

Histamine H₂-Receptor Plays Only a Minor Role in Histamine-Induced Wheal Response in the Squirrel Monkey and Guinea Pig

Hiddenobu Yuki, Keiji Miyata, Takeshi Kamato, Akito Nishida, Hiroyuki Ito, Masaaki Takeda and Kazuo Honda

*Neuroscience & Gastrointestinal Research Laboratories, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co., Ltd.,
21, Miyukigaoka, Tsukuba, Ibaraki 305, Japan*

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ABSTRACT—We examined the contribution of the histamine H₂-receptor to the histamine-induced wheal response in squirrel monkeys and guinea pigs. Intradermal injection of histamine, 2-pyridylethylamine (a selective H₁-agonist), and dimaprit (a selective H₂-agonist) dose-dependently induced the wheal response in squirrel monkeys and guinea pigs, although the reaction to dimaprit was much weaker than that to the other agonists. Chlorpheniramine dose-dependently depressed the wheal response in squirrel monkeys and guinea pigs at doses of 0.03–1 mg/kg and 0.03–3 mg/kg, p.o., respectively. However, famotidine, ranitidine and cimetidine had no effect at doses up to 30, 100 and 300 mg/kg, p.o. in guinea pigs and up to 1, 10 and 400 mg/kg, p.o. in squirrel monkeys, respectively. Cimetidine (3–300 mg/kg, p.o.) dose-dependently potentiated the inhibitory effects of chlorpheniramine (0.1 mg/kg, p.o.) in guinea pigs, but had no effects in squirrel monkeys. Famotidine and ranitidine did not alter the response to chlorpheniramine in either animal. These results suggest that the histamine H₂-receptor plays only a minor role in the histamine-induced wheal response in squirrel monkeys and guinea pigs.

Keywords: Wheal response, Histamine H₂-receptor, Squirrel monkey

Histamine directly dilates the micro vasculature and increases vascular permeability, when it is intradermally injected. Vascular dilation appears as a localized red spot around the injection site, and the increase in vascular permeability appears as a wheal reaction. These cutaneous histamine responses have been well examined, and the presence and function of histamine H₁- and H₂-receptors in the cutaneous vasculature have been confirmed. Vascular dilatation is mediated by both H₁- and H₂-receptors. On the other hand, increased vascular permeability is mainly mediated by H₁-receptors (1), and the involvement of H₂-receptors remains to be clarified. Histamine H₂-receptors have been reported to mediate the histamine-induced wheal response in humans (2–4), rhesus monkeys (5) and Japanese monkeys (6), but not that in guinea pigs (7–9), rats (10) and mice (11).

To examine more closely the involvement of histamine H₂-receptors in the wheal reaction to histamine, we investigated the effects of H₁- and H₂-receptor antagonists on the histamine-induced wheal response in squirrel monkeys, which are small, convenient animals that have recently been used in several kinds of investigations, and in guinea pigs.

MATERIALS AND METHODS

Animals

Male Hartley guinea pigs weighing 250–350 g were used. The fur of the back was clipped the day before the experiment.

Squirrel monkeys of both sexes weighing 500–750 g were also used. They were anesthetized with ketamine at an intramuscular dose of 10 mg/kg and maintained with further injections of 2–5 mg/kg as required. Prior to the experiment, the abdomen was carefully shaved to avoid flare. Squirrel monkeys were used repeatedly after recovery for at least a week.

For oral administration of the test drugs, the animals were fasted for 18 hr prior to the experiment but allowed free access to water.

Effects of histamine and histamine H₁- and H₂-receptor antagonists

One milliliter of 2% Evans blue solution was injected intravenously into guinea pigs, and 1 ml of 0.5% Evans blue solution was injected intravenously into squirrel monkeys. At the same time, intradermal injections of seri-

al dilutions of histamine or histamine-receptor agonists were applied to the shaved site of each animal. The injection volume was 0.1 ml in guinea pigs and 0.05 ml in squirrel monkeys. Guinea pigs were killed, and the diameters of the blue edema areas on the reflected skin surface were measured at 5, 10, 20 and 40 min after intradermal injection. For squirrel monkeys, the greatest orthogonal diameters of the blue edema area were measured in mm at 5, 10, 20 and 40 min after intradermal injection. The wheal area was expressed as the area of an ellipse calculated from the orthogonal diameters of the blue area (mm^2).

Effects of several kinds of receptor antagonists

In the first series of experiments, the histamine H_1 -receptor antagonist chlorpheniramine or one of the histamine H_2 -receptor antagonists, famotidine, ranitidine or cimetidine, was given orally 60 min before intradermal injection of histamine in squirrel monkeys and guinea pigs.

In the second series of experiments, histamine H_2 -receptor antagonists in combination with chlorpheniramine were dosed orally 60 min before intradermal injection of histamine.

In the third series of experiments, chlorpheniramine, famotidine, atropine, phentolamine or propranolol was injected intravenously 10 min before the intradermal injection of dimaprit.

Statistical analyses

All values represent the mean \pm standard error of the mean (S.E.M). Statistical significance was determined by analysis of variance (ANOVA). Probabilities of less than 5% ($P < 0.05$) were considered significant.

Drugs

Famotidine, 2-pyridylethylamine dihydrochloride (2PEA), dimaprit dihydrochloride, 4-methylhistamine dihydrochloride and thioperamide were prepared at Yamanouchi Pharmaceutical Co., Ltd. The following were obtained from commercial sources: histamine dihydrochloride, cimetidine, ranitidine hydrochloride and chlorpheniramine maleate (Sigma, St. Louis MO, USA); atropine sulfate (Tanabe Seiyaku, Osaka); phentolamine mesylate (Ciba-Gaigy, Basel, Switzerland); propranolol hydrochloride (ICI, Macclesfield, UK); and ketamine hydrochloride (Sankyo, Tokyo). Methysergide was the kind gift of Sandoz, Ltd. (Basel, Switzerland).

Histamine, 2PEA, dimaprit and 4-methylhistamine were dissolved in 0.9% (w/v) sodium chloride solution (saline). All drugs, when given orally, were suspended in 0.5% methylcellulose solution. In experiments using intravenous injection, famotidine, cimetidine and thioperamide were dissolved in N/10 hydrochloric acid and dilut-

ed with saline, with the pH adjusted to 6.5–7.0. Atropine, phentolamine and propranolol were diluted with saline, and the other drugs were dissolved in saline.

RESULTS

Skin reaction to intradermal injection of histamine-receptor agonists

We first performed time-course studies on the wheal responses to histamine, 2PEA and dimaprit. In the guinea pig, histamine (0.25, 2 μg) and 2PEA (100 μg) produced maximal whealing at 20 min after intradermal injection (Fig. 1). A high dose of histamine (8 μg) produced the maximal wheal at 40 min after intradermal injection, but the outline of this wheal was indistinct. The maximal wheal response to dimaprit was observed at 10 min after intradermal injection. To unify the experimental conditions, the wheal area was measured at 20 min after intradermal injection. In the squirrel monkey, maximal wheal responses to 2PEA (500 μg) and dimaprit (500 μg) were observed at 20 min after intradermal injection. In the squirrel monkey, maximal wheal responses to 2PEA (500 μg) and dimaprit (500 μg) were observed at 20 min after intradermal injection. Although the maximal wheal

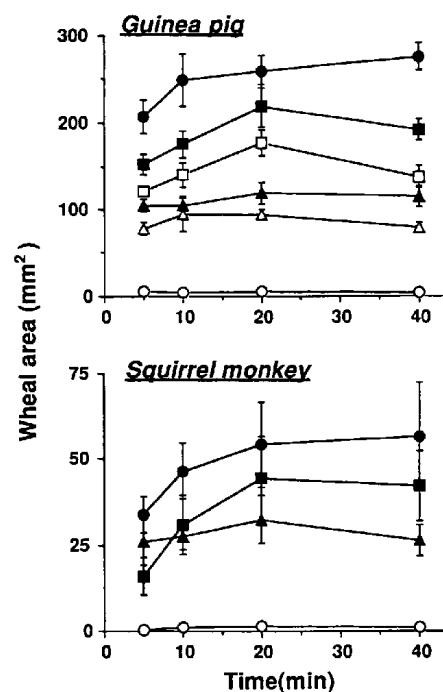


Fig. 1. Time-course of the wheal reaction induced by histamine, 2PEA and dimaprit in the squirrel monkey and guinea pig. Each point represents the mean \pm S.E.M. for 4 to 5 animals. Guinea pig: saline (○); histamine, 0.25 (▲), 2 (■), 8 μg (●); 2PEA, 50 μg (□); dimaprit, 500 μg (△). Squirrel monkey: saline (○); histamine, 50 μg (●); 2PEA, 500 μg (■); dimaprit, 500 μg (▲).

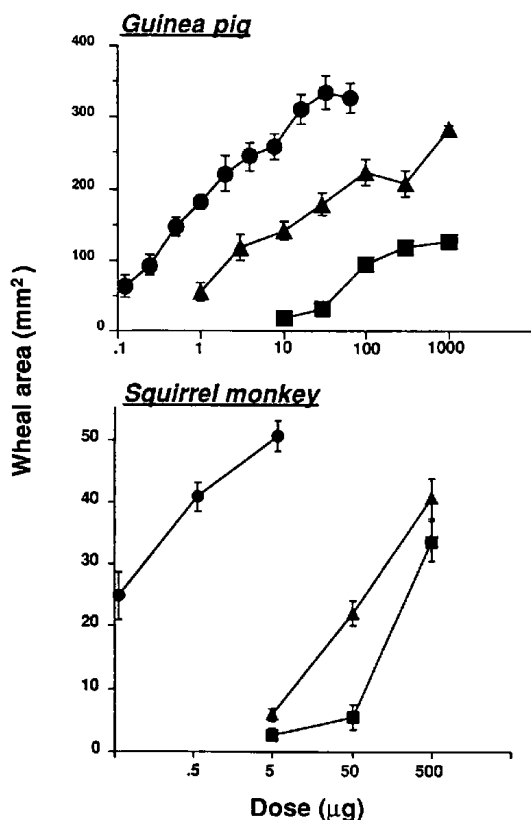


Fig. 2. Wheal response to intradermal injection of histamine (●), 2PEA (▲) and dimaprit (■) in the squirrel monkey and guinea pig. Each point represents the mean \pm S.E.M. for 4 to 6 animals.

response to histamine (50 μ g) was measured at 40 min after intradermal injection, its outline was indistinct and the blue area of skin surface was faded compared with that measured at 20 min after injection (Fig. 1). The wheal was therefore measured at 20 min after injection in the following experiments.

In guinea pigs, histamine (0.125–64 μ g), 2PEA (1–1000 μ g) and dimaprit (30–1000 μ g) produced wheal responses in a dose-dependent manner, but the maximal wheal area to dimaprit was 38% of that to histamine (Fig. 2). Because the outline of the wheal to high doses of histamine (16–64 μ g) was unclear, in the following experiments, doses of histamine and agonists were limited to cause wheals of less than 300 mm². Histamine (1–100 μ g), 2PEA (100–1000 μ g) and dimaprit (100–1000 μ g) also induced wheals in a dose-dependent fashion in the squirrel monkey (Fig. 2). We did not determine the wheal response at higher doses of histamine and agonists in order to avoid skin injury, because the squirrel monkey was used repeatedly.

Effects of histamine receptor antagonists on the wheal response to histamine in guinea pigs

In the guinea pig, chlorpheniramine at 0.01–1 mg/kg, p.o. shifted the histamine wheal dose-response curve to the right in a dose-related, parallel fashion. On the other hand, famotidine (0.3–30 mg/kg, p.o.), ranitidine (1–100 mg/kg, p.o.) and cimetidine (3–300 mg/kg, p.o.) did not affect the wheal response to histamine (Fig. 3).

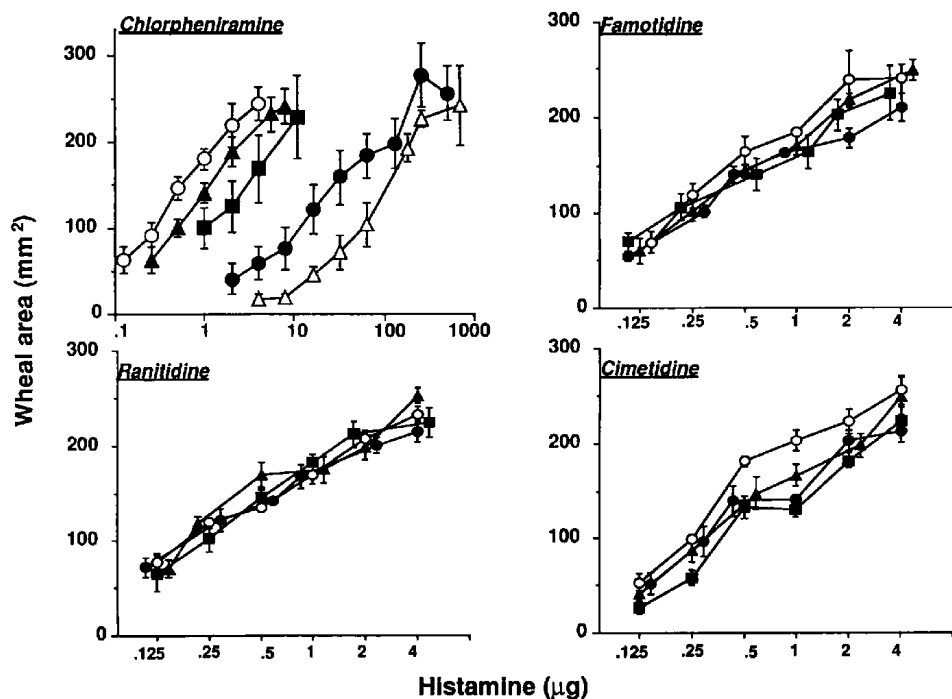
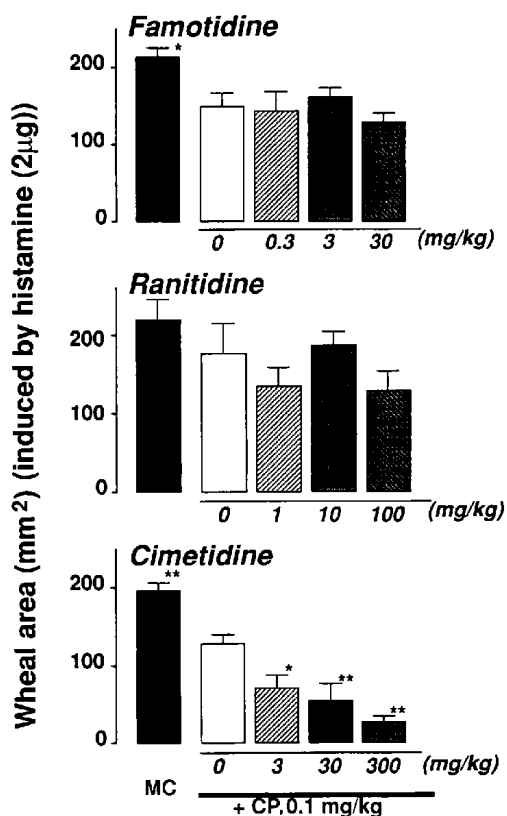


Fig. 3. Effects of chlorpheniramine, famotidine, ranitidine and cimetidine on the wheal response to histamine in the guinea pig. Each point represents the mean \pm S.E.M. for 4 to 5 animals. All drugs and MC (0.5% methylcellulose solution) were dosed orally 60 min before intradermal injection of histamine. Chlorpheniramine: MC (○), 0.03 (▲), 0.1 (■), 0.3 (●), 1 mg/kg (△). Famotidine: MC (○), 0.3 (▲), 3 (■), 30 mg/kg (●). Ranitidine: MC (○), 1 (▲), 10 (■), 100 mg/kg (●). Cimetidine: MC (○), 3 (▲), 30 (■), 300 mg/kg (●).



In combination studies, cimetidine at 3–300 mg/kg, p.o. potentiated the inhibitory effects of chlorpheniramine (0.1 mg/kg, p.o.) on the histamine-induced wheal, whereas famotidine (0.3–30 mg/kg, p.o.) and ranitidine (1–100 mg/kg, p.o.) did not alter the response to chlorpheniramine (Fig. 4).

Effects of histamine receptor antagonists on the wheal response to histamine in squirrel monkeys

Chlorpheniramine (0.03–3 mg/kg, p.o.) dose-dependently and significantly depressed the histamine wheal response in squirrel monkeys, but famotidine (0.3 and 1 mg/kg, p.o.), ranitidine (3 and 10 mg/kg, p.o.) and cimetidine (12 and 400 mg/kg, p.o.) had no effect (Fig. 5).

Moreover, neither famotidine (0.3 mg/kg, p.o.), ranitidine (3 mg/kg, p.o.) nor cimetidine (12 mg/kg, p.o.) al-

Fig. 4. Effects of famotidine, ranitidine and cimetidine in combination with chlorpheniramine (0.1 mg/kg) on the wheal response to histamine (2 µg) in the guinea pig. Each point represents the mean \pm S.E.M. for 5 animals. MC: 0.5% methylcellulose solution, CP: chlorpheniramine. *P < 0.05, **P < 0.01, vs. chlorpheniramine-treated group (open column).

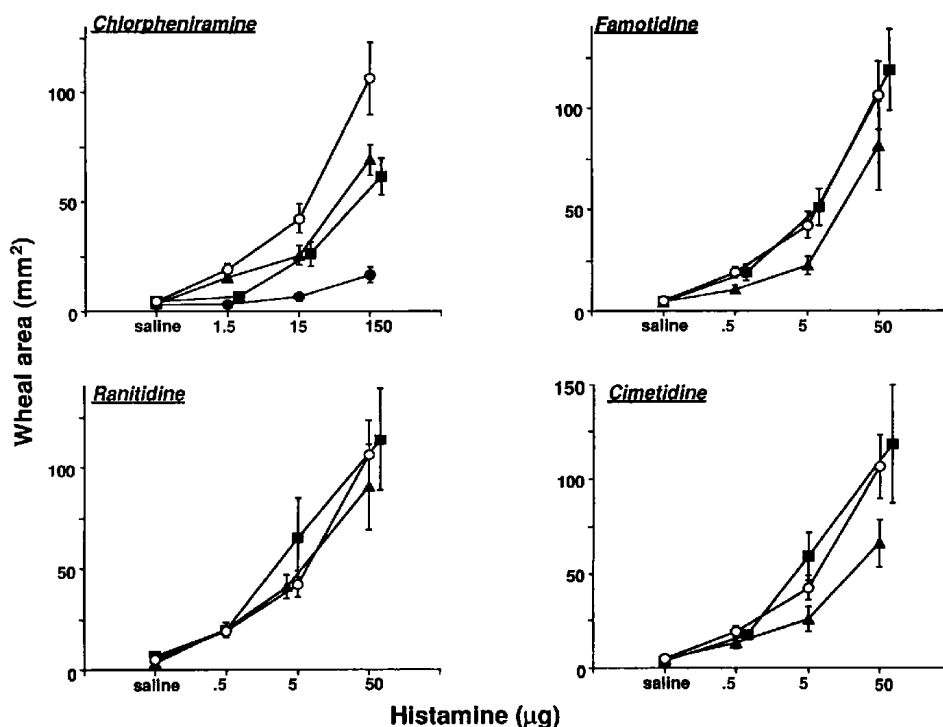


Fig. 5. Effects of chlorpheniramine, famotidine, ranitidine and cimetidine on the wheal response to histamine in the squirrel monkey. Each point represents the mean \pm S.E.M. for 6 animals. All drugs and MC (0.5% methylcellulose solution) were dosed orally 60 min before intradermal injection of histamine. Chlorpheniramine: MC (○), 0.03 (▲), 0.3 (■), 3 mg/kg (●). Famotidine: MC (○), 0.3 (▲), 1 mg/kg (■). Ranitidine: MC (○), 3 (▲), 10 mg/kg (■). Cimetidine: MC (○), 12 (▲), 40 mg/kg (■).

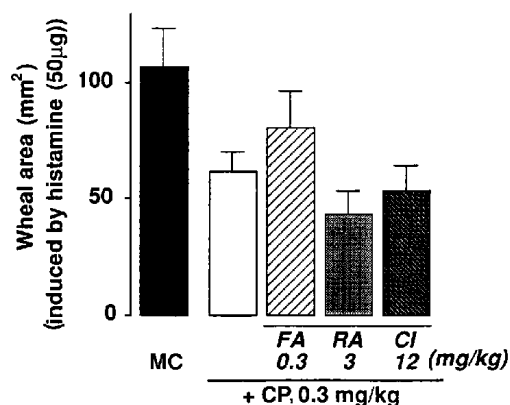


Fig. 6. Effects of famotidine, ranitidine and cimetidine in combination with chlorpheniramine (0.3 mg/kg) on the wheal response to histamine (50 µg) in the squirrel monkey. Each point represents the mean \pm S.E.M. for 6 animals. MC: 0.5% methylcellulose solution. CP: chlorpheniramine. FA: famotidine, RA: ranitidine, CI: cimetidine.

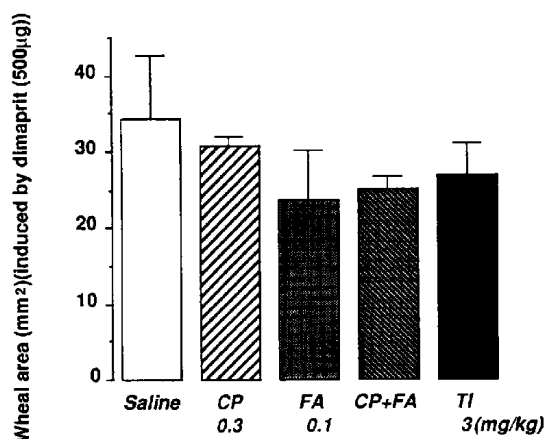


Fig. 7. Effects of chlorpheniramine, famotidine, thioperamide and the combination of chlorpheniramine with famotidine on the wheal response to dimaprit (500 µg) in the squirrel monkey. Each point represents the mean \pm S.E.M. for 6 animals. All drugs and saline were injected intravenously 10 min before intradermal injection of dimaprit. CP: chlorpheniramine, FA: famotidine, TI: thioperamide.

tered the response to chlorpheniramine (0.3 mg/kg, p.o.) when each was given together with this agent (Fig. 6).

Effects of some kinds of antagonists on the wheal response to dimaprit in squirrel monkeys

The dimaprit-induced wheal reaction was not affected by intravenous histamine-receptor antagonists, chlorpheniramine (0.3 mg/kg), famotidine (0.1 mg/kg), the combination of famotidine and chlorpheniramine, or thioperamide (3 mg/kg) (Fig. 7). Neither atropine (1 mg/kg), phentolamine (1 mg/kg), propranolol (1 mg/kg) nor methysergide (3 mg/kg) affected the wheal reaction to dimaprit (Fig. 8).

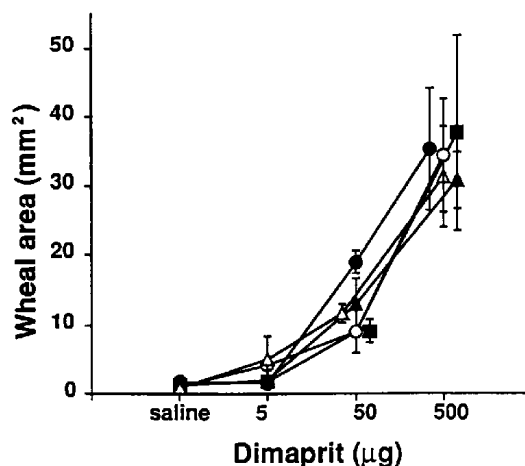


Fig. 8. Effects of saline (○), atropine (▲), phentolamine (■), propranolol (●) and methysergide (△) on the wheal response to dimaprit in squirrel monkeys. Each point represents the mean \pm S.E.M. for 3 animals. All drugs were injected intravenously 10 min before intradermal injection of dimaprit or 4-methylhistamine.

DISCUSSION

Intradermal histamine increases vascular permeability by the contraction of papillary endothelium, resulting in the leakage of plasma proteins, dye and liquid components, which appears as a wheal response. The involvement of histamine receptors in the wheal response to histamine has been well examined in many animal species including humans. It is apparent that histamine H₁-receptor plays an important role in the histamine-induced wheal response, whereas it still remains to be confirmed whether the H₂-receptor is involved in the wheal response to histamine (2–4). This may be caused by histamine H₂-receptor antagonists. Previous studies concerning the role of histamine H₂-receptors have been almost entirely restricted to using cimetidine and metiamide. These H₂-receptor antagonists are devoid of significant H₁-receptor antagonistic activity (12), but their H₂-receptor antagonistic activity is not so potent. Moreover, cimetidine has been reported to interact with other drugs. The mechanisms by which cimetidine causes drug interaction have been demonstrated as follows: cimetidine binds reversibly to the hepatic cytochrome P-450 system, resulting in decreased metabolism of drugs, and cimetidine decreases the hepatic blood flow with resultant reduction of hepatic clearance of drugs (13, 14). Structurally, metiamide as well as cimetidine is a 4,5-substituted imidazole, and many drugs with this structure demonstrate an ability to inhibit hepatic microsomal drug metabolism. Therefore, metiamide is also suggested to interact with other drugs.

Out of previous reports which suggest the involvement

of H_2 -receptors in the histamine-induced wheal response, only Marks and Greaves showed that cimetidine alone significantly inhibited the histamine-induced wheal response in healthy volunteers (2); and in any of the other reports, the participation of histamine H_2 -receptors was demonstrated only after H_1 -receptors were antagonized (3, 4). Recently, Sussman et al. reported that higher serum concentration of hydroxyzine, a histamine H_1 -receptor antagonist, was observed following both hydroxyzine and cimetidine administration, and that the enhancement of efficacy against chronic urticaria was noted compared to when hydroxyzine was given alone in patients (but the differences in efficacy were not statistically significant) (15), suggesting that cimetidine-induced enhancement of efficacy is attributable to drug interaction rather than H_2 -receptor blocking.

Histamine H_2 -receptor antagonists-induced significant potentiation of the inhibitory effect of H_1 -receptor antagonists on intradermal histamine-induced wheal response has been reported solely in guinea pigs (16) besides in human. In rhesus monkeys, a species closely related to humans, Hutchcroft et al. reported that cimetidine showed a tendency to potentiate the efficacy of chlorpheniramine ($P < 0.1$) (5); and Ohmi et al. reported that metiamide alone inhibited the histamine-induced wheal response in the Japanese monkey, although it was not statistically significant ($P < 0.1$) (6). Therefore, in the present study, we examined the involvement of H_2 -receptors in the intradermal histamine-induced wheal response using squirrel monkeys, which has never been evaluated, and compared the results with those in guinea pigs. In addition to examining the effects of cimetidine on the wheal response, we also investigated the effects of two other compounds, famotidine and ranitidine, both which possessed more potent H_2 -receptor blocking activity than cimetidine but did not interact with other drugs.

This study showed that famotidine and ranitidine had no effect on the histamine-induced wheal response and did not affect the inhibitory effect of an H_1 -receptor antagonist, chlorpheniramine, on the wheal response to histamine in squirrel monkeys at doses sufficient to block histamine-stimulated gastric acid secretion in rats, dogs and humans (17–20). Moreover, as mentioned above, although metiamide alone showed the inhibitory effect on the histamine-induced wheal response in Japanese monkey (6) and cimetidine potentiated the inhibitory effect of chlorpheniramine on the wheal response to histamine in rhesus monkey (5), these were not statistically significant ($P < 0.1$). Taken all together, histamine H_2 -receptors may not be involved in the histamine-induced wheal response in monkeys.

In guinea pigs, famotidine and ranitidine also had no effect on the histamine-induced wheal response and had

no influence on the inhibitory effect of chlorpheniramine, whereas cimetidine potentiated the efficacy of chlorpheniramine without affecting the histamine-induced wheal response when given alone, like the results reported by Cheng et al. (16). The apparent discrepancies of the effect of cimetidine between squirrel monkeys and guinea pigs may be due to the difference in animal species, especially in the hepatic microsomal enzyme system. The recent development of gene technology has permitted quantitative comparison of the properties of cytochrome P-450, which is a family of enzymes playing major roles in the metabolism of a variety of drugs, among various species. The results indicate that monkeys show a low level of homology in the cDNA sequences of guinea pigs (21). Nevertheless, since potent and selective H_2 -receptor antagonists such as famotidine and ranitidine did not potentiate the efficacy of chlorpheniramine on the histamine-induced wheal response, cimetidine-induced potentiation in guinea pig is suggested not to be attributable to H_2 -receptor antagonistic activity.

2PEA is a relatively selective H_1 -receptor agonist, and the effect of 2PEA is approximately 18 times weaker than that of histamine in guinea pig ileum (H_1 -receptor) (22). In the present study, 2PEA was about 30 times weaker than histamine in the wheal reaction, indicating the result to be well consistent with that in guinea pig ileum. These data show that 2PEA as well as histamine induces the wheal via H_1 -receptors.

Dimaprit is a highly selective H_2 -receptor agonist, and the ratio of H_1 - to H_2 -potency is 710000 (22). It has been reported that dimaprit increases vascular permeability and edema volume (23) in rats and produces eosinophil chemotaxis in rabbits (24), and that histamine H_2 -receptors are not involved in these inflammatory responses to dimaprit. In the present studies, dimaprit induced wheal in squirrel monkeys, but its maximum area of the wheal was 38% that of histamine, and the dimaprit-histamine potency ratio differed from both results in guinea pig ileum (H_1 -receptors) and atrium (H_2 -receptors). Moreover, the wheal response to dimaprit was not affected by chlorpheniramine, famotidine, thioperamide, phentolamine, propranolol, atropine and methysergide, suggesting that the following types of receptors are not involved in the wheal induced by dimaprit: histamine H_1 , H_2 , H_3 ; adrenergic α , β ; muscarinic; and 5-HT $_{1,2}$.

In summary, it is suggested that the histamine H_2 -receptor plays only a minor role in the wheal response to histamine in squirrel monkeys and guinea pigs, and that the potentiating effect of cimetidine on H_1 -receptor antagonists is attributable to drug interaction rather than H_2 -receptor antagonism.

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