Selective and Competitive Histamine H₂-Receptor Blocking Effect of Famotidine on the Blood Pressure Response in Dogs and the Acid Secretory Response in Rats

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Abstract—Famotidine has been already demonstrated to be a competitive H₂-receptor antagonist in the stomachs of dogs and cats. The present experiments were carried out to examine the effects of famotidine on changes in blood pressure induced by dimaprit and several other agonists in vagotomized, anesthetized dogs and on changes in gastric acid secretion induced by histamine in stomach-perfused, anesthetized rats. Famotidine caused a parallel displacement of the dimaprit dose-response curve to the right with a DR₁₀ value of 0.059 μ mol/kg, indicating that famotidine is 166 times more potent than cimetidine in vascular H₂-blocking activity. On the contrary, famotidine did not affect the depressor responses to 2-pyridylethylamine and histamine that were antagonized by mepyramine. The histamine dose-response curve was displaced to the right more markedly after simultaneous administration of mepyramine and famotidine than after mepyramine alone. The effects of methacholine, phenylephrine and isoproterenol on blood pressure were not influenced by famotidine in doses up to 720 nmol/kg. In rats, famotidine also caused a parallel displacement of the acid dose-response curve to histamine to the right with a DR₅ value of 24 μ mol/kg/hr in stomach-perfused rats anesthetized with pentobarbital, exhibiting a potency 108 times greater than that of cimetidine. Analysis of the acid dose-response curve with the Edie-Hofstee transformation showed that famotidine, like cimetidine, was a competitive H₂-receptor antagonist.

The actions of histamine on blood pressure are well-established to be mediated through H₁- and H₂-receptors (1, 2), while its effects on gastric acid secretion are mediated through H₂-receptors (3). In *in vivo* tests on cats, metiamide antagonized the blood pressure response to a selective H₂-agonist, dimaprit (4), without affecting the vascular action of other agonists including 2-pyridylethylamine (H₁-agonist) and acetylcholine (2, 5). In contrast, metiamide and cimetidine inhibited gastric acid secretion induced by not only histamine or dimaprit but also pentagastrin and methacholine in dogs (6, 7). Among the H₂-antagonists, cimetidine and ranitidine competitively antagonized vascular and gas-

tric H₂-receptors (8, 9), whereas loxidine inhibited histamine-induced gastric acid secretion in a non-competitive manner (9).

Famotidine has been reported to be a potent H₂-antagonist *in vitro* (10–14) and *in vivo* (7) with greater antisecretory and anti-ulcer activities than cimetidine (15–17). The present paper describes the effects of famotidine on blood pressure responses to dimaprit and other vasoactive substances in anesthetized dogs, and on histamine-induced gastric acid secretion in stomach-perfused, anesthetized rats.

Materials and Methods

Animals and materials: Mongrel dogs of

either sex weighing 8 to 15 kg and female Sprague-Dawley rats weighing 190 to 220 g were used. Rats were deprived of food with free access to water for 18 hr before the secretory tests.

Famotidine (molecular weight: 337.4), cimetidine (molecular weight: 252.3), dimaprit dihydrochloride, 2-pyridylethylamine dihydrochloride and phenylephrine hydrochloride were synthesized at the Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd. Other drugs used were mepyramine maleate (Sigma Chemical), histamine dihydrochloride (Wako Pure Chemical), methacholine chloride (Nacalai Tesque), l-isoproterenol hydrochloride (Nikken Chemicals) and glucose (Nacalai Tesque). The H_2 -antagonists were dissolved in 0.1 N HCl solution, and the pH of the solution was adjusted to 6 with solid $NaHCO_3$. Glucose was dissolved in distilled water, and the other drugs were dissolved in physiological saline.

Blood pressure responses to dimaprit and other agonists: Dogs were anesthetized with i.v. injection of pentobarbital (30 mg/kg). The animals were artificially respired with room air through an endotracheal tube at a rate of 20 strokes/min (Shinano Seisakusho, SN-480-4) and vagotomized bilaterally at the neck level. Systemic blood pressure was recorded on a polygraph (Nihon Kohden, RM-150 or RM-2600) through a pressure transducer (Nihon Kohden, MPU-0.5) connected to a catheter placed in the femoral artery. The femoral vein was also cannulated for drug injection and anesthetic supplement.

Dose-response curves were constructed for peak changes in diastolic blood pressure caused by dimaprit, a selective H_2 -agonist (4); 2-pyridylethylamine, a selective H_1 -agonist (1); and histamine. Four doses of the agonists were successively given at intervals of 3 min or longer before and 10 min after each dose of the antagonists, which was given at intervals of approximately 1 hr. The shifts in the dose-response curves to the right were expressed as the ratios of two agonist doses to cause the half maximal response in the presence and absence of antagonists. The dose of antagonists required to produce an agonist dose-ratio of 10 (DR_{10}) and the slope of the regression lines were calculated ac-

cording to the method of Arunlakshana and Schild (18). When the effects of famotidine on the depressor response to 2-pyridylethylamine and histamine were tested, mepyramine was also given at the end of the experiments to study the combined effect of the antagonists on the action of the agonists.

By the same procedure, the effects of famotidine on blood pressure responses to methacholine (0.1, 0.3, 1 and 3 nmol/kg), isoproterenol (0.3, 1, 3 and 10 nmol/kg) and phenylephrine (10, 30, 100 and 300 nmol/kg) were also examined. Throughout the present studies, all of the agonists were given intravenously, and 4 to 6 animals were used to analyze individual agonist and antagonist interaction. Doses of the antagonists were expressed in terms of cumulative doses. The ED_{50} values of antagonists, doses of histamine and other agonists to elicit 40 and 30 mmHg changes in diastolic blood pressure, respectively, were calculated from the dose-response curves and used for calculation of the agonist-dose ratios.

Gastric acid secretion: The effects of famotidine and cimetidine on gastric acid secretion were studied using a perfused stomach preparation of rats (19). Rats were anesthetized with i.p. injection of pentobarbital (50 mg/kg). Perfusion of the stomach and administration of drugs were performed according to Brittain et al. (9). The jugular vein was cannulated for drug administrations, and a perfusion cannula was inserted into the stomach to facilitate perfusion of acid secreting mucosa at 3 ml/min with 5% glucose solution, pH 7.0, at 37°C. The gastric effluent was passed continuously over a pH electrode (TOA Electronic, GS-80) and the pH recorded via a pH meter (TOA Electronic, HM-16S) on a flat-bed recorder (Graphtec, MC6621). In each anesthetized rat, one secretory dose-response curve was obtained to histamine by infusing progressively increasing doses for 1 hr each. In the control experiments, saline alone was infused for 1 hr; and then histamine was infused at 0.09, 0.27, 0.9 and finally 2.7 μ mol/kg/min, i.v. In the test experiments, an i.v. bolus dose of famotidine or cimetidine was given at time zero followed by i.v. infusion throughout the experiment. One hour later, infusion was started, and the doses of

histamine were increased hourly up to the maximum tolerated dose of 9 or 27 $\mu\text{mol/kg/min}$. Gastric acid secretion was measured immediately before starting the histamine infusion and at the peak secretory response to each dose of histamine. Results were expressed as changes in acid output in $\mu\text{mol H}^+/\text{min}$, which were calculated according to the following formula:

$$[\text{H}^+]\text{secretion} = [10^{-(\text{pH measured})} - 10^{-7}] \text{mol/l} \\ = [10^{-(\text{pH measured})} - 10^{-7}] \\ \times [3/1000] \times 10^6 \mu\text{mol/min}$$

Mean $\pm$ S.E. values were then calculated for each histamine dose level in the control and test groups. The control and each dose level of famotidine and cimetidine were tested in 3 to 5 rats.

The shifts in the dose-response curves to the right were expressed as the ratios of histamine doses to cause the half maximal response in the presence and absence of the antagonist. The dose of the antagonists required to produce a histamine dose-ratio of 3 (DR_3) and the slopes of regression lines were calculated according to the method of Arunlakshana and Schild (18). The data used for the dose-response curves were also analyzed by the Edie-Hofstee transformation to examine the nature of antagonism (20). In this case, the responses to the lowest doses of histamine were excluded from the analysis because of poor fit to the calculation line (21).

Statistical analysis: Student's paired *t*-test, the method of least squares and the test of parallelism were used for statistical data.

Results

Depressor response to dimaprit in anesthetized dogs: Dimaprit decreased blood pressure dose-dependently in a dose range from 0.1 to 3 $\mu\text{mol/kg}$. The i.v. bolus injection of famotidine and cimetidine produced a parallel displacement to the right of the dimaprit dose-response curve (Fig. 1). As shown in Fig. 2 and Table 1, the Schild slope parameters for the H₂-antagonists were not significantly different from unity. Famotidine was 166 times more potent than cimetidine in blocking the depressor action of the H₂-agonist on the basis of the DR_{10} values.

Depressor response to 2-pyridylethylamine in anesthetized dogs: Famotidine in i.v. doses up to 234 nmol/kg did not affect the depressor action of 2-pyridylethylamine. On the contrary, mepyramine caused a parallel shift of the dose-response curve to the right (Fig. 3). The DR_{10} and slope (95% confidence limits, 6 experiments) derived from the Arunlakshana-Schild plot for mepyramine were 0.45 (0.33–0.59) $\mu\text{mol/kg}$ and 0.93 (0.67–1.20), respectively. In the presence of famotidine (0.41 $\mu\text{mol/kg}$), mepyramine (0.4 $\mu\text{mol/kg}$) displaced the 2-pyridylethylamine dose-response curve to the right with a dose-ratio of 9.23 (7.04–11.40), which was nearly equal to that obtained with mepyramine alone. Thus, famotidine did not modify the interaction between the H₁-agonist and antagonist.

Depressor response to histamine in anesthetized dogs: Famotidine had little influence on the depressor response to histamine in i.v.

Fig. 1. Inhibitory effects of famotidine and cimetidine on depressor response to dimaprit in anesthetized, vagotomized dogs. (○) No antagonist; famotidine, 18 (△), 72 (□) and 252 (●) nmol/kg, i.v.; cimetidine, 4 (△), 16 (□) and 56 (●) $\mu\text{mol/kg}$, i.v. Each mark represents mean $\pm$ S.E. from 6 animals.

doses of 234 (Fig. 4) and 590 nmol/kg in a preliminary experiment. Mepyramine, 0.1 μ mol/kg, displaced the histamine dose-

Fig. 2. Regression lines of famotidine and cimetidine for dimaprit antagonism of diastolic blood pressure in anesthetized, vagotomized dogs. Each mark represents the mean and 95% confidence limits from 6 animals. Dose ratios for dimaprit were calculated from the data shown in Fig. 1.

response curve to the right with a dose-ratio of 1.98 (1.52–2.43, 95% confidence limits from 6 experiments). When mepyramine was given in a dose of 1.1 μ mol/kg, the dose ratios were 4.67 (2.66–6.67) after mepyramine alone and 15.26 (9.09–21.43) after combination of mepyramine and famotidine (0.41 μ mol/kg). Thus, a further shift of the curves to the right was observed after high doses of mepyramine and famotidine (Fig. 4) as reported by Black et al. (1) with mepyramine and metiamide.

Blood pressure response to methacholine, isoproterenol and phenylephrine in anesthetized dogs: The specificity of famotidine as an H_2 -antagonist was further studied with the non-histamine agonists. As summarized in Table 2, famotidine affected neither the hypotensive response to methacholine and isoproterenol nor the hypertensive response to phenylephrine in i.v.-doses up to 720 nmol/kg.

Gastric acid secretory response to hista-

Fig. 3. Effects of famotidine and mepyramine on the depressor response to 2-pyridylethylamine in anesthetized, vagotomized dogs. (○) No antagonist; famotidine, 54 (△), 234 (□) nmol/kg, i.v.; famotidine, 0.41 plus mepyramine 0.4 μ mol/kg, i.v. (●); mepyramine, 0.1 (△), 1.1 (□) and 11 (●) μ mol/kg, i.v. Each mark represents the mean $\pm$ S.E. from 6 animals.

Table 1. Inhibitory effects of famotidine and cimetidine on depressor response to dimaprit in anesthetized, vagotomized dogs

Drug	DR ₁₀ (μ mol/kg)	Slope ^a
Famotidine	0.059 (0.047–0.072) ^b	1.16 (0.96–1.37)
Cimetidine	9.77 (8.13–11.8)	1.07 (0.91–1.22)

^aSlope of regression lines for Schild plot in Fig. 2. ^bFigures in parentheses indicate 95% confidence limits from 6 animals.

mine in anesthetized rats: The inhibitory effects of famotidine and cimetidine on histamine-induced gastric acid secretion are shown in Fig. 5. In control animals, histamine

Fig. 4. Effects of famotidine and mepyramine on the depressor response to histamine in anesthetized, vagotomized dogs. (○) No antagonist; famotidine, 54 (△), 234 (□) nmol/kg, i.v.; famotidine, 0.41 plus mepyramine, 1.1 (●); and famotidine, 0.59 plus mepyramine, 11.1 (▲) μ mol/kg; mepyramine, 0.1 (△), 1.1 (□) and 11.1 (●) μ mol/kg, i.v. Each mark represents the mean $\pm$ S.E. from 6 animals.

Fig. 5. Inhibitory effects of famotidine and cimetidine on acid response to histamine in the perfused stomach preparation of anesthetized rats. (○) No antagonist; famotidine, 0.03 (△) and 0.3 (□) μ mol/kg/hr; cimetidine, 4.0 (△) and 11.9 (□) μ mol/kg/hr. Each mark represents the mean $\pm$ S.E. from 3 to 5 animals.

Table 2. Effect of famotidine on blood pressure response to methacholine, isoproterenol and phenylephrine in anesthetized, vagotomized dogs

Famotidine (nmol/kg, i.v.)	Displacement of dose-response curve to right		
	Methacholine	Isoproterenol	Phenylephrine
180	0.98 (0.71–1.24) ^a	1.46 (0.38–2.54)	1.29 (0.82–1.77)
720	1.06 (0.76–1.36)	1.28 (0.80–1.75)	1.05 (0.63–1.46)

^aFigures in parentheses indicate 95% confidence limits from 4 animals.

Fig. 6. Linear transformation of histamine dose-response curves in Fig. 5. Abscissae: response ($\mu\text{mol H}^+/\text{min}$)/dose of histamine ($\mu\text{mol/kg/hr}$). Regression lines for famotidine and cimetidine are as follows: no antagonist ($\circ$): $y = -0.1x + 6.9$, $r = 0.95$; famotidine, $0.03 \mu\text{mol/kg/hr}$ ($\triangle$): $y = -0.4x + 7.1$, $r = 0.96$; $0.3 \mu\text{mol/kg/hr}$ ($\square$): $y = -1.5x + 7.3$, $r = 0.87$; cimetidine, $4 \mu\text{mol/kg/hr}$ ($\triangle$): $y = -0.4x + 6.1$, $r = 0.85$; $11.9 \mu\text{mol/kg/hr}$ ($\square$): $y = -1.3x + 6.9$, $r = 0.92$.

at 0.09 – $2.7 \mu\text{mol/kg/min}$ produced dose-dependent increases in gastric acid output, the maximum being about $4.9 \mu\text{mol H}^+/\text{min}$. The i.v.-infusion of famotidine and cimetidine caused a dose-dependent and parallel shift to the right of the histamine dose-response curve. The DR_3 was 0.024 for famotidine and $2.6 \mu\text{mol/kg/hr}$ for cimetidine. Judging from these DR_3 values, famotidine was 108 times more potent than cimetidine. In the kinetic analysis by Edie-Hofstee transformation, famotidine and cimetidine altered the slope of the control histamine line without reducing maximal responses estimated from the Y-intercept (Fig. 6). These results indicate that famotidine, like cimetidine, behaves as a competitive antagonist of gastric H_2 -receptors in anesthetized rats.

Discussion

In the present studies with anesthetized dogs, famotidine and cimetidine behaved as competitive inhibitors of vascular H_2 -receptors as in the case of cimetidine and ranitidine reported by Daly et al. (8). Mepyramine competitively inhibited 2-pyridylethylamine-induced hypotension, which was not affected by famotidine. The blood pressure response to lower doses of histamine was antagonized

by mepyramine with doses similar to those used to block the response to lower doses of the selective H_1 -agonist. On the contrary, the hypertensive action of histamine in higher doses was refractory to the H_1 -antagonist in cats and dogs as shown by Folkow et al. (22) and fully antagonized by the combination of mepyramine and famotidine. These results are consistent with the concept that both of the H_1 - and H_2 -receptors may participate (1, 2) and that the H_1 -receptors may be predominantly involved (23) in the vasodepressor action of histamine.

Famotidine was a highly selective antagonist of the vascular H_2 -receptors because famotidine did not modify the effects of 2-pyridylethylamine, phenylephrine and isoproterenol on blood pressure. Similar results have been reported for metiamide (5) and ranitidine (8). In the in vivo experiments on gastric acid secretion, however, their selective H_2 -receptor blocking activity is obscured by the observations that the H_2 -antagonists inhibited not only the gastric acid responses to histamine or dimaprit but also those in response to pentagastrin and cholinergic stimulants (7, 24, 25). Nevertheless, famotidine was qualitatively similar to the competitive H_2 -antagonist cimetidine since famotidine competitively antagonized the action of dimaprit on gastric acid secretion in dogs (7) and cats (26, 27) and its action on blood pressure in dogs in the present studies. As mentioned above, these antagonists also caused the surmountable inhibition of gastric acid secretion induced by histamine in rats. From these results, the mode of interactions between the antagonists and H_2 -receptors may be the same in the vascular and gastric acid secretory tissues, but the degree of involvement of H_2 -receptors may be different in the regulation of blood pressure and gastric acid secretion in vivo.

Black et al. (13) have reported using isolated guinea pig right atria and mouse stomachs that there is no need to postulate heterogeneity of H_2 -receptors. Famotidine was 166 and 108 times more potent than cimetidine in blocking the blood pressure response to dimaprit in dogs and the acid response to histamine in rats, respectively, in the present studies. The values are in good agreement with their inhibitory effect on

dimaprit-induced gastric acid secretion in dogs (7). Ranitidine was also consistently more potent than cimetidine in blocking the effects of histamine on blood pressure after a blockade of H₁-receptors (8) and on gastric acid secretion in dogs induced by histamine (6, 25). Based on the similarity of the relative potencies among the H₂-antagonists in the two tissues, it is not conceivable that any of the H₂-antagonists mentioned above can produce differential antagonism of vascular and gastric H₂-receptors.

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