mg/kg) or omeprazole (30 mg/kg) was given subcutaneously 1 hr before administration of histamine. Acid secretion was measured every 15 min, and the results were expressed as nEq/15 min.

Preparation of drugs: Urethane and histamine 2HCl were dissolved in saline. Indomethacin, cimetidine and omeprazole were suspended in 1% carboxymethylcellulose solution.

Statistics: Data are presented as the mean±S.E. from 4 to 8 rats per group. Statistical analysis was performed using a two-tailed Dunnett's multiple comparison test (13), and values of P<0.05 were regarded as significant. A regression analysis was used to determine a correlation coefficient between two different variates.

**Results**

Effects of histamine on gastric PD, pH and mucosal injury caused by 0.6 N HCl

PD and pH: Normal stomachs generated a PD of −35 mV to −40 mV (mucosa negative) and secreted acid to keep the luminal pH of 2.8 to 3.3. Subcutaneously administered histamine (3–20 mg/kg) produced a reduction in both PD and pH, in a dose-related manner, and a significant effect was achieved at 10 and 20 mg/kg (Fig. 1A). Following administration of histamine (20 mg/kg), the PD dropped from −35.3±1.3 mV to −25.0±0.4 mV, and the pH was decreased...
from 3.1±0.1 to 2.5±0.1 within 1 hr, and those effects persisted for 2 hr. Indomethacin (5 mg/kg) had no effect on changes in both parameters caused by histamine (20 mg/kg), while cimetidine (100 mg/kg) itself significantly increased the pH and completely blocked the decreased PD and pH responses caused by histamine (Fig. 1B). Omeprazole (30 mg/kg) alone significantly raised both PD and pH, and these parameters remained elevated even after administration of histamine (not shown).

**Mucosal protection:** Subcutaneously administered histamine (3–20 mg/kg) dose-dependently reduced the severity and size of gastric mucosal injury induced by 0.6 N HCl in conscious rats, the inhibition being 39.2%, 62.4% and 88.1% at the doses of 3, 10 and 20 mg/kg, respectively (Table 1A). The protective action of histamine (20 mg/kg) was totally abolished by pretreatment of the animals with either indomethacin (5 mg/kg) or cimetidine (100 mg/kg) (Table 1B). The severity of lesions induced by 0.6 N HCl in these rats was not significantly different from that observed in control animals given 0.6 N HCl plus saline. Gastric cytoprotection afforded by histamine against 0.6 N HCl-induced mucosal injury was also significantly mitigated by pretreatment with omeprazole (30 mg/kg), although the lesion index was still significantly lower under these conditions.

| Treatment (mg/kg) | No. of rats | Lesion index (mm²) | Inhibition (%) |
|------------------|-------------|--------------------|---------------|
| Exp. A           |             |                    |               |
| Control (saline) | 8           | 141.1±19.8         |               |
| Histamine 3      | 8           | 85.8±24.5          | 39.2          |
| Histamine 10     | 8           | 53.0±19.4*         | 62.4          |
| Histamine 20     | 8           | 18.8±4.8*          | 88.1          |
| Exp. B           |             |                    |               |
| Control          | 8           | 177.0±16.4         |               |
| Saline+Histamine 20 | 8     | 10.8±4.7*          | 93.9          |
| Indomethacin 5+Histamine 20 | 8   | 180.7±22.1*       | -1.7          |
| Cimetidine 100+Histamine 20 | 8  | 146.4±10.1*       | 17.3          |
| Omeprazole 30+Histamine 20 | 8  | 55.2±5.7*         | 68.8          |

Values are presented as the mean±S.E. from 8 rats per group. Gastric lesions were induced by oral administration of 1 ml of 0.6 N HCl, and the animals were killed 1 hr later. Histamine was given subcutaneously 1 hr before administration of 0.6 N HCl. In Exp. B, the animals were pretreated with subcutaneous administration of indomethacin, cimetidine or omeprazole 30 min before histamine treatment (30 mg/kg). *, #Statistically significant difference from the control and the group treated with saline plus histamine (Exp. B), respectively, at P<0.05.

| Treatment | Dose (mg/kg) | No. of rats | Lesion index (mm²) | Inhibition (%) |
|-----------|--------------|-------------|--------------------|---------------|
| Control   | —            | 8           | 148.6±18.2         |               |
| Indomethacin | 5   | 8           | 188.1±16.5         | -26.6         |
| Cimetidine | 100         | 8           | 149.1±21.8         | -0.3          |
| Omeprazole | 30          | 8           | 152.1±17.8         | -2.4          |

Values are presented as the mean±S.E. from 8 rats per group. Gastric mucosal injury was induced by oral administration of 1 ml of 0.6 N HCl, and the animals were killed 1 hr after administration of 0.6 N HCl. Indomethacin, cimetidine or omeprazole was given subcutaneously 1.5 hr before administration of 0.6 N HCl. Note that none of the compounds tested significantly affected the formation of gastric mucosal injury in response to 0.6 N HCl.
as compared to control animals given 0.6 N HCl without histamine treatment. Indomethacin itself tended to worsen the lesions induced by 0.6 N HCl without reaching statistical significance, while both cimetidine and omeprazole had no effect on gastric mucosal injury in response to 0.6 N HCl (Table 2).

Effects of exogenous acid on gastric PD, pH and mucosal injury caused by 0.6 N HCl

PD and pH: Exposure of the stomach for 10 min to 2 ml of dilute HCl (0.1 N–0.35 N) caused a reduction of PD and an increase of pH in a concentration-related manner, the maximal reduction of PD being 24.3±3.4 mV after exposure to 0.35 N HCl (Fig. 2A). After the exposure, the pH in the luminal perfusate was rapidly increased from 2.9±0.2 to 5.2±0.2 within 30 min in the case of 0.35 N HCl, and it remained elevated thereafter. The reduction of PD and the increase of pH in response to dilute HCl were significant at the concentrations of 0.25 N and 0.35 N, and 0.1 N HCl had no effect on both parameters. After removal of HCl (0.15 N–0.35 N) from the stomach, the reduced PD gradually normalized with time.

After exposure of the stomach to 0.35 N HCl, the PD dropped from –38.2±2.1 mV to –12.6±1.9 mV with a concomitant increase of pH from 3.0±0.2 to 5.3±0.2 within 30 min (Figs. 2B and 3). This treatment itself produced damage in the surface cells, similar to other mild irritants (14), but did not induce any macroscopic lesions in the mucosa. Pretreatment of the animals with subcutaneously administered indomethacin (5 mg/kg) significantly suppressed both the increase of pH and the recovery of PD seen after exposure to 0.35 N HCl, without any effect on the PD reduction. Cimetidine (100 mg/kg) itself significantly increased the pH, but had no effect on the PD reduction and pH responses in the stomach after exposure to 0.35 N HCl. The reduced PD was recovered in rats pretreated

![Fig. 2.](image-url) Effects of intraluminal application of various concentrations of HCl on PD and pH of the stomach in anesthetized rats (A) and those of indomethacin and cimetidine on changes in PD and pH caused by exposure of the stomach to 0.35 N HCl (B). The stomachs were exposed for 10 min to 2 ml of HCl solution (0.1, 0.15, 0.25 and 0.35 N) and were perfused with saline before and after the exposure. Indomethacin (5 mg/kg) or cimetidine (100 mg/kg) was given subcutaneously 30 min before exposure of the stomach to 0.35 N HCl. Data are presented as the mean±one S.E. from 6 rats per group. *Statistically significant difference from the controls, at P<0.05.
with cimetidine as faster as observed in the control animals. Similar phenomena were observed in the stomach after exposure to 0.35 N HCl in the presence of omeprazole (30 mg/kg) (not shown).

**Mucosal protection:** When the stomach was treated with prior exposure to dilute HCl (0.1 N–0.35 N), the gastric mucosal injury caused by 0.6 N HCl was prevented in a concentration-related manner (Table 3A). A significant effect was obtained by dilute HCl at the concentration of 0.25 N and 0.35 N, the inhibition being 51.9% and 91.6%, respectively. The degrees of protection were in parallel with those of PD reduction and increase of pH observed in the stomach exposed to these HCl solutions (Fig. 4A).

When changes in PD and pH were plotted against % inhibition of the lesions caused by 0.6 N HCl, a significant relationship was found between the mucosal protective activity and the PD reduction or the increase of pH induced by dilute HCl, the correlation coefficient (r) being 0.9903 or 0.9703, respectively (Fig. 4B).

Pretreatment of the animals with subcutaneously administered indomethacin (5 mg/kg) totally abolished the protective action of 0.35 N HCl against gastric lesions caused by 0.6 N HCl (Table 3B). The degree of protection afforded by 0.35 N HCl was 89.3% in the absence of indomethacin, and it was highly significant when compared with that (-26.8%) obtained in the presence of this
Table 3. Effects of various concentrations of HCl solution on gastric mucosal injury caused by 0.6 HCl in conscious rats

| Treatment (mg/kg) | Exp. A | Exp. B          |
|------------------|-------|-----------------|
| Control (saline) | 156.6±13.7 | 144.6±16.5   |
| 0.1 N HCl        | 147.4±16.8 | 15.4±3.9*      |
| 0.15 N HCl       | 104.5±20.3 | 183.4±27.3*    |
| 0.25 N HCl       | 76.3±14.7* | 23.5±11.6*     |
| 0.35 N HCl       | 13.3±4.9*  | 21.3±8.4*      |
| Indomethacin 5+0.35 N HCl | 183.4±27.3* | -26.8         |
| Cimetidine 100+0.36 N HCl | 23.5±11.6* | 83.8          |
| Omeprazole 30+0.35 N HCl | 21.3±8.4*  | 85.3          |

Values are presented as the mean±S.E. from 8 rats per group. Gastric mucosal injury was induced by oral administration of 1 ml of 0.6 N HCl, and the animals were killed 1 hr later. In Exp. A, dilute HCl (1 ml) was given orally by esophageal intubation 30 min before administration of 0.6 N HCl. In Exp. B, indomethacin, cimetidine or omeprazole was given subcutaneously 30 min before administration of 0.35 N HCl (1 hr before 0.6 N HCl treatment). * Statistically significant difference from the control and the group treated with 0.35 N HCl plus saline (Exp. B), respectively, at P<0.05.

Effects of indomethacin, cimetidine and omeprazole on gastric acid secretion

To define the role of intraluminal acid in the protective action of histamine, the effects of indomethacin, cimetidine and omeprazole on gastric acid secretion were investigated in anesthetized rats given histamine (20 mg/kg). A single injection of histamine increased acid secretion from 7.1±1.8 μEq/15 min to 32.3±6.4 μEq/15 min within 1 hr (Fig. 5). Subcutaneously administered cimetidine (100 mg/kg) or omeprazole (30 mg/kg) significantly reduced the basal acid secretion within 30 min and all but completely blocked the increased acid secretion in response to histamine. In both cases, the rates of acid secretion were 1 to 4 μEq/15 min during the entire period of the 2 hr experiment after administration of histamine. In contrast, indomethacin (5 mg/kg) had no effect on acid secretion caused by histamine.

Discussion

The present study confirmed the findings of Arakawa et al. (6) that histamine protected the rat gastric mucosa from injury caused by 0.6 N HCl, and it further suggested that this action may not be solely accounted for by adaptive cytoprotection induced by acid secreted in the lumen.

Several investigators reported that when acid secretion is stimulated by gastric secretagogues such as histamine, PGs output in the luminal contents is increased, probably via a negative feedback mechanism to suppress acid secretion (2-4). Gerkens et al. (15) and Gerber and Nies (16) found an increased mucosal blood flow in the canine fundic mucosa following administration of histamine and gastrin. Since both cimetidine and indomethacin blocked the increased mucosal blood flow caused by histamine to similar degrees, they suggested that histamine may enhance the production and/or release of endogenous PGs through stimulation of H2-receptors. Arakawa et al. (6), in fact, demonstrated that subcutaneous administration of histamine significantly increased PG biosynthesis in the rat gastric mucosa. These findings together with the present results suggest that histamine may afford gastric cytoprotection through stimulation of H2-receptors, mediated with endogenous PGs.
Fig. 5. Effects of indomethacin, cimetidine and omeprazole on gastric acid secretion induced by histamine in anesthetized rats. Acid secretion was stimulated by subcutaneous administration of histamine (20 mg/kg). Indomethacin (5 mg/kg), cimetidine (100 mg/kg) or omeprazole (30 mg/kg) was given subcutaneously 1 hr before administration of histamine. Data are presented as the mean±one S.E. of values determined every 15 min from 4 rats per group. *Statistically significant difference from the controls, at P<0.05.

On the other hand, the PD and pH responses caused by histamine and exogenous acid suggest that adaptive cytoprotection induced by endogenous acid cannot solely account for the mucosal protection afforded by histamine. We previously showed that mild irritants such as 1 M NaCl and 1% acetic acid produced a PD reduction with a concomitant increase of the pH, and suggested that these two phenomena may be adaptive responses of the stomach against mild injury manifested as a lowering of PD (8-10, 14). In fact, exogenous acid (>0.15 N HCl) as a mild irritant produced these changes, and the degrees of mucosal protection induced by exogenous acid were in parallel with the magnitude of PD reduction and pH responses. The fact that these responses caused by exogenous acid were significantly blocked by indomethacin also supports the involvement of endogenous PGs in adaptive cytoprotection induced by mild irritants (1). However, since the concentration of endogenous acid secreted in the lumen is in the range of 0.15 N, it may be assumed that the adaptive cytoprotection induced by exogenous acid is not a physiological phenomenon, and histamine cytoprotection may not appear through adaptive cytoprotection afforded by endogenous acid.

On the other hand, histamine also produced a reduction in the PD but decreased the pH as well. These responses were significantly counteracted by cimetidine and omeprazole, but not by indomethacin. In the present study, we used PD mainly as an indicator of the barrier disruption caused by a mild irritant. However, since PD is generated in accordance with Ohm's law by a combination of active transport processes carrying ions and producing current, plus the physical characteristics of the mucosa that determine resistance, changes in PD may be produced by alterations in the processes of active transport, especially in the mucosa without barrier disruption (17, 18). Thus, the decreased PD responses caused by histamine may be due to an increase of ionic conductance (Cl-, K+).
coupled with acid secretion, and therefore the inhibition by cimetidine and omeprazole of these responses may be assumed to be accounted for by an inhibition of this process. Similar phenomena were reported by others using both in vitro and in vivo experiments (19, 20). Although the interpretation of PD responses caused by substituted benzimidazoles remains without agreement, the sophisticated study using in vitro frog stomachs showed that the increased PD caused by omeprazole may be explained by an increase of net Cl⁻ transport which is unmasked by suppression of H⁺ transport due to blockade of the H⁺/K⁺ ATPase located on the vesicular membrane of the parietal cell (19, 21). Based on these findings, both PD and pH responses caused by histamine may simply appear as the result of stimulation of acid secretion, and not of mild irritation of the mucosa. This contention is also supported by the fact that the degree of mucosal protection induced by 20 mg/kg of histamine was equivalent to that obtained in the stomach pretreated with 0.35 N HCl and was much greater than that afforded by 0.15 N HCl.

Yet, there remains the possible involvement of the dilution factor in the mechanism of histamine cytoprotection. As histamine increases the volume of gastric contents by stimulation of acid secretion, the concentration of an irritant (0.6 N HCl) subsequently applied to the stomach may be diluted by secreted acid. This factor can be removed by complete inhibition of acid secretion using cimetidine or omeprazole. The latter agent is known to inhibit acid secretion much more potently than cimetidine by suppressing the H⁺/K⁺ ATPase activity on the vesicular membrane of the parietal cell (21, 22). As shown in the present study, both cimetidine and omeprazole, in contrast to indomethacin, had no effect on adaptive cytoprotection induced by exogenous acid. As expected, histamine exerted a significant protective action even in the presence of omeprazole, although the degree of protection (68.8%) was significantly lower as compared with that (93.9%) obtained in the absence of this agent. Since cimetidine totally abolished the protective action of histamine, a dilution factor, if any, seems not to play a major role in the mechanism of histamine cytoprotection through stimulation of H₂-receptors. Thus, it may be assumed that histamine protects the gastric mucosa against 0.6 N HCl-induced mucosal injury through a mechanism which is not associated with the stimulation of acid secretion itself. Since 0.15 N HCl reduced the formation of gastric mucosal injury caused by 0.6 N HCl to around 65% of that in the control rats, the part of histamine cytoprotection that disappeared in the presence of omeprazole may be ascribed to adaptive cytoprotection induced by luminal acid secreted by histamine.

Taken together, the present study extended the findings of others (5–7), and they suggested that (a) protective action of histamine against 0.6 N HCl-induced gastric mucosal injury may be mediated by endogenous PGs, probably through two different mechanisms: mainly by stimulation of H₂-receptors and partly though adaptive cytoprotection induced by endogenous acid secreted in the lumen; and (b) the adaptive cytoprotection afforded by endogenous acid may be less important in the physiological mechanism of mucosal protection in the stomach.

Acknowledgments: This work was supported in part by grants from the Ministry of Education, Science and Culture of Japan.

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