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Protective Effect of Lafutidine, a Novel H_2-Receptor Antagonist, on Reflux Esophagitis in Rats Through Capsaicin-Sensitive Afferent Neurons

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Abstract. We examined the effect of lafutidine, a novel histamine H_2-receptor antagonist, on acid reflux esophagitis in rats in relation to capsaicin-sensitive afferent neurons. The esophagitis was induced in rats by ligating both the pylorus and forestomach for 4 h. Lafutidine (1 – 30 mg /kg) and cimetidine (100 mg/kg) were administered either intragastrically or intraduodenally, while capsaicin (1 – 30 mg/kg) was administered intragastrically after the dual ligation. Intragastrical administered lafutidine at >3 mg/kg significantly prevented the hemorrhagic esophageal damage induced by the dual ligation, and this effect was mimicked by neither capsaicin nor cimetidine given intragastrically, but totally abolished by sensory deafferentation. In contrast, lafutidine and cimetidine given intraduodenally were both protective against the esophageal damage in a sensory deafferentation-resistant manner. The acid secretion in pylorus-ligated stomachs was significantly inhibited by these agents given intraduodenally, but not intragastrically. Vanilloid receptor subtype 1 (VR1) was expressed abundantly in the stomach, but very weakly expressed in the esophagus as assessed by Western blotting. These results suggest that lafutidine is effective against the esophageal lesions induced by acid reflux through inhibition of acid secretion and capsaicin-sensitive afferent neurons. The latter mechanism, not shared by cimetidine, may be due to the interaction of lafutidine with unidentified sites on sensory neurons other than VR1.

Keywords: lafutidine, acid reflux esophagitis, capsaicin-sensitive afferent neuron, acid secretion, vanilloid receptor subtype 1

Introduction

Gastroesophageal reflux disease (GERD) is considered to be caused mainly by acid reflux due to acid hypersecretion and dysfunction of the lower esophageal sphincter (LES), the latter unable to prevent gastric acid from refluxing into the esophagus (1). It has been believed that pH control is important in the management of GERD (2). Indeed, several antisecretory drugs, such as histamine H_2-receptor antagonists and proton pump inhibitors, have been shown to be effective against acid reflux esophagitis in humans and animals (3 – 5).

Capsaicin-sensitive afferent neurons are selectively stimulated by capsaicin, a pungent of hot chili peppers, through binding to vanilloid receptor subtype 1 (VR1), which has recently been cloned as a capsaicin receptor (6), resulting in the liberation of the neurotransmitter calcitonin gene-related peptide (CGRP) and affecting several physiological functions (7). In the gastrointestinal tract, these neurons play an important role in maintaining mucosal integrity (8 – 12). In addition, Bass et al. (13) demonstrated that these neurons in the esophagus were local effectors of mucosal protection, showing that intraluminal capsaicin prevented the esophageal damages induced by ethanol through an increase of blood flow in rabbits. Thus, it is likely that these neurons play an important role in maintaining the integrity of the esophagus.

Lafutidine [(±)-2-(furfurylsulfinyl)-*N*-[4-[4-(piperi-

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dinomethyl)-2-pyridyl]oxy-(*Z*)-2-butenyl]acetamide], a novel histamine H_2-receptor antagonist, has been shown to exhibit potent gastroprotective activity in addition to a gastric acid antisecretory effect (14, 15). It has been also reported that the gastroprotective activity of lafutidine was independent of antisecretory activity but partially or fully mediated by capsaicin-sensitive afferent neurons (16). Indeed, several studies demonstrated that lafutidine significantly prevented gastrointestinal damage in experimental animal models through these neurons (16 – 18). Thus, it is of interest to examine whether or not lafutidine has any protective action in the esophagus through capsaicin-sensitive afferent neurons.

In the present study, we examined the effect of lafutidine on acid reflux esophagitis in relation to anti-secretory effects and capsaicin-sensitive afferent neurons.

Materials and Methods

Animals

Male Sprague-Dawley rats (200 – 230 g; Nippon Charles River, Shizuoka) were used. The experiments were performed using 4 – 6 rats per group under unanesthetized conditions after 18 h fasting, unless otherwise specified. All experimental procedures described were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University.

Induction of acid reflux esophagitis

Under ether anesthesia, the abdomen was incised along the middle and then both the pylorus and the junction between the forestomach and corpus were ligated, according to the method of Nakamura et al. (19). The animals were killed with deep ether anesthesia 4 h later, and then the esophagus and stomach were removed and treated with 2% formalin for fixation of the tissues. The total area (mm^2) of lesions that had developed in the esophagus was measured under a dissecting microscope (×10). The person measuring the lesions did not know the treatments given to the animals. Lafutidine (1 – 30 mg/kg), capsaicin (1 – 30 mg/kg), and cimetidine (100 mg/kg) were given intragastrically (i.g.) through esophageal intubation or intraduodenally (i.d.) immediately after the ligation.

Defunctionalization of capsaicin-sensitive afferent neurons

The ablation of capsaicin-sensitive afferent neurons was performed chemically by subcutaneous (s.c.) injection of capsaicin once daily for three consecutive days (total dose: 100 mg/kg) two weeks before the experiment (12). All capsaicin injections were performed under ether anesthesia, and the rats were pretreated intramuscularly with terbutaline (0.1 mg/kg) and aminophylline (10 mg/kg) before capsaicin injection to counteract the respiratory impairment associated with capsaicin injections. To check for the effectiveness of the treatments, a drop of capsaicin solution (0.1 mg/ml) was instilled into one eye of each rat, and the wiping movements were counted as previously reported (8). Control animals received saline s.c. as the vehicle for capsaicin.

Determination of basal acid secretion

Under ether anesthesia, the abdomen was opened and the pylorus was ligated. The animals were then allowed to recover from the anesthesia. Four hours later, the animals were killed under deep ether anesthesia, the stomachs were removed, and the gastric contents were collected. After centrifugation for 10 min at 1,600 × *g*, each sample was measured for volume and titrated with 100 mM NaOH to pH 7.0 using an automatic titrator (Commtite 550; Hiranuma, Ibaraki) for titratable acidity. Lafutidine (10 mg/kg) and cimetidine (100 mg/kg) were given i.g. or i.d. immediately after the ligation.

Expression of VR1 by Western blotting

Under deep ether anesthesia, the rats were killed, and the esophagus, stomach, and spinal cord were removed. Each tissue was homogenized in ice-cold 50 mM Tris HCl buffer (pH 7.4), containing 1 mM phenylmethylsulfonyl fluoride, 32 mM sucrose, 1 mm dithiothreitol, 10 μg/ml soybean trypsin inhibitor, 10 mg/ml leupeptin, and 2 μg/ml aprotinine. Then, the homogenized samples were centrifuged at 100,000 × *g* for 1 h at 4°C. The supernatant was removed and the pellet was re-suspended in the homogenized buffer. The protein concentrations in the supernatants were determined using a BCA protein assay kit (Pierce, Rockford, Illinois, USA) and adjusted to 10 μg/ml using Tris-HCl buffer. Then, the samples (10 μg/lane) were electrophoretically separated on 10% SDS-polyacrylamide gels, and transferred electrophoretically to nitrocellulose membranes. Each membrane was incubated with anti-VR1 antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and treated with horseradish peroxidase-conjugated anti-goat IgG (Santa Cruz Biotechnology). The immune complexes were visualized using the enhanced chemiluminescence detection system (NEN, Boston, MA, USA).

Preparation of drugs

Drugs used in this study were lafutidine (UCB Japan Co., Ltd., Tokyo), capsaicin (Wako, Osaka) and cimetidine (Nacalai Tesque, Kyoto). Lafutidine and cimetidine were suspended in a 0.5% carboxymethylcellulose

(CMC) (Nacali Tesque) solution. Capsaicin was dissolved in Tween 80 / ethanol solution (10% ethanol / 10% Tween 80 / 80% saline, w/w) for s.c. injection, while it was suspended in 0.5% CMC for i.g. administration. Other drugs were dissolved in saline. All drugs were prepared immediately before use and administered i.g., i.d., or s.c. in a volume of 0.5 ml / 100 g body weight.

Statistics

Data are presented as the mean ± S.E.M. from 4 to 6 rats per group. Statistical analyses were performed using the two-tailed Student's *t*-test or ANOVA followed by Dunnett's multiple comparison test, and values of $P<0.05$ were regarded as significant.

Results

Effects of lafutidine and cimetidine on acid reflux esophagitis

With ligation of both the pylorus and forestomach, severe hemorrhagic lesions developed in the thoracic esophagus in all animals 4 h later, the lesion score being 124.2 ± 5.4 mm^2 (Figs. 1 and 2). Lafutidine (1, 3, 10, and 30 mg/kg) given i.g. prevented the lesions, the inhibition being 13.0%, 30.7%, 57.7%, and 49.1%, respectively; and a significant effect was observed at a dose of 3 mg/kg or greater. In contrast, cimetidine (100 mg/kg) given i.g. did not affect the severity of esophageal lesions, the inhibition being 11.4%.

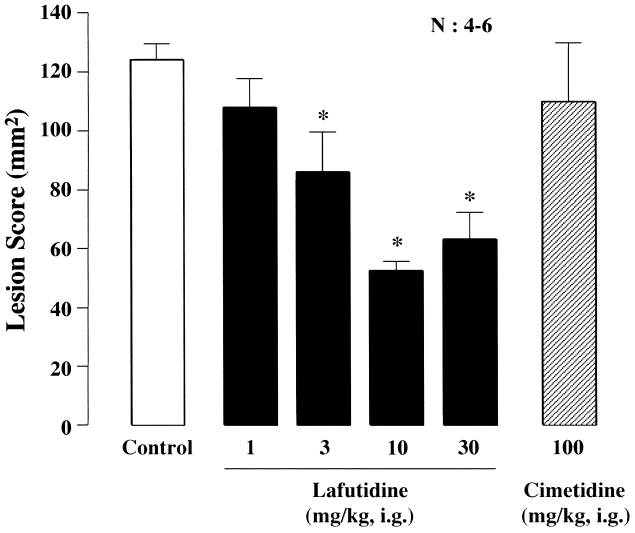

Fig. 1. Effects of lafutidine and cimetidine on acid reflux esophagitis in rats. Under ether anesthesia, both the pylorus and forestomach were ligated, and the esophageal mucosa was examined 4 h later. Lafutidine (1 – 30 mg/kg) and cimetidine (100 mg/kg) were given intragastrically (i.g.) through esophageal intubation, immediately after the ligation. Data are presented as the mean ± S.E.M. from 4 – 6 rats. *Significant difference from the control, at $P<0.05$.

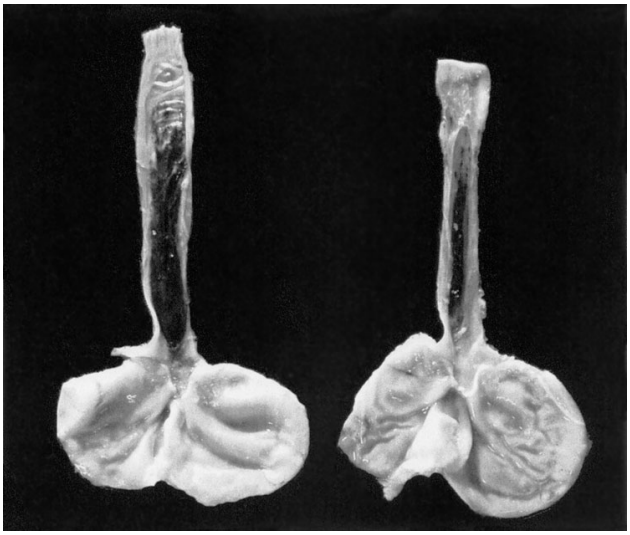

Fig. 2. Macroscopic appearance of esophageal lesions induced by ligation of both the pylorus and forestomach for 4 h. Lafutidine (10 mg/kg) was given i.g. through esophageal intubation immediately after the ligation. Note that lafutidine apparently reduced the severity of hemorrhagic esophageal lesions.

When lafutidine (10 and 30 mg/kg) was given i.d., the severity of esophageal lesions was also reduced in a dose-dependent manner. A significant effect was observed at 30 mg/kg, the inhibition being 76.4% (Fig. 3). Similarly, cimetidine given i.d. at 50 mg/kg significantly prevented the development of esophageal lesions, the inhibition being 50.2%.

Influence of sensory deafferentation on the protective effect of lafutidine

In normal rats, when lafutidine was given i.g. (10 mg /kg) and i.d. (30 mg/kg), the severity of the esophageal lesions induced by ligation of both the pylorus and forestomach was significantly reduced, the inhibition being 52.0% and 74.5%, respectively (Fig. 4). The protective effect of lafutidine given i.g. was significantly mitigated by chemical ablation of capsaicin-sensitive afferent neurons, the lesion score being 95.7 ± 4.8 mm^2, which was almost equivalent to the value for sensory deafferented control rats (110 ± 8.2 mm^2). In contrast, sensory deafferentation had no effect on the protective action of lafutidine given i.d.; and the lesion score was 48.0 ± 4.7 mm^2, the inhibition being 60.0%. Sensory deafferentation alone had no effect on the development of esophageal lesions.

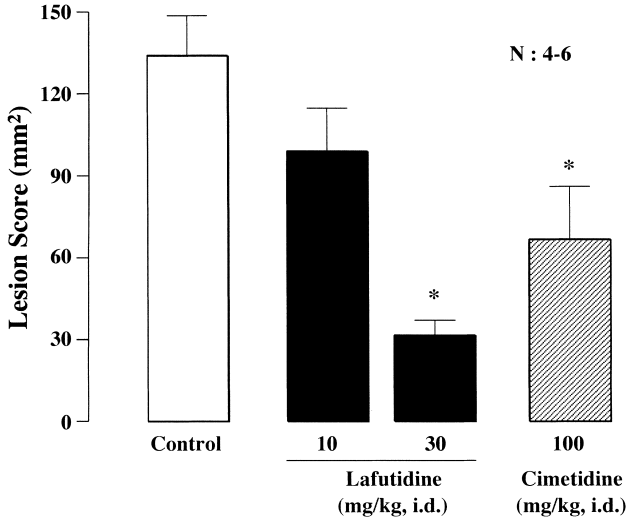

Fig. 3. Effects of lafutidine and cimetidine on acid reflux esophagitis in rats. Under ether anesthesia, both the pylorus and forestomach were ligated, and the esophageal mucosa was examined 4 h later. Lafutidine (10 and 30 mg/kg) and cimetidine (100 mg/kg) were given intraduodenally (i.d.) immediately after the ligation. Data are presented as the mean ± S.E.M. from 4 – 6 rats. *Significant difference from the control, at $P<0.05$.

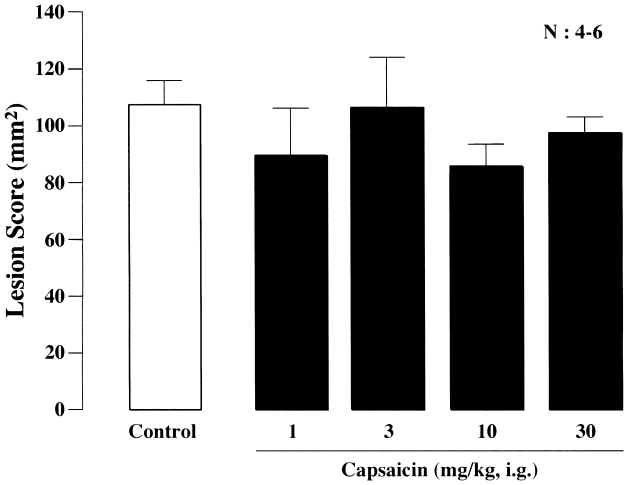

Fig. 5. Effects of capsaicin on acid reflux esophagitis in rats. Under ether anesthesia, both the pylorus and forestomach were ligated, and the esophageal mucosa was examined 4 h later. Capsaicin (1 – 30 mg/kg) was given intragastrically (i.g.) through esophageal intubation immediately after the ligation. Data are presented as the mean ± S.E.M. from 4 – 6 rats.

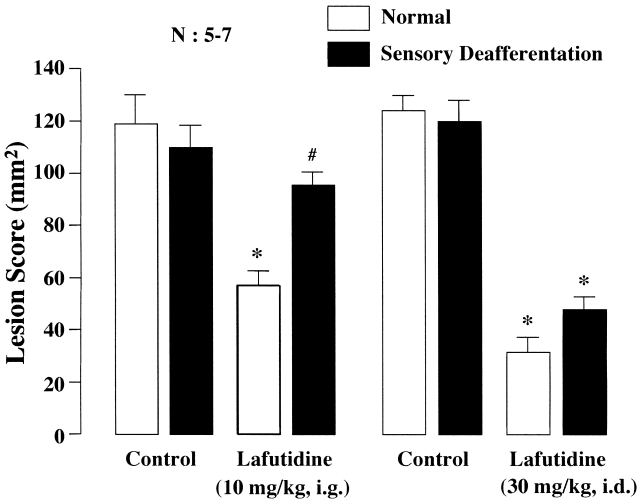

Fig. 4. Influence of sensory deafferentation on lafutidine-induced protection from reflux esophageal lesions in rats. Under ether anesthesia, both the pylorus and forestomach were ligated, and the esophageal mucosa was examined 4 h later. Sensory deafferentation was achieved by giving consecutive s.c. administrations of capsaicin (total 100 mg/kg) 2 weeks before the experiment. Lafutidine was given i.g. (10 mg/kg) or i.d. (30 mg/kg) immediately after the ligation. Data are presented as the mean ± S.E.M. from 5 – 7 rats. Significant difference at $P<0.05$, * from the corresponding control; # from the corresponding normal rats.

Effect of capsaicin on acid reflux esophagitis

Since the protective effect of lafutidine given i.g. on the esophageal lesions was attenuated by sensory deafferentation, stimulation of capsaicin-sensitive afferent neurons is expected to be effective against acid reflux esophagitis. To test this possibility, we examined the effect of capsaicin given i.g. on the esophageal lesions induced by ligation of both the pylorus and forestomach. As shown in Fig. 5, however, capsaicin (1, 3, 10, and 30 mg/kg) failed to affect the development of esophageal lesions, the severity of damage at all dose levels being equivalent to that of the control.

Effect of lafutidine and cimetidine on basal acid secretion

Pylorus-ligated stomachs accumulated about 5 ml of gastric contents within 4 h, the acid output being 122 – 125 μEq/h (Table 1). Intraduodenal administration of both lafutidine (10 and 30 mg/kg) and cimetidine (100 mg/kg) significantly reduced the acid output, the inhibition being 41.9%, 60.9%, and 64.4%, respectively. Neither of these agents when given i.g. had any effect on acid secretion in pylorus-ligated rats.

Expression of VR1 in the esophagus, stomach, and spinal cord

With Western blotting, the expression of VR1 was observed in the rat spinal cord as well as the stomach (Fig. 6). However, the expression of VR1 in the rat esophagus was very weakly, in comparison with the other two tissues.

Table 1. Effects of lafutidine given orally and intraduodenally on gastric acid secretion in pylorus-ligated rats

Drugs	Doses (mg/kg)	No. of rats	Acid output (μEq/h)
i.g.			
Control		4	122.8 ± 8.8
Lafutidine	10	4	139.5 ± 23.9
Lafutidine	30	4	145.0 ± 6.2
Cimetidine	100	5	141.5 ± 13.9
i.d.			
Control		4	124.6 ± 25.0
Lafutidine	10	4	72.4 ± 25.6*
Lafutidine	30	5	48.7 ± 10.7*
Cimetidine	100	5	44.3 ± 5.7*

Basal acid output was measured in pylorus-ligated rats for 4 h. Lafutidine or cimetidine was administered p.o. or i.d. immediately after the ligation. Data are presented as the mean ± S.E.M. from 4 or 5 rats per group. *Significant difference from the corresponding control at $P<0.05$.

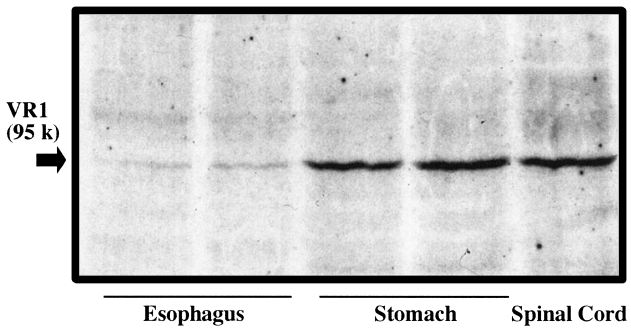

Fig. 6. Western blot analysis for VR1 in the rat esophagus, stomach, and spinal cord. Note that VR1 (around 95 kDa) was detected in the membrane fraction, but the expression in the esophagus was very weak in comparison with those in the other two tissues.

Discussion

The present study showed that lafutidine prevented esophageal lesions induced by ligation of both the pylorus and forestomach in rats. The protective action of lafutidine is due to two different mechanisms; one is mediated by an anti-secretory action induced by H_2-receptor antagonism while the other is mediated by capsaicin-sensitive afferent neurons.

Lafutidine has been launched on the market in Japan as a novel histamine H_2-receptor antagonist with gastroprotective as well as antisecretory activities (14, 15). This protective action of lafutidine was independent of the antisecretory activity and partly or fully mediated by capsaicin-sensitive afferent neurons, since it was totally abolished by sensory deafferentation (16). In the present study, we used intragastric administration for examining a direct effect of lafutidine on the mucosa, while intraduodenal administration was used for examining a systemic effect of lafutidine. Since the animals used in this experiment were subjected to pylorus ligation, the drug given intragastrically did not act systemically, unless absorbed in the stomach through the mucosa. Interestingly, we observed that lafutidine given i.g. significantly prevented the development of esophageal lesion induced by ligations of both the pylorus and forestomach. In contrast, cimetidine, another H_2-receptor antagonist, when given i.g., failed to significantly reduce the severity of esophageal lesions. We further observed that intragastric administration of lafutidine and cimetidine at the dose used did not affect basal acid secretion in pylorus-ligated rats, suggesting that neither of these agents is successfully absorbed through the intact gastric wall. These findings support that intragastric lafutidine protects the esophagus, via capsaicin-sensitive afferent neurons, independent of the antisecretory action due to antagonism of the H_2-receptor.

Capsaicin-sensitive sensory neurons, distributed widely in the upper gastrointestinal tract, including the esophagus (20, 21), have been demonstrated to play an important role in mucosal defensive mechanisms (22). Previous studies showed that the protective effect of lafutidine in the gastrointestinal mucosa was mimicked by capsaicin, inasmuch as this action was attenuated by sensory deafferentation (16 – 18). Indeed, several studies demonstrated the protective action of capsaicin in the esophagus. Bass et al. (13) reported that the topical application of capsaicin prevented esophageal damage by ethanol in rabbits and suggested the involvement of capsaicin-sensitive sensory neurons in maintaining the mucosal integrity of the esophagus. In the present study, however, the protective effect of lafutidine was not mimicked by intragastric capsaicin at any doses used. Although the reason for these different results remains unclear, it may be due to the difference in experimental models and animal species used in these studies. Further study is certainly required for resolving the discrepancy.

In the present study, Western blot analysis showed that the expression of VR1 in the esophagus was very weak in comparison with that in the stomach. This finding may explain why capsaicin failed to affect the esophageal damage and suggests that the protective action of lafutidine is not mediated by VR1, despite being dependent on the sensory neurons. We recently reported that lafutidine did not directly induce an increase in gastric mucosal blood flow and duodenal

bicarbonate secretion, but enhanced these responses to acid or capsaicin in rats (23). We also showed that lafutidine did not evoke an increase in intracellular calcium in rat VR1-transfected HEK293 cells (23). These results support that lafutidine may augment the response to acid or capsaicin by sensitizing capsaicin-sensitive afferent neurons through an unknown site other than VR1. Indeed, several vanilloid receptor subtypes and related channels have been cloned, and they have the different affinity to capsaicin or acid from the authentic VR1 (24, 25). It is thus unlikely that the protective effect of lafutidine in the esophagus is mediated by VR1. Further study is required on this point, including determining the specific binding site of lafutidine on capsaicin-sensitive afferent neurons or the process by which lafutidine activates these afferent neurons.

Several defensive factors, such as mucosal blood flow, mucus secretion, and bicarbonate secretion, are involved in the mucosal protection mediated by capsaicin-sensitive afferent neurons (12, 26 – 29). Lafutidine has also been demonstrated to increase mucosal blood flow, as well as mucus and bicarbonate secretions in the gastrointestinal mucosa mediated by capsaicin-sensitive afferent neurons (17, 21, 30, 31). Thus, it is possible that the lafutidine-induced esophageal protection observed in this study is also associated with alterations of these functions.

Gastric acid is the major factor in the pathogenesis of reflux esophagitis (1), and pH control has been thought to be important in the management of GERD (2). Indeed, several antisecretory drugs, such as histamine H_2-receptor antagonists and proton pump inhibitors, have been shown to be effective against acid reflux esophagitis in humans and animals (3 – 5). In the present study, intraduodenally administered lafutidine significantly reduced the severity of esophageal lesions, concomitantly with the inhibition of basal acid secretion, and these effects were mimicked by cimetidine. It should be noted, however, that the protective effect of lafutidine (30 mg/kg, i.d.) was more potent than that of cimetidine (100 mg/kg, i.d.), although the anti-secretory actions of these agents were almost the same. Thus, it is assumed that the protective action of lafutidine given i.d. is attributable mainly to the inhibition of gastric acid secretion and prevention of acid reflux into the esophagus and partly to the stimulation of sensory neurons.

In conclusion, lafutidine is effective against acid reflux esophagitis through inhibition of acid secretion caused by H_2-receptor antagonism and activation of capsaicin-sensitive afferent neurons. The latter mechanism, not shared by cimetidine, may be due to the interaction of lafutidine with unidentified sites on sensory neurons other than VR1. Thus, lafutidine is expected to be useful for the treatment of acid reflux esophagitis in patients.

References

1 DeMeester TR, Wernly JA, Bryant GH, Little AG, Skinner DB. Clinical and in vitro analysis of determinants of gastroesophageal competence: a study of the principles of antireflux surgery. Am J Surg. 1979;137:39–46.

2 Hunt RH. Importance of pH control in the management of GERD. Arch Intern Med. 1999;159:649–657.

3 Meuwissen SGM, Klinkenberg-Knol EC. Treatment of reflux oesophagitis with H_2-receptor antagonist. Scand J Gastroenterol. 1988;23 Suppl 146:201–213.

4 Klinkenberg-Knol EC, Jansen JBMJ, Lamers CBHQ, Neils F, Snel P, Meuwissen SGM. Use of omeprazole in the management of reflux oesophagitis resistant to H_2-receptor antagonists. Scand J Gastroenterol. 1989;24 Suppl 166:88–93.

5 Inatomi N, Nagaya H, Takami K, Shino A, Satoh H. Effects of a proton pump inhibitor, AG-1749 (lansoprazole), on reflux esophagitis and experimental ulcers in rats. Jpn J Pharmacol. 1991;55:437–451.

6 Caterina MJ, Schumacher MA, Tominaga M, Rose TA, Levine JD, Julius D. The capsaicin receptor; a heat-activated ion channel in the pain pathway. Nature. 1997;389:816–824.

7 Szallasi A, Blumberg PM. Vanilloid (capsaicin) receptor and mechanisms. Pharmacol Rev. 1999;51:159–211.

8 Holzer P, Sametz W. Gastric mucosal protection against ulcerogenic factors in the rat mediated by capsaicin-sensitive afferent neurons. Gastroenterology. 1986;91:975–981.

9 Evangelista S, Maggi CA, Meli A. Involvement of capsaicin-sensitive mechanism(s) in the antiulcer defence of intestinal mucosa in rats. Proc Soc Exp Biol Med. 1987;184:264–266.

10 Evangelista S, Meli A. Influence of capsaicin-sensitive fibers on experimentally induced colitis in rats. J Pharm Pharmacol. 1989;41:574–575.

11 Goso C, Evangelista S, Tramontana M, Manzini S, Blumberg PM, Szallasi A. Topical capsaicin administration protects against trinitrobenzene sulfonic acid-induced colitis in the rat. Eur J Pharmacol. 1993;249:185–190.

12 Takeuchi K, Matsumoto J, Ueshima K, Okabe S. Role of capsaicin-sensitive afferent neurons in alkaline secretory response to luminal acid in the rat duodenum. Gastroenterology. 1991;101:954–961.

13 Bass LB, Trad KS, Harmon JW, Hakki FZ. Capsaicin-sensitive nerves mediate esophageal mucosal protection. Surgery. 1991; 110:419–426.

14 Yamaura T, Shibata M, Inaba N, Onodera S, Chida Y, Ohnishi H. Effects of FRG-8813, a new-type histamine H_2 receptor antagonist, on various experimental gastric and duodenal lesions in rats. Folia Pharmacol Jpn (Nippon Yakurigaku Zasshi). 1992;99:401–410 (text in Japanese with English abstract).

15 Shibata M, Yamaura T, Inaba N, Onodera S, Chiba Y, Ohnishi H. Gastric antisecretory effect of FRG-8813, a new histamine H_2 receptor antagonist, in rats and dogs. Eur J Pharmacol. 1993;235:243–253.

16 Onodera S, Shibata M, Tanaka M, Inaba N, Yamaura T, Ohnishi H. Gastroprotective activity of FRG-8813, a novel histamine

H_2-receptor antagonist, in rats. Jpn J Pharmacol. 1995;68:161–173.

17 Kato S, Tanaka A, Kunikata T, Umeda M, Takeuchi K. Protective effect of lafutidine against indomethacin-induced intestinal ulceration in rats: relation to capsaicin-sensitive sensory neurons. Digestion. 2000;61:39–46.

18 Ogawa Y, Okayama M, Nakashima M, Kanatsu K, Kato S, Takeuchi K. Protective effect of lafutidine, a novel histamine H_2-receptor antagonist, on dextran sulfate sodium-induced colonic inflammation through capsaicin-sensitive afferent neurons in rats. Gastroenterology. 2002;122 Suppl 1:A-511.

19 Nakamura K, Ogawa Y, Furuta Y, Miyazaki H. Effects of sodium polyacrylate (PANa) on acute esophagitis by gastric juice in rats. Jpn J Pharmacol. 1982;32:445–456.

20 Leek BF. Abdominal and pelvic visceral receptors. Br Med Bull. 1977;33:133–148.

21 Buck SH, Burks TF. The neuropharmacology of capsaicin: review of some recent observation. Pharmacol Rev. 1986;38:179–226.

22 Holzer P. Neural emergency system in the stomach. Gastroenterology. 1998;114:823–839.

23 Mimaki H, Kagawa S, Aoi M, et al. Effect of lafutidine, a histamine H_2-receptor antagonist, on gastric mucosal blood flow and duodenal HCO_3^- secretion in rats; relation to capsaicin-sensitive afferent neurons. Dig Dis Sci. 2002;47:2696–2703.

24 Schumacher MA, Moff I, Sudanagunta SP, Levine JD. Molecular cloning of an N-terminal splice variant of the capsaicin receptor. J Biol Chem. 2000;275:2756–2762.

25 Gunthorpe MJ, Benham CD, Randall A, Davis JB. The diversity in the vanilloid (TRPV) receptor family of ion channels. Trends Pharmacol Sci. 2002;23:183–191.

26 Holzer P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. Pharmacol Rev. 1991;43:143–195.

27 Holzer P, Livingston EH, Guth PH. Sensory neurons signal for an increase in rat gastric mucosal blood flow in the face of pending acid injury. Gastroenterology. 1991;101:416–423.

28 Laporte JL, Dauge-Geffroy MC, Chariot J, Roz C, Potet F. Sensory fibers sensitive to capsaicin can modulate secretion of the duodenal mucus: morphometric study in rats. Gastroenterol Clin Biol. 1993;17:535–541.

29 Kang JY, Teng CH, Wee A, Chen FC. Effects of capsaicin and chili on ethanol induced gastric mucosal injury in the rat. Gut. 1995;36:664–669.

30 Onodera S, Shibata M, Tanaka M, et al. Gastroprotective mechanism of lafutidine, a novel anti-ulcer drug with histamine H_2-receptor antagonistic activity. Arzneimittelforschung. 1999;49:519–526.

31 Kagoshima M, Kodaira H, Tanaka M, Shimada H. Effect of FRG-8813, a new histamine H_2-receptor antagonist, on gastric mucus production in rats. Folia Pharmacol Jpn (Nippon Yakurigaku Zasshi). 1995;106:385–392. (text in Japanese with English abstract).