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Lafutidine Protects the NSAID-Induced Small Intestinal Lesions Mediated by Capsaicin-Sensitive Afferent Neurons

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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin damage the small intestine as well as the stomach, although the ulcerogenic dose is much lower in the former [1-3]. Several factors such as intestinal hypermotility, enterobacteria, neutrophils, nitric oxide (NO), and inducible NO synthase (iNOS) are involved in the pathogenesis of these intestinal lesions [3-7], yet a deficiency of endogenous prostaglandins (PGs) due to cyclooxygenase (COX) inhibition is most important in the background for the intestinal ulcerogenic response to NSAIDs [8-10]. Recent clinical studies, using capsule endoscopes or double-balloon endoscopes, confirmed that NSAIDs damage the small intestine in patients at a higher incidence than previously thought. Unfortunately, antisecretory drugs such as proton pump inhibitors and histamine H₂ receptor antagonists are reported to be ineffective against NSAID-induced small intestinal damage [11,12] and even worsen the severity of these lesions [12], though these drugs prevent gastric ulcerogenic response to NSAIDs [13].

Capsaicin-sensitive sensory neurons are known to play an important role in modulating the gastric mucosal integrity [14]. It has previously been reported that stimulation of these sensory neurons by capsaicin prevented the occurrence of experimental colitis as well as indomethacin-induced intestinal ulceration in rats, while sensory deafferentation increased both the degree and incidence of the latter lesion model [11,15,16]. These findings suggest the role of capsaicin-sensitive sensory neurons in maintaining the integrity of the intestinal mucosa, similar to the gastric mucosa.

Lafutidine, a histamine H₂-receptor antagonist, has been shown to exhibit a potent gastroprotective activity in addition to gastric antisecretory action [17,18]. Onodera et al. [19] reported

that the gastroprotective action of lafutidine was independent of its antisecretory effect and partially mediated by capsaicin-sensitive sensory neurons.

In the present report, we described the protective effect of lafutidine against NSAID-induced enteropathy and suggested the involvement of capsaicin-sensitive afferent neurons in this action.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats (240~280 g; Nippon Charles River, Shizuoka, Japan) were used. Studies were carried out using four to eight animals without fasting in a conscious state, unless otherwise specified. All experimental procedures described here were approved by the Experimental Animal Research Committee of Kyoto Pharmaceutical University.

2.2. Induction of small intestinal lesions

Animals were given loxoprofen (60 mg/kg, p.o.) and killed 24 h later under deep ether anesthesia. The small intestine was excised, treated with 2% formalin for fixation of the tissue wall for 10 min and opened along the antimesenteric attachment. The area of macroscopically visible damage (mm²) was measured under a dissecting microscope with square grids (x10), summed per tissue and used as a lesion score. Lafutidine (10 and 30 mg/kg), cimetidine (100 mg/kg) or famotidine (30 mg/kg) was given p.o. twice, 0.5 h before and 6 h after the administration of loxoprofen, while omeprazole (100 mg/kg) was given p.o. once, 0.5 h before loxoprofen. On the other hand, ablation of capsaicin-sensitive sensory neurons was performed by s.c. injection of capsaicin once daily for 3 consecutive days (total dose 100 mg/kg) 2 weeks before the experiment [20]. All capsaicin injections were done under ether anesthesia, and the rats were pretreated with terbutaline (0.1 mg/kg, i.m.) and aminophylline (10 mg/kg, i.m.) to prevent respiratory impairment. The effectiveness of the treatment was tested by examining the protective wiping movements of the eye.

2.3. Determination of enterobacterial counts

Enterobacteria were enumerated according to a method described by Deitch et al. [21]. Twenty-four hours after loxoprofen treatment (60 mg/kg, p.o.), the animals were killed under deep diethyl ether anesthesia, and the small intestines were excised. Aliquots of the homogenate of intestine were placed on blood agar and Gifu anaerobic medium agar (Nissui, Tokyo, Japan). Blood agar plates were incubated at 37°C for 24 h under aerobic conditions, whereas Gifu anaerobic medium agar plates were incubated for 24 h under standard anaerobic conditions (BBL Gas Pack Pouch Anaerobic System; BD Biosciences, San Jose, CA). Plates containing 10 to 300 colony-forming units (CFU) were examined for numbers of enterobacteria, and the data were expressed as log CFU per gram of tissue. Lafutidine (10 and 30 mg/kg) was given p.o. twice, 0.5 h before and 6 h after the administration of loxoprofen.

2.4. Determination of iNOS and Muc2 mRNA Expression by RT-PCR

Expression of iNOS and Muc2 mRNA in the small intestinal mucosa was measured by RT-PCR. The animals were killed under deep ether anesthesia 6 h after the administration of loxoprofen, and the small intestines were removed, frozen in acetone/dryice, and stored at -80°C prior to use. Tissue samples were pooled from 2 to 3 rats for extraction of total RNA, which was prepared by a single-step acid phenol-chloroform extraction procedure by use of Sepasol RNA-I (Nacalai Tesque, Kyoto, Japan). Total RNA primed by random hexadeoxy ribonucleotide was reverse-transcribed with the Rever Tra Ace-a (Toyobo, Osaka, Japan). An aliquot of the RT reaction product served as a template in 35 cycles of PCR with 0.5 min of denaturation at 95°C and 1 min of extension at 68°C by Advantage-2 (BD Biosciences, Palo Alto, CA, USA) on a thermal cycler (PC806; ASTEC, Fukuoka, Japan). A portion of the PCR mixture was electrophoresed in 1.8% agarose gel in TAE buffer, and the gel was stained with ethidium bromide and photographed (Bio Doc-It Imaging System; UVP, Upland, CA, USA). Lafutidine (30 mg/kg) was given p.o. twice, 0.5 h before and 6 h after the administration of loxoprofen.

2.5. Determination of mucus secretion in small intestine

The amount of mucus secreted in the small intestine was determined by periodic acid-Schiff (PAS) staining. Three hours after the administration of loxoprofen (60 mg/kg, p.o.), the animals were killed under deep diethyl ether anesthesia, and the small intestines were removed. The removed tissues were fixed in Carnoy's fluid (ethanol : acetic acid : chloroform = 6 : 1 : 3) for 24 h, embedded in paraffin, and sectioned at a thickness of 6 µm. PAS staining was subsequently performed according to the conventional method. Lafutidine (30 mg/kg) was given p.o. with or without co-administration of loxoprofen. In the combined administration, this agent was given p.o. 30 min before the administration of loxoprofen.

2.6. Preparation of drugs

The drugs used were lafutidine, cimetidine, famotidine, loxoprofen, ampicillin (Sigma Chemicals, St. Louis, MO), and omeprazole. Lafutidine, cimetidine, famotidine, omeprazole or loxoprofen was suspended in a 0.5% hydroxy propyl cellulose solution (Wako). All drugs were prepared immediately before use and administered p.o. or s.c. in a volume of 0.5 ml/100 g body weight. Control animals received the vehicle alone.

2.7. Statistics

Data are presented as the mean ± SE for four to eight rats per group. Statistical analyses were performed using the two-tailed Dunnett's multiple comparison test, and values of $P < 0.05$ were considered significant.

3. Results

3.1. Effect of anti-secretory drugs on loxoprofen-induced small intestinal lesions

Orally administered loxoprofen (10-100 mg/kg) in normally fed rats dose-dependently produced multiple hemorrhagic lesions in the small intestine, mainly in the jejunum and ileum. The severity of these lesions induced by loxoprofen at 60 mg/kg was similar to that of the lesions produced by indomethacin at 10 mg/kg. When animals were pretreated with lafutidine (10 and 30 mg/kg) given p.o., this treatment dose-dependently prevented the development of intestinal lesions in response to loxoprofen (60 mg/kg), and the effect was significant at 30 mg/kg; the inhibition rate was around 50 % (Figure 1). By contrast, neither cimetidine (100 mg/kg) nor famotidine (30 mg/kg), given p.o., had significant effect on the intestinal ulcerogenic response to loxoprofen. Similarly, omeprazole (100 mg/kg, p.o.) did not affect the severity of loxoprofen-induced intestinal lesions.

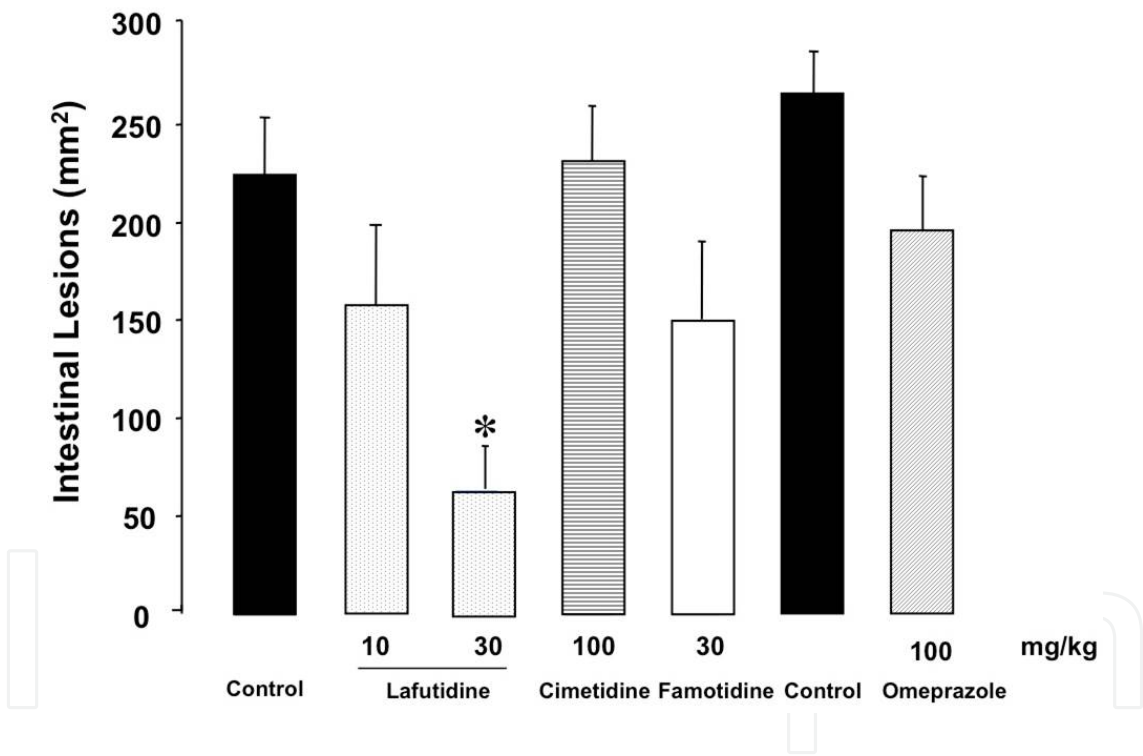


Figure 1. Effects of various agents on the intestinal lesions induced by loxoprofen in rats. Animals were given loxoprofen (60 mg/kg) p.o. and killed 24 h later. Lafutidine (10 and 30 mg/kg), cimetidine (100 mg/kg) or famotidine (30 mg/kg) was given p.o. twice, 30 min before and 6 h after administration of loxoprofen, while omeprazole (100 mg/kg) was given p.o. once, 30 min before. Data are presented as the mean±SE from 5~8 rats. *Significant difference from the corresponding control, at P<0.05. Data adapted after modification of ref. [26].

On the other hand, the severity of intestinal lesions induced by loxoprofen was significantly aggravated by chemical ablation of capsaicin-sensitive sensory neurons, about 1.4 times greater than the capsaicin nontreated animals (Figure 2). Lafutidine (30 mg/kg, p.o.) again significantly suppressed the intestinal ulcerogenic response to loxoprofen, but this effect was

totally attenuated by sensory deafferentation, the lesion score was almost equivalent to the control value in the sensory deafferented animals.

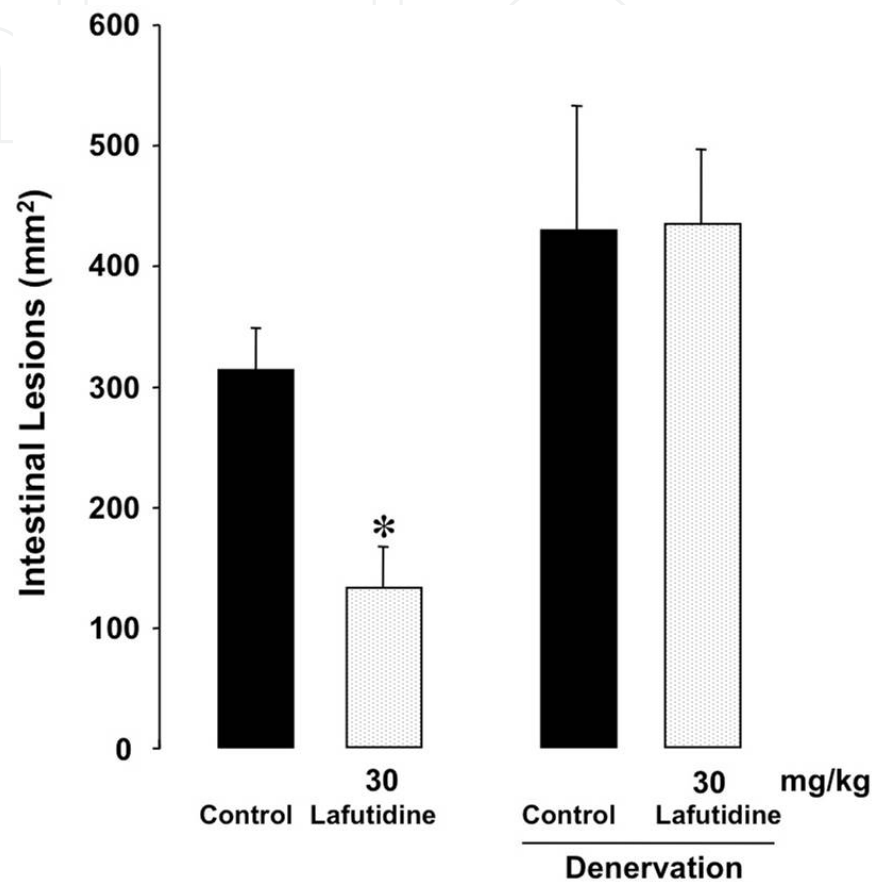


Figure 2. Effect of lafutidine on the intestinal lesions induced by loxoprofen in normal and sensory deafferented rats. Animals were given loxoprofen (60 mg/kg) p.o. and killed 24 h later. Sensory deafferentation was performed by 3 consecutive s.c. injections of capsaicin (total 100 mg/kg) 2 weeks before the experiment. Lafutidine (30 mg/kg) was given p.o. twice, 30 min before and 6 h after loxoprofen. Data are presented as the mean±SE from 6~7 rats. *Significant difference from control in normal rats, at $P<0.05$. Data adapted after modification of ref. [26].

3.2. Effect of lafutidine on mucosal invasion of enterobacteria caused by loxoprofen

Following oral administration of loxoprofen (60 mg/kg), the bacterial counts in both aerobic and anaerobic conditions were markedly increased compared to normal group, 24 h later (Table 1). Pretreatment of the animals with lafutidine (30 mg/kg) significantly prevented bacterial invasion in the mucosa following the administration of loxoprofen. The mucosal invasion of enterobacteria was also increased after loxoprofen treatment in sensory deaffer-

ented animals. The inhibitory effect of lafutidine on bacterial invasion was totally attenuated in the animals with sensory deafferentation.

Numbers of Bacteria (Log CFU/g)		
	aerobic	anaerobic
<u>Normal</u>		
Control	6.79±0.99	7.62±0.56
Loxoprofen Na	9.51±0.42 ^a	9.58±0.45 ^a
+Lafutidine	7.88±0.34 ^b	7.84±0.46 ^b
<u>Denervation</u>		
Control	6.45±0.41	7.30±0.12
Loxoprofen Na	8.99±0.36 ^a	9.30±0.19 ^a
+Lafutidine	8.82±0.29	8.95±0.12

The animals were given loxoprofen (60 mg/kg, p.o.) and killed 24 h later. Lafutidine (30 mg/kg, p.o.) was given twice, 30 min before and 6 hr after the administration of sodium loxoprofen. Data are presented as the mean±SE from 4~5 rats. Significant difference at P<0.05; a) from the corresponding control, b) from loxoprofen in the normal group. Data adapted after modification of ref. [26].

Table 1. Effect of Lafutidine on Bacterial Counts in Rat Small Intestine

3.3. Changes in mucosal expression of iNOS and Muc2 mRNA

The iNOS mRNA expression was hardly detected in the normal intestinal mucosa, but markedly up-regulated after the administration of loxoprofen (60 mg/kg, p.o.) when examined 6 h later (Figure 3a). The up-regulation of iNOS expression following loxoprofen was markedly suppressed by pretreatment of the animals with lafutidine (30 mg/kg). Loxoprofen (60 mg/kg) similarly increased iNOS mRNA expression in sensory deafferented animals. In these animals, however, lafutidine did not affect the expression of iNOS mRNA in the small intestinal mucosa.

On the other hand, the expression of Muc2 mRNA was clearly detected in the normal intestinal mucosa, but apparently down-regulated after the administration of loxoprofen (60 mg/kg) when examined 6 h later (Figure 3b). The decrease in Muc2 expression caused by loxoprofen was almost totally reverted by pretreatment of lafutidine (30 mg/kg), but this effect was not

observed in the animals with sensory deafferentation, similar to the inhibitory effect on the iNOS expression.

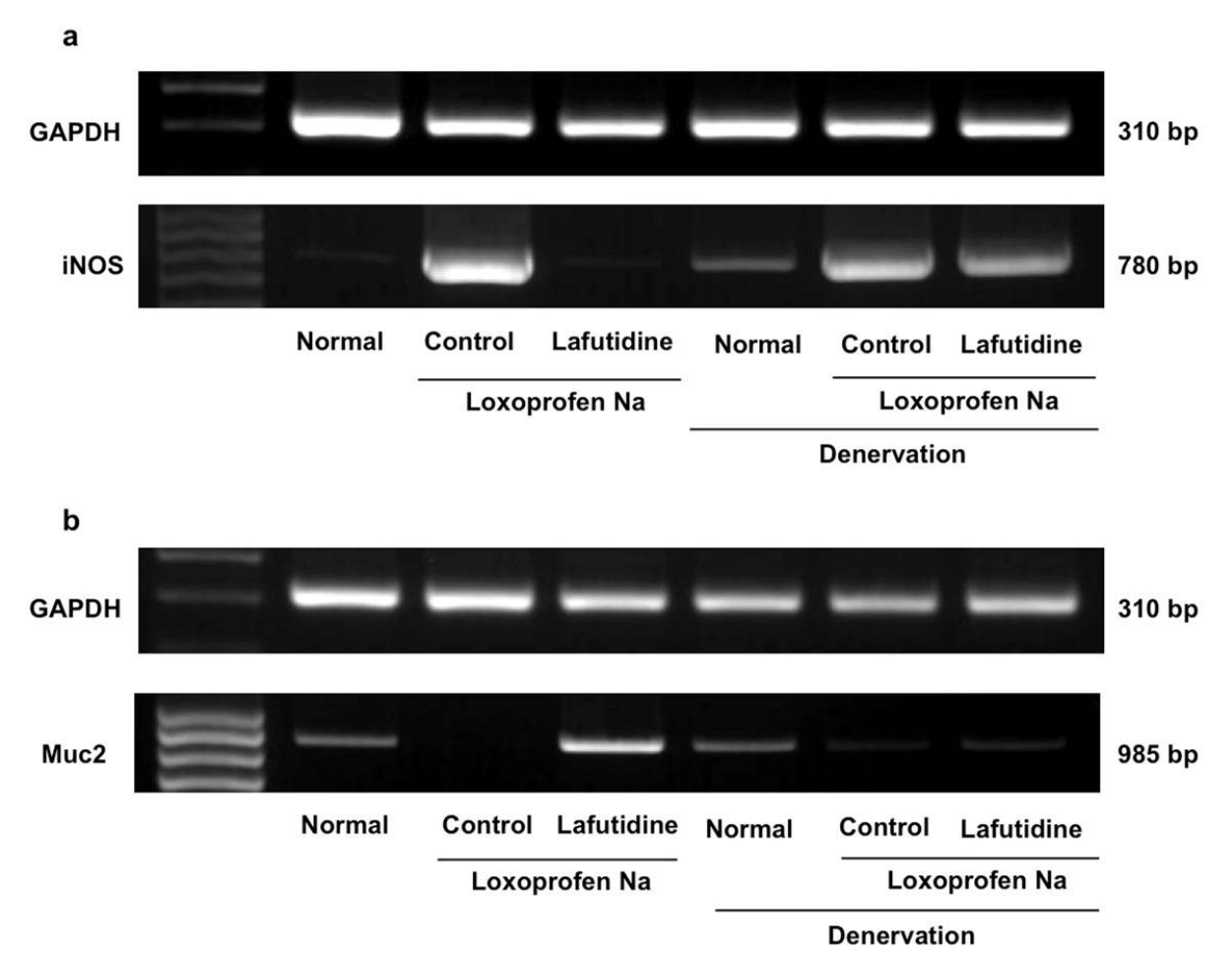


Figure 3. Effect of lafutidine on the expression of iNOS and Muc2 mRNAs in rat small intestine. Animals were given loxoprofen (60 mg/kg) p.o. and killed 6 h later. Sensory deafferentation was performed by 3 consecutive s.c. injections of capsaicin (total 100 mg/kg) 2 weeks before the experiment. Lafutidine (30 mg/kg) was given p.o. 30 min before the administration of loxoprofen. Data adapted after modification of ref. [26].

3.4. Effect of Lafutidine on PAS-Positive Substances in Small Intestine

In the normal intestinal mucosa, PAS-positive substances were observed over the surface epithelial cells and along the glands (Figure 4A). Loxoprofen (60 mg/kg, p.o.) apparently reduced the amount of PAS-positive substances in the epithelial cells as well as the glands (Figure 4B). However, the reduction in PAS staining was markedly restored when lafutidine (30 mg/kg) was administered prior to loxoprofen treatment (Figure 4C). In addition, lafutidine by itself increased the amount of PAS-positive substances in the mucosa compared to the control mucosa (Figure 4D).

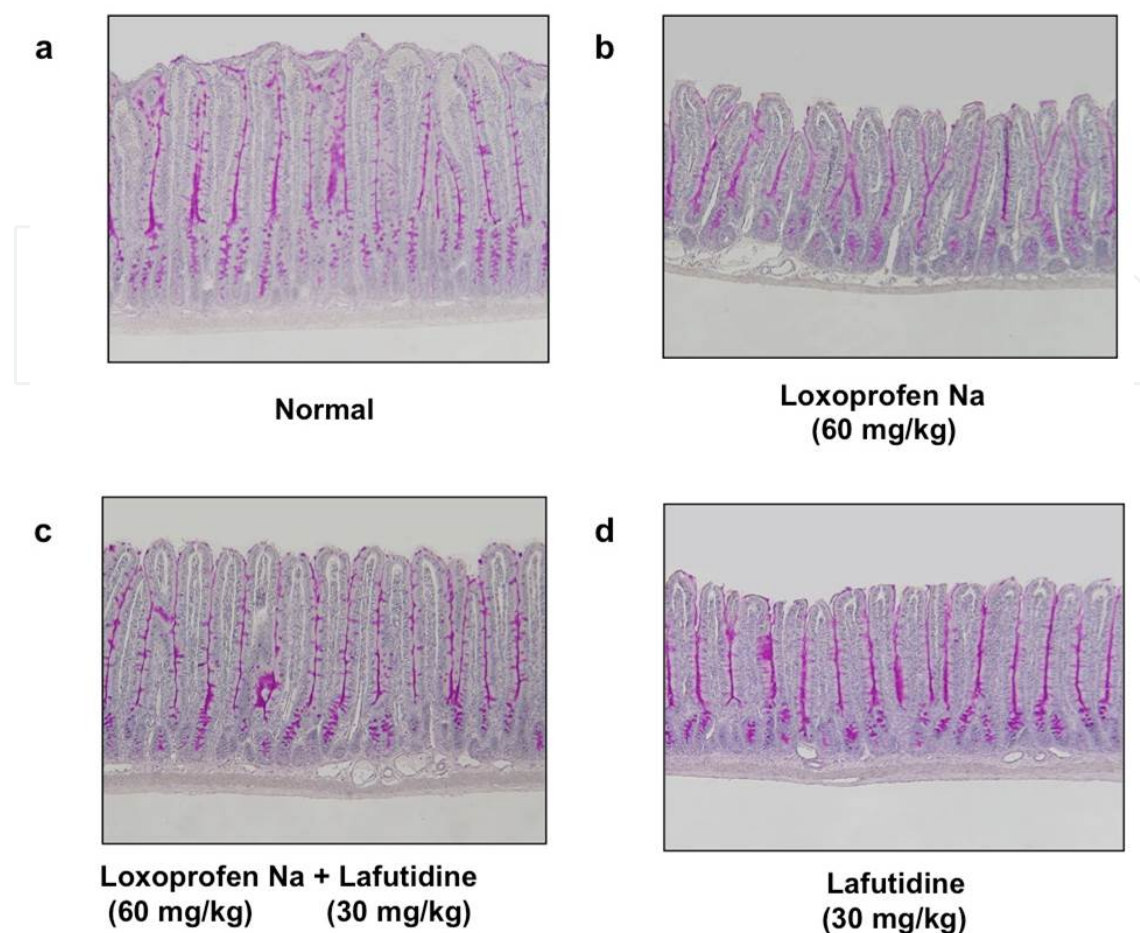


Figure 4. Microscopic observations of the rat small intestinal mucosa. The animals were given loxoprofen (60 mg/kg) p.o. and killed 3 h later. Lafutidine (30 mg/kg) was given p.o. 30 min before the administration of loxoprofen. Figures show; a: normal; b: loxoprofen alone; c: lafutidine plus loxoprofen; d: lafutidine alone. (PAS; x100). Data adapted after modification of ref. [26].

4. Commentary

The present study demonstrated that oral administration of loxoprofen induced multiple hemorrhagic lesions in the small intestine, similar to indomethacin [5], and that lafutidine protected these intestinal lesions, mediated by capsaicin-sensitive sensory neurons.

We confirmed that loxoprofen produced hemorrhagic lesions in the small intestine, and the severity of these lesions at 60 mg/kg was almost equivalent to that of the lesions generated by indomethacin. The onset of these lesions was accompanied by the mucosal invasion of enterobacteria and the up-regulation of iNOS expression, those events being similarly observed after indomethacin treatment. We also confirmed that the ulcerogenic response induced by loxoprofen in the small intestine was significantly prevented by pretreatment of the animals with dmPGE₂ as a supplement for PG deficiency or ampicillin as an antibiotic, the same was reported using the intestinal indomethacin-induced intestinal lesions [3-5].

Lafutidine is a histamine H₂-receptor antagonist with both antisecretory and gastroprotective action [17,18]. Onodera et al. [19] reported that the mucosal protective action of lafutidine was mediated by capsaicin-sensitive sensory neurons and independent of the antisecretory activity, because the action was not mimicked by cimetidine, another H₂-receptor antagonist, and was totally abolished by chemical deafferentation of sensory neurons. In the present study we observed that lafutidine protected the small intestine from loxoprofen-induced intestinal lesions. Certainly, this effect is not brought about by inhibition of gastric acid secretion, since omeprazole, an inhibitor of H⁺/K⁺ATPase, had no effect on this lesion model, similar to cimetidine. These drugs at the doses used (100 mg/kg) reportedly caused nearly a complete inhibition of acid secretion [22,23], supporting the idea that acid does not participate in the pathogenesis of loxoprofen-induced small intestinal lesions.

Lafutidine has been previously shown to prevent indomethacin-induced enteropathy and this effect was significantly attenuated by chemical ablation of capsaicin-sensitive sensory neurons [11]. Consistent with these findings, we found that lafutidine dose-dependently reduced the severity of intestinal lesions produced by loxoprofen and this action disappeared in the animals with sensory deafferentation. The peptidergic afferent innervation of the intestine has been demonstrated in various species of animals including the rat [14,24,25]. Several studies have demonstrated that stimulation of sensory neurons by capsaicin significantly prevented the occurrence of colitis as well as intestinal ulceration induced experimentally in rats [15,16]. We also noted that the ulcerogenic response to loxoprofen in the rat intestine was significantly aggravated by ablation of these sensory neurons. These results together with previous studies [11,15,16] strongly suggest that capsaicin-sensitive sensory neurons play a role in maintaining the mucosal integrity of the intestine against noxious stimuli, similarly in the stomach.

The intestinal ulcerogenic response to loxoprofen was also markedly suppressed by prior administration of ampicillin, an antibiotics, similar to that induced by indomethacin [26]. These findings were supported by the fact that NSAID-induced small intestinal lesions do not occur in germ-free animals or fasting animals [5,27], suggesting a major pathogenic role for enterobacteria in these lesions. Because lafutidine significantly mitigated the bacterial invasion in the mucosa after loxoprofen treatment, this effect may account, at least partly, for the prophylactic effect of this agent against the intestinal lesions produced by loxoprofen. As mentioned earlier, the protective effect of lafutidine was almost totally attenuated by sensory deafferentation following capsaicin pretreatment. We also found in the present study that the suppression by lafutidine of the enterobacterial invasion following loxoprofen treatment was not observed in the sensory deafferented animals. Since mucus plays an important part in the innate host defense against intestinal pathogens and irritants, it is possible that a decreased mucus production/ secretion plays a role in the pathogenic mechanism of NSAID-induced intestinal damage by accelerating bacterial invasion in the mucosa. We have previously reported that indomethacin at an ulcerogenic dose reduced the amount of mucus secreted in the small intestine, in a PGE₂-sensitive manner, and this effect preceded bacterial invasion [10]. Lafutidine increased mucus secretion in the stomach, at least partly mediated by capsaicin-sensitive sensory neurons [28,29]. We observed in the present study that lafutidine by itself markedly increased levels of PAS-positive materials in the intestinal mucosa and reverted the reduced

response to loxoprofen. Furthermore, it was found that lafutidine increased the expression of Muc2 mRNA in the small intestine and this response was totally mitigated by ablation of capsaicin-sensitive sensory neurons. Muc2, one of important mucin genes, plays an important role in the dimerization of secretory mucins, an essential step in the formation of the gastrointestinal mucus-gels [30]. It is possible that lafutidine up-regulates Muc2 expression and mucus secretion through a sensory neuron-dependent mechanism and thereby increases the mucus gel thickness and hampers enterobacterial invasion in the mucosa.

Lafutidine prevented the up-regulation of iNOS expression in the small intestine, an important event in the occurrence of intestinal lesions caused by NSAIDs [2,31]. Boughton-Smith et al. [32] reported that bacterial endotoxin from *E. coli* enhanced the intestinal permeability through up-regulation of iNOS and overproduction of NO in the mucosa. Since lafutidine was found to prevent bacterial invasion, probably by up-regulating Muc2/mucus expression, it would be understandable that this agent suppressed the increase of iNOS expression in the small intestine following loxoprofen treatment. We previously reported that the mucosal protective drugs, such as irsogladine, rebamipide and teprenone, all significantly increased mucus secretion and suppressed bacterial invasion and iNOS expression, thereby reduced the severity of intestinal lesions produced by indomethacin [33]. These results together support a cause-effect relationship between changes in the above three events; ie., mucus secretion, bacterial invasion, and iNOS expression.

5. Summary

Lafutidine protects the small intestine against loxoprofen-induced lesions. This effect is not associated with inhibition of acid secretion due to the blockade of histamine H₂-receptors and appears to be mediated by capsaicin-sensitive sensory neurons. The exact mechanism underlying the intestinal protection by lafutidine remains unknown, yet it is assumed that lafutidine prevents the process of enterobacterial invasion in the mucosa by increasing the mucus gel layer through the up-regulation of Muc2 mRNA expression, and thereby suppresses iNOS induction, resulting in prevention of the occurrence of intestinal lesions following loxoprofen treatment.

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The author declares no conflict of interest.

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