Increasing Action of Teprenone, a New Antiulcer Agent, on High-Molecular-Weight Glycoprotein in Gastric Mucus during the Healing Process of Acetic Acid-Induced Ulcer in Rats

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Accepted February 8, 1986

Abstract—The effects of teprenone on quantitative changes in gastric mucus glycoprotein during the healing process of acetic acid-induced ulcer in rats were investigated in comparison to those of cimetidine and proglumide. When estimated on the 15th day after operation, teprenone (50 and 100 mg/kg x 2/day, p.o.) significantly decreased the ulcer index by approx. 30%. On the other hand, cimetidine (100 mg/kg x 2/day, p.o.) and proglumide (500 mg/kg x 2/day, p.o.) did not significantly affect it. The high-molecular-weight glycoprotein (HMG, molecular weight of 2x10^6 or more) concentration in the gastric mucus of the control group (non-medicated ulcer rats) was 48.7% lower than that of the normal group (non-medicated rats without ulcer). On the contrary, the lower-molecular-weight glycoprotein (LMG, molecular weight between 5x10^5 and 2x10^6) concentration of the control group was 95.3% higher than that of the normal group. Teprenone (at both doses) remarkably increased the concentration and secretion of the HMG. In contrast, those of the LMG were decreased by this drug. Cimetidine significantly decreased both the concentration and secretion of the total glycoprotein (HMG+LMG). Proglumide showed only slight increases in the concentration and secretion of the HMG, although it pronouncedly increased the total glycoprotein secretion. These results indicate that teprenone may strengthen the defensive force of gastric mucosa by increasing the HMG with a polymeric structure. In contrast, cimetidine may weaken the mucosal defense.

Gastric mucus forms a thin, continuous gelatinous cover over the gastric mucosal surface and is believed to protect the stomach wall from acid and pepsin digestion. The gastric mucus obtained from humans and pigs contains a glycoprotein with a molecular weight of 2x10^6 or more (high-molecular-weight glycoprotein, HMG) that has viscous and gel-forming properties (1, 2). Azumii et al. (3) observed that the decrease in the HMG derived from gastric mucosa occurred before macroscopical damage of the mucosa following oral administration of aspirin to rats. From these results, they suggested that the gastric damage induced by aspirin was caused by a deficiency of gastric mucosal HMG. Teprenone, a new antiulcer agent, has already been shown by Oketani et al. (4) to protect against the decrease in the HMG amount in gastric mucus plus mucosa as well as protect against gastric damage in aspirin-induced ulcers of rats. On the other hand, our previous study (5) indicated that this agent remarkably promoted the regeneration of the defective mucosa during the healing process of acetic acid-induced ulcer in rats. Recently, we reported a marked decrease in the amount of the HMG and an increase in the amount of a glycoprotein with a molecular weight between 5x10^5 and 2x10^6 (lower-molecular-weight glycoprotein, LMG) in the gastric mucus obtained not only from the ulcerated part but also from the non-ulcerated part during the healing process...
of this chronic ulcer model (6). This result suggests that the gastric mucus glycoprotein of rats with acetic acid-induced ulcer may have lost much of the viscous and gel-forming properties of polymeric native glycoprotein, possibly resulting in weakening of the mucosal defense against pepsin and HCl.

The purpose of the present study was to clarify whether or not teprenone, having mucosal regeneration-promoting action, can increase the HMG amount in the gastric mucus during the healing process of acetic acid-induced ulcer in rats. Furthermore, the effects of this agent were compared to those of cimetidine and proglumide.

Materials and Methods

Animals: Male Sprague-Dawley strain SPF rats weighing approx. 180 g (Shizuoka Agricultural Cooperative Association for Laboratory Animals, Shizuoka) were used in the experiment. These animals were housed in an air-conditioned room at 23±1 °C.

Drugs: Drugs used were teprenone (6, 10, 14, 18-tetramethyl-5, 9, 13, 17-nonadecatetraene-2-one, Eisai), cimetidine (extracted from a commercial product, Tagamet, Fuzisawa) and proglumide (extracted from a commercial product, Promid, Kaken). Teprenone was emulsified in 5% gum arabic and 0.6% Tween 80, and the other two drugs were suspended in these detergents.

Ulcer inductions: Gastric ulcer was induced in rats by the injection of 20% acetic acid in a volume of 0.05 ml into the serosal layer in the glandular part of the stomach in accordance with the method described by Takagi et al. (7).

Drug administration: Each test drug, emulsified or suspended, was given orally, twice a day in a volume of 1 ml/100 g of body weight for 14 consecutive days beginning the day of acetic acid injection. Control animals with acetic acid-induced ulcer and normal animals were given the vehicle orally.

Measurement of ulcer index (UI): On the 15th day, the animals were sacrificed by rapid decapitation. The stomach was then removed and cut open along the greater curvature. The cut open stomach was lightly rinsed in 70% ethanol to remove the gastric contents and then spread on a gum plate without making creases. The longitudinal and abscissal lengths of the upper-opened part of the ulcer were quickly measured under the observation with a stereoscopic microscope setting a micrometer, and the product of both lengths (mm²) was expressed in terms of the UI.

Collection of gastric mucus specimens and analysis of the mucus glycoprotein by gel filtration: After measuring the ulcer size, the mucosal layer containing the mucus from all parts of the glandular stomach was carefully scraped with a scalpel and then lyophilized. The lyophilized material (25 mg) was homogenized in 0.2 M NaCl (2 ml), incubated at 50°C for 1 hr and then centrifuged at 12,500 g for 30 min. The supernatant (2 ml) was applied on a column (100 cm x 1.5 cm) of Cellulofine GCL-2000-sf (Seikagaku Kogyo) and eluted with 0.2 M NaCl. The eluted fractions (1.1 ml) were collected, and a part of each fraction was assayed for glycoprotein by the modified Periodic Acid Schiff (PAS) method of Mantle and Allen (8) or for hexose, an indicator of sugar residues of glycoprotein by the phenol-sulfuric acid method (9). In this case, mucin from bovine submaxillary glands (type 1) [Sigma] was used as a standard for glycoprotein. On the other hand, D-galactose (Yoneyama) was used as the standard for hexose.

Statistical analysis: Results obtained were expressed as the mean±S.E. Student’s t-test was used for statistical analysis.

Results

1. Effects of teprenone, cimetidine and proglumide on the UI

As shown in Fig. 1, teprenone at doses of 50 and 100 mg/kg x 2/day, p.o., significantly decreased the UI by 26.0 and 35.4%, respectively. On the other hand, cimetidine at a dose of 100 mg/kg x 2/day, p.o., decreased the UI by 13.4%, but not significantly. Proglumide at a dose of 500 mg/kg x 2/day, p.o., showed little effect on the index.

2. Elution patterns of glycoprotein and hexose in gastric mucus of rats treated with teprenone, cimetidine or proglumide

Glycoprotein (Fig. 2): When fractions from
gel filtration were assayed for glycoprotein, it was found to be eluted only near the void volume between tubes 39 and 60. Most of the glycoprotein in the gastric mucus from normal rats were eluted between tubes 39 and 50, and the elution pattern showed a high, sharp peak. On the other hand, the glycoprotein in the gastric mucus from control rats with the ulcer was eluted over a relatively wide range from tubes 39 to 60, and the elution pattern formed a low, wide incline as compared to that of the normal rats.

![Fig. 1](image1.png)

**Fig. 1.** Effects of teprenone, cimetidine and proglumide on ulcer index of acetic acid-induced ulcer in rats. Each column denotes the mean value with S.E. (Control: N=20, Test drug: N=17 or 20). ** and *** , Significantly different from the control at P<0.01 and P<0.001, respectively.

![Fig. 2](image2.png)

**Fig. 2.** Elution patterns of glycoprotein in gastric mucus of rats treated with teprenone, cimetidine or proglumide by gel filtration on Cellulofine GCL-2000-sf in acetic acid-induced ulcer.
results indicate that the control samples contain more glycoprotein of lower molecular weight than normal samples. The elution profiles of the glycoprotein in the samples from the ulcer rats treated with 50 and 100 mg/kg×2/day, p.o., of teprenone were very similar to those from the normal rats, indicating a high, sharp peak. On the other hand, by the treatment with 100 mg/kg×2/day, p.o., of cimetidine, the elution profile showed a low, though sharp, peak. In the case of the treatment with 500 mg/kg×2/day, p.o., of proglumide, the elution profile was similar to that of the control, forming a low, wide incline.

Hexose (Fig. 3): Hexose-containing materials were eluted near the void volume between tubes 39 and 60, in which the glycoprotein was detected, and in the total volume between tubes 115 and 140. This result indicates that the first peak of hexose is gastric mucus glycoprotein. Therefore, the first peak of hexose was compared to each other. The elution patterns of hexose in each group were roughly similar to those of glycoprotein. In the cimetidine (100 mg/kg×2/day, p.o.)-treated group, the hexose peak was slightly lower as compared with that of the normal group, although the glycoprotein peak was very low.

3. Effects of teprenone, cimetidine and proglumide on glycoprotein concentration (Fig. 4)

The glycoprotein fractions were further divided into the glycoprotein with a molecular weight of 2×10⁶ or more (HMG), which eluted in tubes 39 to 46, and that with a molecular weight between 5×10⁵ and 2×10⁶ (LMG), which eluted in tubes 47 to 60.

Glycoprotein: The HMG and LMG amounts of the normal group were 14.2±1.5 and 4.3±0.5 mg/100 mg lyophilized sample, respectively, while the HMG and LMG amounts of the control group were 7.3±1.1 and 8.5±1.9 mg/100 mg lyophilized sample, respectively. Thus, the ulceration caused a 48.7% reduction in HMG concentration and a 95.3% increase in the LMG concentration. Teprenone at doses of 50 and 100 mg/kg×2/day, p.o., remarkably increased the HMG concentration by 79.5 and 93.3%, respectively, compared to that of the control. In contrast, with the HMG concentration, the LMG concentration was remarkably decreased 42.9 and 54.8%, respectively, by 50 and 100 mg/kg×2/day, p.o., of this drug. On the other hand, proglumide at a dose of 500 mg/kg×2/day, p.o., showed only a slight increase of 28.8% on the HMG concentration, and it did not affect the LMG concentration. However, cimetidine at a dose of 100 mg/kg×2/day, p.o., significantly
decreased both the HMG and LMG concentrations. The total glycoprotein (HMG+LMG) concentration tended to be increased by teprenone (both doses) and proglumide. Nevertheless, cimetidine pronouncedly decreased the total glycoprotein concentration by 52.2%.

Hexose: The glycoprotein concentration in gastric mucus was also expressed as hexose concentration. The HMG and LMG amounts of the normal group were 0.87±0.08 and 0.33±0.04 mg/100 mg lyophilized sample, respectively. On the other hand, the HMG and LMG amounts of the control group were 40.2% lower and 103.0% higher, respectively, than those of the normal group. Teprenone at both doses remarkably increased the HMG concentration by approx. 90% and decreased the LMG concentration by 40–50%. On the other hand, proglumide significantly affected neither the HMG nor LMG concentration. Cimetidine had a tendency to increase the HMG concentration, although this drug significantly decreased the concentration of the HMG when measured by the modified Periodic Acid Schiff method.

4. Effects of teprenone, cimetidine and proglumide on HMG and LMG concentration ratios (Fig. 5)

Glycoprotein: The HMG or LMG amount was expressed as a percentage of the total amount of glycoprotein (HMG+LMG). The gastric mucus of the normal group contained 76.9±0.4% of the HMG and 27.5±3.0% of the LMG. On the other hand, the gastric mucus of the control group contained 46.5±3.1% of the HMG and 53.5±3.1% of the LMG. Thus, in the gastric mucus of the ulcer rats, the ratio of the HMG concentration pronouncedly decreased, compared to that of normal rats, whereas the ratio of the LMG concentration increased. The samples of the teprenone-50 and 100 mg/kg×2/day, p.o.-treated groups contained 71.7±7.3 and 75.4±1.7%, respectively, of the HMG. Thus, in both groups treated with teprenone, the HMG concentration ratio was as high as that in the normal group. Even in the cimetidine-treated group, the HMG showed a relatively high percentage of 62.9±6.0%, although this drug caused a significant reduction in the HMG concentration. However, in the proglumide-treated group, the percentages of the HMG and LMG concentrations were almost similar to those in the control group.

Hexose: When hexose content was determined as an indicator of the glycoprotein in
the gastric mucus, the results of the HMG and LMG concentration ratios of each group coincided with those determined as glycoprotein content.

5. Effects of teprenone, cimetidine and proglumide on glycoprotein secretion (Fig. 6)

Glycoprotein: The amount of gastric mucus glycoprotein secreted was expressed as mg/glandular stomach/rat. The HMG and LMG amounts of the normal group were 1.58±0.17

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Fig. 5. Effects of teprenone, cimetidine and proglumide on high-molecular-weight glycoprotein (HMG) and lower-molecular-weight glycoprotein (LMG) concentration ratios in gastric mucus of acetic acid-induced ulcer in rats. *, ** and ***. Significantly different from the control at P<0.05, P<0.01 and P<0.001, respectively. For other references, see legend to Fig. 4.

Fig. 6. Effects of teprenone, cimetidine and proglumide on glycoprotein secretion in gastric mucus of acetic acid-induced ulcer in rats. *, ** and ***. Significantly different from the control at P<0.05, P<0.01 and P<0.001, respectively. For other references, see legend to Fig. 4.
and 0.47±0.05 mg, respectively. On the other hand, the HMG and LMG amounts of the control group were 36.7% lower and 146.8% higher, respectively, than those of the normal group. Teprenone at doses of 50 and 100 mg/kg×2/day, p.o., pronouncedly increased the HMG secretion by 159.0 and 163.0%, respectively. Furthermore, it was interesting that the amounts of the HMG secreted by treatment with both doses of this agent were over 60% higher than the normal level. Proglumide (500 mg/kg×2/day, p.o.) increased the HMG secretion by 82.0%, significantly, and increased the LMG secretion by 46.6%, though not significantly. In contrast to proglumide, cimetidine (100 mg/kg×2/day, p.o.) not only tended to decrease the HMG secretion but also significantly decreased the LMG by 68.1%. On the other hand, the total glycoprotein (HMG+LMG) secretion was significantly increased 68.5, 54.6 and 63.0% by teprenone at 50 and 100 mg/kg×2/day, p.o., and proglumide, respectively. Unlike both drugs, cimetidine significantly decreased the total glycoprotein secretion by 41.2%.

Hexose: When the amount of gastric mucus glycoprotein secreted was expressed as hexose content/glandular stomach/rat, the HMG and LMG amounts of the normal group were 0.097±0.009 and 0.036±0.004 mg, respectively. On the other hand, the HMG and LMG amounts of the control group were 25.8% lower and 152.8% higher, respectively, than those of the normal group. Teprenone and proglumide showed almost the same results as those determined as glycoprotein. Cimetidine resulted in a 47.2% significant increase in the HMG secretion, although this drug decreased the secretion when expressed as glycoprotein. In addition, cimetidine little affected the total glycoprotein (hexose) secretion.

Discussion

It has been shown that human and pig gastric mucus glycoproteins (2×10^6 or more molecular weight) having a polymeric structure are composed of four glycoprotein subunits (approx. 5×10^6 molecular weight each) joined by a disulfide bridge (1, 10) and are dissociated into the glycoprotein subunits which have lost much of the viscous and gel-forming properties of native mucus by pepsin and other proteolytic enzymes (2, 11). Younan et al. (12) observed significant increases in the amount of LMG of about the same size as the glycoprotein subunits in gastric mucus from patients with gastric ulcer as well as in those with duodenal ulcer when compared with individuals without ulceration.

Our previous study demonstrated an increase in the amount of LMG with a molecular weight between 5×10^5 and 2×10^6 in the gastric mucus obtained during the healing process of acetic acid-induced ulcer in rats (6).

In the present study, the modified PAS (8) and phenol-sulfuric acid (9) methods were used for determining the glycoprotein content in samples obtained from column chromatography. The gastric mucus glycoprotein contains galactose, fucose, N-acetylgalactosamine, N-acetylgalactosamine and sialic acid as carbohydrate chains (13). Total hexose contents have been usually determined by the phenol-sulfuric method for the glycoprotein. However, this method has very low sensitivity to N-acetylgalactosamine, N-acetylgalactosamine and sialic acid when examined preliminarily. On the other hand, the modified PAS method is applicable not only to glycoproteins but also to other polysaccharides oxidized by periodate (8). The measurement of rat gastric glycoprotein by the modified PAS method was about three times more sensitive than the phenol- sulfuric method. Therefore, both methods were used for glycoprotein determination. When in the preliminary experiment, marker materials of molecular weights were applied to the column, blue dextran of 2×10^6 molecular weight and ferritin of 4.4×10^5 molecular weight were eluted with their peaks at tubes 46 and 64, respectively. It was postulated from these results that the molecular weight of the glycoprotein eluted in tubes 39 to 46 (HMG) was 2×10^6 or more, whereas that eluted in tubes 47 to 60 (LMG) was between 5×10^5 and 2×10^6. In the present experiment, a marked decrease in the HMG amount and an increase in the LMG amount in the gastric mucus were confirmed.
in acetic acid-induced ulcer in rats. This phenomenon may be perhaps explained on the basis of the following observations: In this experimental ulcer, we also found a marked elevation of free activity of N-acetyl-β-D-glucosaminidase, a hexosamine exoglycosidase, among lysosomal enzymes in the gastric mucosa (6). When the HMG from the gastric mucus in normal rats was incubated with N-acetyl-β-D-glucosaminidase and the digested material was applied to the column, the elution profile of glycoprotein was very similar to that of samples from the control rats with ulcer (M. Ito et al., unpublished data). Sugiyama et al. (14) also observed the elevation of this enzyme activity as well as a marked decrease in PAS-positive substances in the gastric mucosa of rats subjected to the stress by burn injury. In view of our and their observations, it was deduced that in the gastric mucosa of rats with acetic acid-induced ulcer, the native HMG (a molecular weight of 2×10^6 or more) might be dissociated into LMG by N-acetyl-β-D-glucosaminidase released from the gastric mucosal lysosomes. When in the present study, the HMG or LMG amount was expressed as a percentage of the total amount of glycoprotein (HMG+LMG), the HMG concentration ratio markedly reduced in the gastric mucus of ulcer rats as compared with that of normal rats. In contrast, the LMG concentration ratio increased in the ulcer rats. Therefore, a decrease in the HMG concentration ratio or an increase in the LMG one may indicate the degree of degradation of the HMG into the LMG.

In the preliminary experiment, oral administration of only the vehicle (5% gum arabic and 0.6% Tween 80 solution) had no influence on the healing and on the amount of gastric mucus glycoprotein in acetic acid-induced ulcer in rats. Teprenone (50 and 100 mg/kg×2/day, p.o.) remarkably increased the concentration and secretion of the HMG in the gastric mucus. It is worthy of notice that the amount of the HMG secreted by treatment of this drug was over 60% higher than the normal level. In contrast, the concentration and secretion of the LMG were decreased (less than the control level) by this drug. In addition, the LMG concentration ratio of the teprenone-treated group was as low as that of the normal group. It is concluded from these results that teprenone not only remarkably increases the HMG with a polymeric structure but also may protect the degradation of the HMG into the LMG. Possible mechanisms by which teprenone protects the degradation of the HMG are the following: One of the mechanisms may be due to the inhibition of lysosomal enzyme releases from the gastric mucosa. In this connection, we have unpublished data that daily twice oral administration of this drug markedly inhibited the release of N-acetyl-β-D-glucosaminidase from lysosomal granules of the gastric mucosa in the same ulcer model. It has been reported by Slomiany et al. (15) that fatty acids covalently bound to gastric mucus glycoprotein protects the glycoprotein degradation. Teprenone has been demonstrated to stimulate the syntheses of phospholipids (16) as well as the HMG. Therefore, another mechanism is thought to be due to the increase of phospholipids.

Cimetidine, a H2-receptor antagonist, used as a reference drug, is well-known to strongly inhibit gastric acid secretion evoked by various stimulants (17). In the present experiment, cimetidine (100 mg/kg×2/day, p.o.) significantly decreased both the concentration and secretion of the total glycoprotein (HMG+LMG), although they were not affected when hexose content was determined as an indicator of glycoprotein. Thus, excessive inhibition of acid secretion by this drug may result in reduced secretion of gastric mucus glycoprotein as a defensive factor.

On the other hand, proglumide, a gastrin antagonist, has been demonstrated to stimulate glycoprotein synthesis in the glandular stomach of aspirin-induced ulcers in rats (18). Proglumide (500 mg/kg×2/day, p.o.) showed only slight increases in the concentration and secretion of the HMG, although it pronouncedly increased the total glycoprotein secretion. In addition, the LMG concentration ratio in the proglumide-treated group was as high as that in the control group. It is suggested from the data that a large amount of the HMG secreted by treatment with this drug was enzymatically hydrolyzed.
to produce the LMG.

In the present study, teprenone, cimetidine and proglumide showed a different mode of action on gastric mucus glycoprotein during the healing process of acetic acid-induced ulcer in rats. It is concluded from this finding that teprenone is a representative antiulcer agent increasing the gastric mucus HMG as a defensive factor.

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