Effects of a novel zinc compound (polaprezinc), N-(3-aminopropionyl)-L-histidinato zinc, on the mucosal ulcerogenic and healing impairing responses induced by monochloramine (NH₂Cl) were examined in rat stomach. Oral administration of NH₂Cl (> 60 mM) produced severe hemorrhagic lesions in unanesthetized rat stomachs with a marked increase of thiobarbituric acid reactants (TBAR). Pretreatment of the animals with polaprezinc (3 ~ 30 mg/kg, p.o.) showed a dose-dependent inhibition against gastric ulcerogenic and TBAR responses induced by NH₂Cl (120 mM). Likewise, mucosal exposure to NH₂OH (60 mM) in urethane anesthetized stomachs made ischemic by bleeding from the carotid artery (1 ml per 100 g body w.t.) resulted in severe gastric lesions. This ulcerogenic response caused NH₂OH plus ischemia was also attenuated by prior application of polaprezinc as well as taurine (25 mg/ml, 1 ml). On the other hand, the healing of gastric mucosal lesions induced by NH₂Cl occurred more slowly than of ethanol-induced lesions, and the latter was significantly delayed by the repeated administration of NH₂Cl. Polaprezinc (> 10 mg/kg, p.o.) given twice daily for 7 days not only accelerated the healing of NH₂Cl-induced gastric lesions but also antagonized the delayed healing of ethanol-induced lesions in the presence of NH₂Cl as well. Polaprezinc showed a scavenging action against NH₂Cl \textit{in vitro}. These results suggest that NH₂Cl caused deleterious action on the healing of pre-existing acute lesions as well as irritating action to the mucosa in the rat stomach. Polaprezinc not only protects the stomach against injury caused by NH₂Cl but also promotes healing of NH₂Cl-induced gastric lesions as well as the delayed healing of ethanol-induced lesions caused by NH₂Cl. Although the detailed mechanisms underlying these actions of polaprezinc remain unknown, they may be partly attributable to a scavenging action of this agent against NH₂Cl.

**Key words:** ammonia, monochloramine, polaprezinc, gastric lesion healing, \textit{Helicobacter pylori}, rat
INTRODUCTION

Helicobacter pylori (H. Pylori) has been recognized as the major cause of gastritis and peptic ulcer diseases (1, 2). This bacteria has a high activity of urease enzyme, resulting in an abnormally high concentration of ammonia (NH₄OH) in the stomach of infected patients (3). On the other hand, H. pylori-associated chronic active gastritis is characterized by an invasion of neutrophils in the gastric mucosa (1, 2, 4). Since neutrophils utilizes the H₂O₂-myeloperoxidase (MPO)-halide system to generate an oxidant capable of destroying a variety of microorganisms and mammalian cell targets (5, 6), it is assumed that neutrophil-derived hypochlorous acid (HClO) interacts with NH₄OH to generate cytotoxic monochloramine (NH₂Cl) (7—9). Although several papers showed an irritating action of NH₂Cl on the gastric mucosa (9—11), the influence of this substance on the healing of gastric lesions remains to be still unclear.

On the other hand, a novel zinc compound (polaprezinc), N-(3-aminopropionyl)-L-histidinato zinc, is a chelate compound consisting of zinc ion and L-carnosine (Fig. 1). This agent not only prevents gastric mucosal lesions in a wide variety of experimental models but shows the healing promoting action of gastric ulcers as well (12, 13). This action of polaprezinc may be accounted for by cytoprotective and antioxidative activities (12, 14, 15), although the detailed mechanisms remain unknown. Thus, it is of interest to test whether or not this agent has any prophylactic action against gastric ulcerogenic and healing responses induced by NH₂Cl.

In the present study, we demonstrated the devastating effect of NH₂Cl on the gastric mucosal integrity as well as the healing of pre-existing gastric lesions in rat stomachs, and examined the prophylactic effects of polaprezinc on the mucosal ulcerogenic and healing responses induced by NH₂Cl.
MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats, weighing 250 ~ 300 g (Charles River, Shizuoka, Japan). were used in all experiments. The animals were kept in individual cages with raised mesh bottoms and deprived of food but allowed free access to tap water for 18 hr prior to the experiments. Studies were carried out using 4 ~ 6 rats under both conscious and anesthetized conditions induced by urethane (1.25 g/kg, i.p.).

General procedures

The experiments were classified in roughly three sets of studies; one was to investigate the influences of NH₄Cl on the gastric mucosa in unanesthetized rats, the second to investigate the influence on NH₄OH on the gastric mucosa in anesthetized rats subjected to ischemia; under such situations it is assumed that NH₄Cl is generated endogenously from interaction of NH₄OH with neutrophil-derived HClO (9, 10), and the third is to examine the effect of NH₄Cl on the healing response of pre-existing gastric lesions induced by ethanol. In each study, the effect of polaprezinc on the mucosal ulcerogenic and healing responses induced by NH₄Cl were examined. In separate study, we also examined the scavenging action of polaprezinc against NH₄Cl as well as the effect of polaprezinc on the expression of insulin-like growth factor-1 (IGF-1) in vitro experiments.

Induction of gastric mucosal lesions

Study A: Irritant effects of NH₄OH, NaClO and NH₄Cl on the gastric mucosa were compared. The animals were administered 1 ml of NH₄OH (120, 600 and 1,800 mM), NaClO (120 mM), or NH₄Cl (20, 60, and 120 mM), orally by esophageal intubation. The solution of NH₄Cl was prepared by mixing the same concentration of NH₄OH and NaClO, immediately before the administration. The animals were killed 1 hr after the administration of each agent, the stomachs removed, inflated by injecting 8 ml of 2% formalin and immersed in 2% formalin for 10 min to fix the gastric wall, and opened along the greater curvature. The area (mm²) of hemorrhagic lesions was measured under a dissecting microscope with a square grid (x 10). The person measuring the lesions did not know the treatment given the animals. These procedures for evaluating macroscopic lesions were applied to all the subsequent studies. Polaprezinc (3 ~ 30 mg/kg) was administered p.o. 30 min before NH₄Cl treatment. Control animals received 0.5% carboxymethylcellulose solution (CMC) as the vehicle.

Study B: Under urethane anesthesia, the stomach was mounted on an ex-vivo chamber (the exposed area: 13 cm²) (11, 16). The animals were subjected to ischemia by bleeding from the carotid artery (1 ml/100 g body w.t.), and then the mucosa was exposed to 1 ml of CMC, followed by 1 ml of NH₄OH (120 mM; a final concentration is 60 mM) for 1 hr. At the end of the experiment, the mucosa was dissected out, and the area (mm²) of hemorrhagic lesions was measured as described above. Polaprezinc (2, 6 and 12 mg/ml, 1 ml) or taurine (25 mg/ml, 1 ml) was applied to the chamber 10 min before the onset of ischemia and NH₄OH treatment. Control animals received CMC as the vehicle.

Study C: The animals were given 1 ml of absolute ethanol or 120 mM NH₄Cl orally through esophageal intubation, then fed on normal chow from 1 hr later. On various days (1, 3, 5 and 7 days) after induction of lesions, the animals were killed, the stomachs removed, treated with 2% formalin, and the area (mm²) of damage was measured as described above. In half the number of animals treated with ethanol was given NH₄Cl (20 mM) twice daily at 9:00 a.m. and 6:00 p.m. for 6 days. In the latter study, polaprezinc was administered p.o. in a dose of 30 mg/kg twice daily for 6 days, each 30 min before NH₄Cl treatment.

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Determination of lipid peroxidation

The lipid peroxidation in the gastric mucosa was determined as thiobarbituric acid reactant (TBAR) at 1 hr after NH₄Cl treatment, according to the modified method of Ohkawa et al (11). Briefly, the animals were killed under deep ether anesthesia and the stomachs removed. After rinsing the stomach with cold saline, the mucosa was scraped, weighed, and homogenized in 10 ml KCl. The homogenate was supplemented with the mixture of TBAR and boiled at 100°C for 1 hr. The TBAR were then supplemented with 5 ml of the mixture of n-butanol and pyridine, shaken vigorously for 1 min and centrifuged for 100 min at 4000 rpm. Absorbance was measured at 532 nm on Hitachi spectrophotometer and the results were expressed as m mole TBAR per mg protein.

Determination of NH₄Cl scavenging action

The NH₄Cl scavenging actions of polaprezinc as well as taurine were determined in an in vitro experiment, according to the method described by Lapenna et al. (18). It is known that HOCl interacts with β-carotene, inducing vitamin bleaching (19). This phenomenon is characteristic of the chemical reaction of chlorine species with carotene, and thus molecules capable of scavenging chlorine species can specifically antagonize β-carotene. In brief, the reaction mixtures contained 1.3 μmol/L β-carotene in 0.05 mol/L MES buffer, at pH 7.4, with or without polaprezinc or taurine (0.1 ~ 1 mM). NH₄Cl was synthesized by adding HClO to solution of ammonium chloride in 0.05 mol/L MES buffer, at pH 7.0, and added to the reaction mixture at the final concentration of 100 μmol, followed by 15 min incubation at 30°C to bleach β-carotene. β-carotene-related absorbance at 451 nm (A₄₅₁) was then spectrophotomerically recorded against appropriate drug-containing blanks to assess a specific effect. The concentration of NH₄Cl was calculated using a molar extinction coefficient of 429 M⁻¹ cm⁻¹ at 242 nm.

Preparation of drugs

Drugs used in this study were urethane (Tokyo Kasei, Tokyo, Japan), taurine, β-carotene (Sigma Chemicals, St. Louis, Mo., USA) and polaprezinc (Zeria Pharmaceutical Co., Saitama, Japan). Other chemicals used were of reagent grade. Urethane was dissolved in saline. Taurine or polaprezinc was dissolved or suspended with carboxymethylcellulose (CMC) solution, respectively. Each agent was prepared immediately before use. Drugs were administered i.p., p.o. or applied topically to the chamber, in a volume of 1 ml per rat. Control animals received CMC as the vehicle.

Statistics

Data are presented as the means ± SE from 4 ~ 6 rats per group. Statistical analyses were performed using a two-tailed Dunnett’s multiple comparison test, and values of P < 0.05 were regarded as significant.

RESULTS

Mucosal Ulcerogenic Effect of NH₄OH, NaClO and NH₄Cl

Intragastric administration of NH₄OH at a low concentration (120 mM) did not produce any macroscopic damage in the stomach but produced severe
hemorrhagic lesions in the gastric mucosa at the concentration of greater than 600 mM; the lesion score at 600 and 1,800 mM was 65.5 ± 11.0 mm² and 240.2 ± 23.6 mm², respectively. On the other hand, NaClO, the neutrophil-derived oxidant, did not cause any damage in the gastric mucosa at the concentration of 120 mM. However, NH₄Cl generated from a reaction of NaClO with NH₄OH, produced severe hemorrhagic lesions in the rat stomach at the concentration of 60 mM or greater. The lesion score induced by NH₄Cl at 120 mM was 184.7 ± 14.5 mm², which is almost equivalent to that induced by NH₄OH at the concentration of 1,800 mM.

**Effects of Polaprezinc on Mucosal Ulcerogenic and TBAR Responses Induced by NH₄Cl**

Intragastric administration of NH₄Cl produced severe lesions in the stomach with a marked increase for TBAR, an indicator of lipid peroxidation (Fig. 2). These lesions induced by NH₄Cl were prevented by prior p.o. administration of polaprezine (3 ~ 30 mg/kg) in a dose-dependent manner, and a significant effect was observed at 10 mg/kg or greater, the inhibition at 30 mg/kg being 59.3%. In the stomach treated with NH₄Cl, the mucosal levels of lipid peroxidation as determined by TBAR was significantly increased, the values being 1.1 ± 0.12 nmol/mg protein, which is about 6 times greater than the control level. This increase in TBAR induced by NH₄Cl was also significantly reduced when the animals were pretreated with either polaprezine (10 mg/kg) at the doses that significantly prevented the mucosal ulcerogenic response to NH₄Cl, although the values were still significantly higher than those in normal rats.

**Fig. 2.** Effect of polaprezinc on gastric lesions and changes in TBAR induced by NH₄Cl in rats. The animals were administered p.o. with 1 ml of NH₄Cl (120 mM), and killed 1 hr later. Polaprezinc (2 ~ 12 mg/ml) was administered p.o. in a volume of 1 ml/rat 30 min before NH₄Cl treatment. Data are presented as the means ± SE from 5 ~ 6 rats. Statistically significant difference at P < 0.05; * from normal; # from CMC.
Effects of Polaprezinc on Mucosal Ulcerogenic Responses Induced by NH₄OH in Rat Stomach under Ischemic Conditions

To confirm the protective action of polaprezinc on NH₄Cl-induced gastric toxicity, we tested the effect of polaprezinc on the mucosal ulcerogenic response induced by endogenously generated NH₄Cl by application of a low concentration of NH₄OH (60 mM) in the ischemic stomach. As shown in Fig. 3, topical application of NH₄OH in the stomach made ischemic by bleeding from the carotid artery (1 ml per 100 g body w.t.) resulted in severe hemorrhagic lesions within 1 hr, the lesion score being 53.6 ± 12.2 mm². The development of gastric lesions induced NH₄OH in ischemic stomach was totally inhibited when the mucosa was pre-exposed to taurine (25 mg/ml) before ischemia plus NH₄OH treatment. These lesions were also dose-dependently prevented by prior treatment with polaprezinc (2 ~ 12 mg/ml); a significant effect was observed at 6 mg/ml and 12 mg/ml, the inhibition being 87.7% and 91.4%, respectively.

![Fig. 3. Effect of polaprezinc on gastric lesions induced by NH₄OH in anesthetized rat stomachs under ischemic conditions. The stomach was mounted on an ex-vivo chamber, subjected to ischemia by bleeding from the carotid artery (1 ml/100 g body weight), and then exposed to NH₄OH (60 mM) for 1 hr thereafter. Polaprezinc (2 ~ 12 mg/ml) and taurine (25 mg/ml) were applied to the chamber in a volume of 1 ml, starting 10 min before the onset of ischemia and NH₄OH treatment. Data are presented as the means ± SE from 4 ~ 5 rats. * Statistically significant difference from control (CMC), at P < 0.05.](image)

Effect of NH₂Cl on Healing of Gastric Mucosal Lesions

Oral administration of absolute ethanol or 120 mM NH₂Cl induced damage in the gastric mucosa, and the severity of lesions at 1 hr after treatment was almost similar, the lesion score being 173.3 ± 26.7 mm² or 156.4 ± 22.6 mm², respectively. The lesions induced by ethanol healed rapidly within 7 days, and the lesion score on day 7 was 7.0 ± 1.9 mm², which was only 4.0% of the initial damage score (Fig. 4.). On the other hand, the healing of NH₂Cl-induced gastric lesions occurred slowly as compared to those induced by ethanol at any time points, and the lesion score on day 7 was 55.0 ± 15.9 mm², which was still 35.2% of the initial damage score. In addition, the healing of ethanol-induced gastric lesions was significantly delayed when the animals were treated with NH₂Cl given p.o. twice daily for 7 days. The lesion score in
Fig. 4. The healing process of acute gastric lesions induced by absolute ethanol and 120 mM NH$_2$Cl in rats. Gastric lesions were induced by p.o. administration of 1 ml of absolute ethanol or 120 mM NH$_2$Cl, and the animals were killed 1 hr or various days after administration of these agents. Data are presented as the means ± SE from 5 ~ 6 rats. * Statistically significant difference from ethanol-treated group, at P < 0.05.

these animals was significantly greater at any time points than that in control animals treated with ethanol alone; the values on day 5 were 21.1 ± 1.6 mm$^2$ or 49.5 ± 4.8 mm$^2$ in the absence or presence of NH$_2$Cl treatment, respectively (Fig. 5).

![Graph showing healing process](image)

Fig. 5. Influence of NH$_2$Cl on the healing of ethanol-induced gastric lesions in rats. Gastric lesions were induced by p.o. administration of absolute ethanol. NH$_2$Cl (20 mM) was given p.o., twice daily for 7 days, starting from 12 hr after ethanol treatment. Data are presented as the means ± SE from 5 ~ 6 rats. * Statistically significant difference from ethanol-alone, at P < 0.05.

**Effect of Polaprezinc on Healing Response of Gastric Mucosa**

We examined the healing promoting effect of polaprezinc in two kinds of studies; the one was performed using NH$_2$Cl-induced gastric lesions, and the other using the delayed healing of ethanol-induced gastric lesions in the presence of NH$_2$Cl. Repeated p.o. administration of polaprezinc (30 and 60 mg/kg) for 5 days caused a dose-dependent healing promoting action on NH$_2$Cl-induced gastric lesions, and a significant effect was observed at 60
mg/kg, the healing rate being 43.6% (Fig. 6.). Likewise, polaprezinc showed a healing promoting action against the delayed healing of ethanol-induced gastric lesions in the presence of NH$_2$Cl. As shown in (Fig. 7), the healing of gastric lesions induced by ethanol was significantly delayed by daily administration of NH$_2$Cl for 5 days, the lesion score being 49.5 ± 4.8 mm$^2$, which was significantly greater than that (17.1 ± 2.3 mm$^2$) in control animals. Concurrent administration of polaprezinc (10 ~ 60 mg/kg) with NH$_2$Cl counteracted the delayed healing of these lesions in a dose-dependent manner, and a significant effect was observed at 30 mg/kg or greater.

**Fig. 6.** Effect of polaprezinc on the healing of NH$_2$Cl-induced gastric lesions in rats. Gastric lesions were induced by p.o. administration of 120 mM NH$_2$Cl. Polaprezinc (30 and 60 mg/kg) was given p.o. twice daily for 5 days, starting from 12 hr after NH$_2$Cl treatment. Data are presented as the means ± SE from 6 rats. * Statistically significant difference from control, at P < 0.05.

**Fig. 7.** Effect of polaprezinc on the delayed healing of ethanol-induced gastric lesions caused by NH$_2$Cl in rats. Gastric lesions were induced by p.o. administration of absolute ethanol. The healing was delayed by the repeated administration of NH$_2$Cl (20 mM), given p.o. twice daily for 5 days, starting from 12 hr after ethanol treatment. Polaprezinc (10 ~ 60 mg/kg) was given p.o. twice daily for 5 days, each 30 min before administration of NH$_2$Cl. Data are presented as the means ± SE from 6 ~ 8 rats. Statistically significant difference at P < 0.05; # from ethanol alone; * from control.

**Scavenging Action of Polaprezinc against NH$_2$Cl**

Scavenging action of polaprezinc and taurine on NH$_2$Cl was examined in an in vitro study, using β-carotene bleaching test (18). Polaprezinc (0.1 ~ 1 mM) exhibited a concentration-dependent scavenging action against NH$_2$Cl as determined by inhibition rate of the NH$_2$Cl-induced β-carotene bleaching, the EC$_{50}$ being about 0.03 mM (Fig. 8). The same effect was observed by taurine at similar concentration ranges, although the potency was less than that of polaprezinc, the EC$_{50}$ being 0.25 mM.
DISCUSSION

The present study showed that NH\textsubscript{2}Cl, either administered exogenously or generated endogenously through interaction of NH\textsubscript{4}OH with neutrophil-derived HO\textsubscript{2}Cl\textsubscript{2}, exhibited a potent irritating action in rat stomachs and demonstrated that polaprezinc, a chelate compound of zinc ion and L-carnosine, affords a protection against such gastric damage induced by NH\textsubscript{2}Cl. In addition, we also showed that NH\textsubscript{2}Cl even at a low concentration impaired the healing of acute gastric lesions, and polaprezinc counteracted the deleterious effect of NH\textsubscript{2}Cl on the healing response, exhibiting a healing promoting action.

\textit{H. pylori} has a high activity of urease enzyme, resulting in an abnormally high concentration of ammonia (NH\textsubscript{4}OH) in the stomach of infected patients (3). It is also known that NH\textsubscript{4}OH interacts with neutrophil-derived HO\textsubscript{2}Cl\textsubscript{2} to generate cytotoxic NH\textsubscript{4}Cl, a powerful oxidant capable of destroying a variety of microorganisms as well as mammalian cell targets (5—8). Murakami \textit{et al.} (9) demonstrated that NH\textsubscript{4}OH-induced gastric mucosal lesions were significantly inhibited by taurine, a scavenger of HO\textsubscript{2}Cl\textsubscript{2} in rats, suggesting a pathogenic role of NH\textsubscript{2}Cl in the development of these lesions. We also confirmed that even low concentration of NH\textsubscript{4}OH damages the mucosa when the stomach was subjected to ischemia. It is generally accepted that ischemia activates xanthine oxidase, which is responsible to the production of reactive oxygen metabolites such as H\textsubscript{2}O\textsubscript{2}, and that the generation of HO\textsubscript{2}Cl\textsubscript{2} by neutrophils is dependent on the quantity of H\textsubscript{2}O, and that the generation of HO\textsubscript{2}Cl\textsubscript{2} by neutrophils is dependent on the quantity of H\textsubscript{2}O\textsubscript{2} produced (5, 6). It is assumed that NH\textsubscript{4}OH even at low concentrations produces NH\textsubscript{2}Cl by interaction with HO\textsubscript{2}Cl\textsubscript{2} in the ischemic stomach, resulting damage in the mucosa. Indeed, the mucosal lesions...
induced by NH₄OH in the ischemic stomach were totally prevented in the presence of taurine.

Polaprezinc, a chelate compound of zinc ion and L-carnosine significantly prevented the mucosal ulcerogenic responses induced by NH₄Cl in the normal stomach or by NH₄OH in the ischemic stomach, confirming our previous results (22). We also reported the protective action of polaprezinc against NH₂Cl-induced gastric injury was not affected by either sensory differentiation, indomethacin or L-NAME, excluding the involvement of endogenous prostaglandins and nitric oxide as well as sensory neurons in its mechanism (23). This compound has been shown to exhibit various actions, including membrane stabilization (24) and anti-oxidative action (13). Since the generation of NH₄Cl in the ischemic stomach exposed to NH₄OH is a process depending on the presence of superoxide radicals, it is possible that the protective action of polaprezinc in such stomach may be accounted for by its anti-oxidative action. Indeed, the amount of TBAR was increased by NH₄Cl, suggesting an increase of lipid peroxidation in the gastric mucosa, and these changes were significantly prevented by either polaprezinc. Although a cause-effect relationship between these two events remains unclear, it was evident in the present study that polaprezinc has a scavenging property against NH₂Cl. Again it should be noted in this study that the mucosal lesions induced by NH₄OH in the ischemic stomach were totally prevented in the presence of taurine, the scavenger of NH₂Cl.

On the other hand, NH₂Cl significantly impaired the healing of pre-existing gastric lesions induced by ethanol. Indeed, gastric lesions induced by NH₂Cl healed slowly as compared to those induced by ethanol. These results strongly suggest that NH₂Cl has a devastating effect on the healing response of gastric lesions, in addition to a irritating action on the gastric mucosa. The healing of chronic ulcers is reportedly modified in the presence of superoxide radicals (25—27). Naito et al (27) showed that treatment with dimethylsulfoxide (DMSO) or rebamipide, a novel hydroxyl radical scavenger, counteracted the exacerbation or relapse of acetic acid-induced gastric ulcers in rats. Thus, it is possible that a cytotoxic action of NH₂Cl as a radical species might contribute to its deleterious effect on the healing response. Certainly, the influence of NH₂Cl on other functions such as gastric mucosal blood flow should also be considered as well. As expected, polaprezinc exhibited a significant accelerating effect on the healing of NH₂Cl-induced gastric lesions as well as the delayed healing of ethanol-induced lesions in the presence of NH₂Cl. It is not unreasonable to speculate that the healing promoting effect of polaprezinc may also be due to its scavenging action against NH₂Cl. Alternatively, this action of polaprezinc might be accounted for by its stimulating effect on cell prolif-
eration. Zinc, an essential trace element in animals, is known to be involved in enzymes and transcription factors responsible for several biological functions such as nucleotide synthesis, protein synthesis, and gene expression in cellular proliferation and differentiation (28). Zinc deficiency retards growth in animals and the healing of several injuries such as gastric ulcers (29, 30). Polaprezinc, a compound containing zinc, has been shown to reverse the retardation of gastric ulcer healing caused by zinc deficiency in rats (30). Dorup et al (21) reported that zinc deficient rats showed lower values of serum concentration of insulin-like growth factor-1 (IGF-1), which are reversed by supplementation with zinc. Morita et al. (31) recently reported that polaprezinc increased the gene expression of IGF-1 mRNA in the stomachs of streptozotocin diabetic rats. Thus, it may be possible that polaprezinc exerts a healing promoting action through the expression of IGF-1.

The present results taken together suggest that NH₃Cl, either administered exogenously or generated endogenously, damages the gastric mucosa and impairs the healing of acute gastric lesions. Polaprezinc not only protects the stomach against injury caused by NH₃Cl but also promotes the delayed healing of acute gastric lesions caused by NH₃Cl as well. Although the detailed mechanisms underlying these actions of polaprezinc remain unknown, they are partly attributable to its scavenging action of NH₃Cl. Since an important feature of H. pylori infection in the stomach is infiltration of neutrophils in the gastric mucosa (1, 2, 4), it is highly possible that NH₃Cl is formed in the inflamed gastric mucosa, where neutrophil and H. pylori are located in juxtaposition. Thus, the present study also suggests that polaprezinc may have therapeutic potential in the prevention and/or treatment of gastric mucosal damage related with H. pylori.

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Author's address: Koji Takeuchi, Ph.D., Department of Pharmacology and Experimental Therapeutics, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8414, Japan. E-mail: takeuchi@mb.kyoto-phu.ac.jp.