Roles of Gastric Motility Changes in Cytoprotection Induced by Acetazolamide and Cysteamine in Rats

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Abstract—The present study was undertaken using acetazolamide (AZ) and cysteamine (Cys) to investigate the relationship between gastric motor activity and the phenomenon of "cytoprotection" in rats. Both AZ (10–100 mg/kg) and Cys (10–100 mg/kg), given either p.o. or s.c., significantly reduced the formation of gastric mucosal injury caused by HCl-ethanol (1 ml of 60% ethanol in 150 mM HCl, p.o.). The protective effect of Cys appeared within 10 min, reached the maximal levels 30 min later, while that of AZ appeared from 30 min after administration and became potent with a latency period after treatment. Neither indomethacin (IM: 5 mg/kg, s.c.) nor N-ethylmaleimide (NEM: 5 mg/kg, s.c.) significantly affected the protective effect of Cys, whereas that of AZ was almost totally antagonized by IM. Both AZ and Cys, given either intragastrically or s.c., significantly inhibited gastric motor activity measured as intraluminal pressure recordings, but had minimal effect on acid and alkaline secretion. IM significantly attenuated the inhibitory effect of AZ on the motor activity, while NEM did not affect the inhibited motor responses caused by AZ and Cys. A significant relationship was found between the inhibitory effects of these two drugs on gastric motor activity and HCl-ethanol-induced mucosal injury, the correlation coefficient being 0.819 (P< 0.01). When the mucosal folds were visualized with Gentian Violet (1 ml of 0.5% v/v, p.o.), both AZ and Cys significantly prevented the localized staining along the mucosal folds, suggesting dissolution of the folds. These results suggest that both AZ and Cys protect the gastric mucosa against injury caused by HCl-ethanol, probably through a dissolution of mucosal folds due to inhibition of gastric motor activity.

The term "cytoprotection" is the property to protect the gastric mucosal tissue located under the surface epithelium from becoming necrotic after exposure to necrotizing agents (1, 2). Although this ability was considered as the specific property of prostaglandins (PGs) (1–4), recent studies showed that a variety of compounds including acetazolamide and cysteamine which have no structural similarity with PGs also share the above property (5–9). While gastric cytoprotection of acetazolamide and cysteamine has been shown to be mediated with endogenous PGs and sulfhydryls, respectively (5, 8), the physiological mechanisms by which these two drugs exert cytoprotection remain to be defined.

We recently reported using 16,16-dimethyl PGE2 (10) and mast cell stabilizers (11) that inhibition of gastric motor activity may be associated with the phenomenon of "cytoprotection" in the rat stomach after exposure to necrotizing agents. Therefore, it is of interest to know (a) whether acetazolamide and cysteamine affect gastric motor activity at cytoprotective doses and (b) whether their effects on gastric motor activity are associated with gastric cytoprotection mediated with endogenous PGs and sulfhydryls.

In the present study, we examined the
effects of acetazolamide and cysteamine on gastric motor activity and secretion in rats and correlated their effects with the inhibitory action against HCl-ethanol-induced gastric mucosal injury. We discuss the relationship between the phenomenon of "cytoprotection" and the dissolution of mucosal folds due to inhibition of gastric motor activity.

Materials and Methods

Male Sprague Dawley rats (230–250 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 5–10 rats per group.

Induction of gastric mucosal injury by HCl-ethanol: The animals were given 1 ml of HCl-ethanol (60% in 150 mM HCl) orally by esophageal intubation, and they were killed 1 hr later (6). The stomachs were removed, inflated by injecting 12 ml of 2% formalin, immersed in 2% formalin for 10 min to fix both the inner and outer layers of the gastric wall and opened along the greater curvature. The length (mm) of each macroscopically visible lesion was measured under a dissecting microscope with a square grid (x10), summed, and used as a lesion index. Since in the present study we used the word "cytoprotection" as protective action against macroscopically visible lesions, quantitation of the histological injury was not performed. Either acetazolamide (10–100 mg/kg) or cysteamine (10–100 mg/kg) was given both orally and subcutaneously 30 min before administration of HCl-ethanol; and at 100 mg/kg, these agents were given subcutaneously 30 min before administration of HCl-ethanol and at 100 mg/kg, these agents were given subcutaneously at various times (10, 30, 60, 90 and 120 min) before HCl-ethanol treatment. In another experiments, the effects of indomethacin (5 mg/kg) and N-ethylmaleimide (5 mg/kg) were examined on the protective action of the above two drugs. These agents were given subcutaneously 30 min before administration of acetazolamide (100 mg/kg, s.c.) or cysteamine (100 mg/kg, s.c.); and they were given 60 min before HCl-ethanol treatment. In all studies, the person measuring the lesions did not know the treatment given to the animals.

Determination of gastric acid and alkaline secretion: The effects of acetazolamide and cysteamine on gastric acid and alkaline secretions were investigated in the saline-perfused stomach under unanesthetized conditions according to our previous paper (12). Briefly, under ether anesthesia, the abdomen was opened, and the stomach and duodenum were exposed. An acute gastric fistula prepared by means of a polyethylene tube was provided in the forestomach. Another polyethylene tube was inserted into the stomach through a slit in the duodenum and was held in place by a ligature around the pylorus. Both cannulas were pulled out through the lateral abdominal wall and placed in a suture. Then, the animals were kept in Bollman cages, and the stomachs were perfused at a flow rate of 1 ml/min with saline which was gassed with 100% O2, heated at 37°C and kept in a reservoir. Gastric acid and alkaline secretions were measured at luminal pH 7.4 using a pH-stat method (Hiranuma Comtite-7) and by adding 100 mM NaOH and 10 mM HCl, respectively. To disclose HCO3− secretion, omeprazole (30 mg/kg) was given intraduodenally at the time of operation to inhibit acid secretion. Acetazolamide (100 mg/kg) or cysteamine (100 mg/kg) was applied topically to the stomach for 30 min through the fistula or given by subcutaneous administration. Gastric acid and alkaline secretions were determined every 15 min for a total period of 3 hr, and the results were expressed in terms of μEq/15 min.

Determination of gastric motor activity: The effects of acetazolamide and cysteamine on gastric motor activity were examined in conscious rats using a balloon positioned in the glandular part of the stomach, according to a previous paper (13). Briefly, under ether anesthesia, a balloon (containing about 1 ml of water), the support catheter and another catheter for intragastric administration of drugs were placed in the glandular stomach through an incision of the forestomach. The animals were then placed in Bollman cages, and the support catheter was connected to a pressure transducer and polygraph device (Nihon Kohden). Gastric motor activity was continuously monitored on a Hitachi recorder (Model 056) as intraluminal pressure.
recordings. Quantitative analysis was performed by counting the number of contractions with an amplitude of 15 cmH\textsubscript{2}O or greater, and by measuring the amplitude of each contraction over a 10 min period, determining the mean of a rat for this period from these values, and then by calculating the mean±S.E. for each time period from 5 rats per group. Either acetazolamide (30, 100 mg/kg) or cysteamine (30, 100 mg/kg) was given intragastrically through the cannula or subcutaneously after basal motor activity had been well stabilized. In some cases, indomethacin (5 mg/kg) or N-ethylmaleimide (5 mg/kg) was given subcutaneously 30 min before administration of the above drugs. Gastric motor activity was measured for a total period of 3 hr.

Visualization of mucosal folds using Gentian Violet: The effects of acetazolamide and cysteamine on formation of the mucosal folds were investigated by visualizing the folds using an acridine dye, Gentian Violet, which selectively stains the membrane protein without precipitation (14, 15). Animals were given 1 ml of Gentian Violet (0.5%, v/v) orally by esophageal intubation and killed 2 min later. The stomachs were removed, treated with 2% formalin, and opened along the greater curvature. The area (mm\textsuperscript{2}) of the mucosa stained deep and light blue was measured separately under a dissecting microscope (x10). Acetazolamide (100 mg/kg) or cysteamine (100 mg/kg) was given subcutaneously 60 min or 30 min before administration of Gentian Violet, respectively.

Drugs: Drugs used were acetazolamide (Sigma), cysteamine (Sigma), indomethacin (Sigma), N-ethylmaleimide (Sigma), omeprazole (H\textregisteredassic) and Gentian Violet (Nakarai). Cysteamine, N-ethylmaleimide and Gentian Violet were dissolved in saline, while acetazolamide and indomethacin were suspended in saline with a trace of Tween 80 (Nakarai). Omeprazole was suspended in 1% carboxymethylcellulose solution. Each agent was given in a volume of 0.5 ml per 100 g of body wt. Control animals were given the vehicle alone.

Statistics: Data are presented as the mean±S.E. from 5 to 10 rats per group. Statistical analysis was performed using a two tailed Dunnett’s multiple comparison test (16) for unpaired variates, 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 acetazolamide and cysteamine on HCl-ethanol-induced gastric mucosal injury

Oral administration of HCl-ethanol (1 ml of 60% ethanol in 150 mM HCl) produced steak necrotic lesions in the gastric mucosa within 1 hr, mostly confined to the corpus region along the mucosal folds. Pretreatment of the animals with acetazolamide and cysteamine, given either p.o. or s.c., significantly reduced the severity of lesions induced by HCl-ethanol (Fig. 1). Although a significant effect was appreciated with acetazolamide even at 10 mg/kg, a dose-related inhibition was not apparent for this drug; the maximal inhibiting being 66.7% when acetazolamide was given s.c. at 100 mg/kg. In contrast, a dose-related inhibition was observed in rats after pretreatment with both s.c. and p.o. administration of cysteamine, the inhibition at 100 mg/kg being 95.0% and 87.0% in the cases of s.c. and p.o. administration, respectively.

In agreement with the findings of Robert et al. (8), the effect of acetazolamide (100 mg/kg) on HCl-ethanol-induced mucosal injury became potent with the latency period after the treatment with this drug, especially in the case of s.c. administration; the maximal inhibition (80.0%) was obtained when acetazolamide was given 2 hr before administration of Gentian Violet, respectively.

Subcutaneously administered indometh-
Effects of acetazolamide and cysteamine on gastric mucosal injury caused by HCl-ethanol in rats. The animals were given 1 ml of HCl-ethanol (60% in 150 mM HCl) orally by esophageal intubation, and they were killed 1 hr later. Acetazolamide (10-100 mg/kg) and cysteamine (10-100 mg/kg) were given orally or subcutaneously 30 min before administration of HCl-ethanol. Data are presented as the mean±one S.E. from 8 rats per group. *Statistically significant difference from the controls at P<0.05.

Gastric acid secretion: Conscious rats secreted acid at the rate of 18-23 μEq/15 min. Acetazolamide (100 mg/kg), given either by topical application to the stomach for 30 min or by subcutaneous administration, had insignificant influence on 2 hr acid output (Fig. 4A). Similarly, topical application of cysteamine (100 mg/kg) did not significantly affect acid secretion, whereas subcutaneously administered cysteamine significantly reduced acid output for 40 min starting from 30 min after the treatment.

Gastric alkaline secretion: In the absence of acid secretion caused by omeprazole, alkaline secretion occurred at the rate of 0.7-1 μEq/15 min. Neither acetazolamide (100 mg/kg) nor cysteamine (100 mg/kg) had significant influence on gastric alkaline secretion when applied topically to the stomach for 30 min or given subcutaneously (Fig. 4B).
Gastric motor activity: The stomachs in normal rats contracted at a frequency of 17.0±2.0/10 min with an amplitude of 17.8±2.5 cmH₂O when determined as intraluminal pressure recordings. Subcutaneously administered acetazolamide (100 mg/kg) and cysteamine (100 mg/kg) significantly reduced both the amplitude and frequency of contractions (Fig. 5), and these effects were observed dose-dependently for these two drugs at 30 mg/kg or greater (not shown). The inhibitory effect of cysteamine appeared within 10 min after administration, reached the maximal levels 30 min later, and remained unaltered for 1.5 hr thereafter. In contrast, the effect of acetazolamide became gradually potent, and it reached the maximal levels roughly 1 hr after administration. A similar time-dependent effect on gastric motor activity was observed when acetazolamide was given intragastrically (Fig. 6). However, intragastric administration of cysteamine inhibited both the amplitude and frequency of contractions to the maximal levels within 10 min, the inhibition persisting for 2 hr thereafter.

Effects of indomethacin and N-ethylmaleimide: Subcutaneous administration of indomethacin (5 mg/kg) by itself slightly increased the amplitude of contractions (not shown), but almost completely antagonized the inhibited gastric motility caused by intragastric or subcutaneous administration of acetazolamide (100 mg/kg) (Figs. 7 and 8).
The inhibitory effect of cysteamine (100 mg/kg) on the motor activity was not, however, influenced by pretreatment with indomethacin. Administration of N-ethylmaleimide (5 mg/kg) had no effect on spontaneous gastric motor activity, and it did not significantly affect the inhibited motor responses caused by both acetazolamide (i.g. and s.c.) and cysteamine (i.g. and s.c.). When % inhibition of gastric motor activity caused by acetazolamide (30 and 100 mg/kg) and cysteamine (30 and 100 mg/kg) was plotted against % inhibition of HCl-ethanol-induced mucosal injury in response to these two drugs, there was a highly significant relationship (P<0.01) between these two factors, the correlation coefficient being 0.819 (Fig. 9).

**Effects of acetazolamide and cysteamine on formation of mucosal folds**

After oral administration of Gentian Violet (1 ml of 0.5% v/v), the mucosa showed a marked localization of staining with this dye; deep blue color was observed along the mucosal folds in the corpus region and in the whole antrum, and light blue color was found in other areas of the corpus region (Fig. 10). Especially, the area stained deep blue in the corpus was well corresponded with that where band-like lesions were normally seen in the stomach after exposure to HCl-ethanol. Pretreatment of the animals with acetazolamide (100 mg/kg, s.c.) or cysteamine (100 mg/kg, s.c.) inhibited the localized staining of the mucosa with Gentian Violet; the corpus mucosa was stained light blue evenly, and clear bands stained deep blue disappeared in the corpus region (see Fig. 10). When the area of the mucosa stained deep blue was measured, acetazolamide and cysteamine significantly reduced the area from 75.7±11.1 mm² to 19.8±3.7 mm² and 14.6±7.6 mm², respectively (Table 1). The degrees of staining in the antral region, however, was not altered in the presence of these drugs (not shown).

**Discussion**

The present study confirmed the findings by others that the formation of gastric mucosal injury caused by ethanol was significantly prevented by acetazolamide and cysteamine (5, 8). The latency period for the cytoprotective action of acetazolamide
Fig. 4. Effects of acetazolamide and cysteamine on gastric acid (A) and alkaline (B) secretion in conscious rats. Acetazolamide (100 mg/kg) and cysteamine (100 mg/kg) were given by topical application to the stomach for 30 min or by subcutaneous administration. Data are presented as the mean±one S.E. of values determined every 15 min from 5 rats per group. *Statistically significant difference from the controls at P<0.05.

Table 1. Effects of acetazolamide and cysteamine on the localized staining of the corpus mucosa after oral administration of Gentian Violet in rats

| Treatment       | Dose (mg/kg) | No. of rats | Area of the mucosa stained blue (mm²) | Total area (mm²) |
|-----------------|--------------|-------------|--------------------------------------|-----------------|
| Control         | —            | 6           | 75.7±11.1                            | 104.1±13.2      |
| Acetazolamide   | 100          | 6           | 19.8±3.7*                            | 129.2±6.2       |
| Cysteamine      | 100          | 6           | 14.6±7.6*                            | 100.2±16.7      |

All values are presented as the mean±S.E. from 6 rats. The animals were given 1 ml of Gentian Violet (0.5%, v/v) orally by esophageal intubation and then killed 2 min later. After light fixation of the tissues with 2% formalin, the areas of the corpus mucosa stained deep and light blue were measured separately under a dissecting microscope (x10). Acetazolamide or cysteamine was given subcutaneously 60 min or 30 min before administration of Gentian Violet. *Statistically significant difference from the control at P<0.05. The degrees of staining in the antral mucosa were not significantly altered by pretreatment with these two drugs (not shown).

was also consistent with the observation by Robert et al. (8), suggesting that similar mechanisms may be involved in the pathogenesis of gastric mucosal injury in response
Fig. 5. Effects of acetazolamide and cysteamine on gastric motor activity in conscious rats. Acetazolamide (100 mg/kg) and cysteamine (100 mg/kg) were given subcutaneously after basal motor activity had been well stabilized. Quantitative analysis of gastric motor activity referred to the section of "Materials and Methods". Data are expressed as the percentage for values in both the amplitude and frequency observed before administration of these drugs and presented as the mean±one S.E. from 5 rats per group. *Statistically significant difference from the controls at $P<0.05$.

Fig. 6. Effects of acetazolamide and cysteamine on gastric motor activity in conscious rats. Acetazolamide (100 mg/kg) and cysteamine (100 mg/kg) were given intragastrically through the catheter. For the detailed protocols, refer to Fig. 5. Data are expressed as the percentage for values in both the amplitude and frequency observed before administration of these drugs and presented as the mean±one S.E. from 5 rats per group. *Statistically significant difference from the controls at $P<0.05$.

to ethanol with or without acid. Since these two drugs exerted gastric cytoprotection by both oral and parenteral (subcutaneous) administration, adaptive cytoprotection induced by mild irritation to the gastric mucosa can be excluded in the mechanism of their protective action.

Recently, Szabo and Trier (17) proposed
that gastric cytoprotection might be mediated through at least two different mechanisms, one concerns PGs, and the other involves sulphydryl-containing substances of the mucosa. In agreement with the previous observation (8), the effect of acetazolamide was almost completely antagonized by pretreatment with indomethacin. Although we cannot totally exclude the possibility that this is a simple epiphenomenon caused by the non-specific action of indomethacin other than cyclooxygenase inhibition (18), the effect of acetazolamide on ethanol-induced mucosal injury may be at least partly mediated with endogenous PGs. On the other hand, N-ethylmaleimide, a sulphydryl blocker (5), failed to affect the protective action of acetazolamide as well as cysteamine. These results suggest that endogenous sulphydryls may not be involved in the mechanism of gastric cytoprotection induced by these drugs. The failure of N-ethylmaleimide on cysteamine cytoprotection would be expected, because cysteamine is one of the sulphydryl-containing compounds and may replace the reduced levels of non-protein sulphydryl substances in the gastric mucosa caused by this blocker. Szelenyi and Brune (19) recently reported that N-ethylmaleimide (10 mg/kg) completely abolished the mucosal protection afforded by N-acetylcysteine (200 mg/kg), another sulphydryl-containing substance, in rats. However, they showed that changes in the sequence of administration did not result in a similar abolishment by N-ethylmaleimide of the mucosal protection; when this blocker was first given, the protective effect of N-acetylcysteine was not diminished, but when N-ethylmaleimide was given after administration of N-acetylcysteine, the protection caused by this sulphydryl drug totally disappeared. Thus, our results seem to agree with their findings, at least based on the time schedule of administration used in the present study.

Physiological mechanisms of "cytoprotection" remain unknown. An increase of HCO$_3^-$/mucus secretion and mucosal blood flow and a layer of hydrophobic phospholipids have been suggested as its mecha-
Fig. 8. Representative figures showing the effects of acetazolamide (100 mg/kg, s.c.) and cysteamine (100 mg/kg, s.c.) on gastric motor activity. Indomethacin (5 mg/kg, s.c.) was given 30 min before administration of acetazolamide.

Fig. 9. The relationship between antigastric motor activity and gastric cytoprotection induced by acetazolamide and cysteamine in the absence or presence of indomethacin and N-ethylmaleimide. Data are taken from Figs. 1, 2, 3, 6, 7 and 8. The values for gastric motor activity (amplitude) were obtained at 60 min and 30 min after administration of acetazolamide and cysteamine, respectively. The correlation coefficient was 0.819 (P<0.05).
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Fig. 10. Gross appearance of gastric mucosa stained with Gentian Violet in rats. The animals were given 1 ml of Gentian Violet (0.5%, v/v) orally by esophageal intubation and killed 2 min later. Cysteamine (100 mg/kg) was given subcutaneously 30 min before administration of Gentian Violet. A: control, B: cysteamine. Note the localized staining of the mucosa with this dye along the mucosal folds in the corpus region of the control rat and the disappearance of such bands stained deep blue color in the animal pretreated with cysteamine.

nism (20–22), but these effects are not without controversy (23, 24). Mersereau and Hinchey (25) proposed that dissolution of the mucosal folds may be associated with the prevention of necrotic gastric lesions along the fold crests in the stomach after exposure to necrotizing agents. Based on the above speculation, gastric motor activity which contributes to formation of mucosal folds may be important for understanding the mechanism of cytoprotection. We previously reported that 16,16-dimethyl PGE2 and mast cell stabilizers significantly inhibited gastric motor activity at the doses which significantly reduced the formation of gastric mucosal injury in response to ethanol (10, 11). Similarly, the inhibited gastric motor activity may be involved in the mechanism of cytoprotection induced by both acetazolamide and cysteamine based on the following reasons: (a) both acetazolamide and cysteamine, given either p.o. or s.c., potently inhibited gastric motor activity at cytoprotective doses, without much effect on gastric secretory activity, (b) the latency period for cytoprotective action of these two drugs was corresponded well with that for their inhibitory effects on gastric motor activity, (c) the inhibited motor responses caused by acetazolamide (p.o. and s.c.) were significantly counteracted by pretreatment with indomethacin at the same dose which completely antagonized the cytoprotective action of this drug, and (d) a highly significant relationship was found between the inhibitory effects of acetazolamide and cysteamine on gastric motor activity and HCl-ethanol-induced mucosal injury (r=0.819, P<0.01). Thus, gastric motor activity seems to be an important element in the development and prevention of mucosal injury of the stomach after exposure to HCl-ethanol.

The most characteristic of the gastric mucosal injuries caused by necrotizing agents is a marked localization of lesions: band-like lesions confined to the fold crests. The inhibition of gastric motor activity leads to dissolution of the mucosal folds and increases the surface area of the mucosa exposed to HCl-ethanol. The above speculation is supported by the fact that oral administration of Gentian Violet induced a localized staining of the mucosa along the fold crest, and this
Localized staining disappeared in the stomach in which motor activity was inhibited by acetazolamide and cysteamine. Thus, it may be possible to assume that a dissolution of the mucosal folds would change the property of necrotizing agents from “strong irritants” to “mild irritants” and thereby reduces the severity of macroscopically visible damage seen after exposure to strong irritants such as HCl-ethanol.

Szabo et al. (26, 27) showed the increased vascular permeability in the gastric mucosa damaged by ethanol in rats, and they suggested that vascular injury is an early pathogenetic factor in the development of ethanol-induced gastric hemorrhagic erosions. PGs and sulfhydryls might prevent the increased vascular permeability to exert gastric cytoprotection. However, Mersereau et al. (28) showed that the primary lesion induced by necrotizing agents is coagulation necrosis along the crest of the gastric mucosal folds and that the vascular sequellae are secondary phenomena preventable by avoiding the occurrence of the initial deep band-like lesions on the fold crests. Thus, a cause-effect relationship between vascular changes and the phenomenon of “cytoprotection” afforded by acetazolamide and cysteamine remains to be defined in further studies.

The present study suggests that both acetazolamide and cysteamine protect the gastric mucosa against injury caused by HCl-ethanol, probably through dissolution of the mucosal folds due to inhibition of gastric motor activity. This study also provides another evidence to show a possible cause-effect relationship between the inhibited gastric motor activity and the phenomenon of “cytoprotection” in the rat stomach. Since PGs cytoprotection disappeared in the distended stomach without mucosal folds (29), the phenomenon of “cytoprotection” might be an epiphenomenon associated with the particular means of inducing lesions in the rat (18) and with action of drugs which inhibit gastric motor activity to induce dissolution of the mucosal folds.

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