

Allergens, IgE, mediators, inflammatory mechanisms

Histamine N-methyltransferase inhibitor potentiates histamine- and antigen-induced airway microvascular leakage in guinea pigs

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Background: Histamine N-methyltransferase (HMT) modulates histamine- and antigen-induced bronchoconstriction. However, it is unclear whether vascular permeability evoked by an allergic reaction can be exaggerated by inhibition of HMT activity.

Methods: We studied the effects of intravenously injected SKF 91488, a specific HMT inhibitor, on increases in plasma extravasation induced by intravenously injected histamine in unsensitized guinea pigs and by intravenously injected ovalbumin antigen in guinea pigs sensitized to ovalbumin in vivo with Evans blue dye as a marker.

Results: Pretreatment with SKF 91488 shifted, in a dose-dependent fashion, the dose-response curves of the leakage of dye to histamine to lower concentrations in the trachea, main bronchi, and nasal mucosa. Likewise, pretreatment with SKF 91488 (20 mg/kg intravenously) significantly increased the leakage of dye induced by ovalbumin antigen (200 µg/kg intravenously) in three parts of the airway ($p < 0.05$). In contrast to SKF 91488, intravenously injected aminoguanidine, a specific inhibitor of diamine oxidase (16 mg/kg intravenously), did not alter the leakage of dye induced by histamine (from 0.001 µg/kg to 10 µg/kg intravenously) ($p > 0.20$). HMT activities were observed in the nasal mucosa, as well as in the trachea and main bronchi, as shown in a previous study.

Conclusion: These findings suggest that HMT modulates the effects of exogenous histamine and endogenously released histamine induced by antigen challenge on plasma extravasation in the airway in guinea pigs in vivo. (*J ALLERGY CLIN IMMUNOL* 1995;96:910-6.)

Key words: Plasma extravasation, bronchial asthma, histamine, allergic rhinitis, mucosal edema

Mucosal edema is one of the prominent pathologic changes of the airways in patients who have died in status asthmaticus¹ and is presumably the result of increased microvascular leakage in bron-

Abbreviations used

DAO: Diamine oxidase
EB: Evans blue
HMT: Histamine N-methyltransferase

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chial circulation.² Histamine, which is stored mainly in mast cells and basophils and is released by antigen-cross-linked IgE, is widely recognized to cause increased microvascular permeability to macromolecules.² In addition, histamine levels are increased in bronchoalveolar lavage fluid of asthmatic patients³ and in nasal secretions of patients with allergic rhinitis.⁴

We have recently shown that the bronchoconstrictor effects of histamine and antigen are modulated by histamine N-methyltransferase (HMT).^{5,6} HMT activity is present in the trachea, bronchi, bronchioles, and parenchymal tissues of guinea pigs; and HMT messenger RNA is found in the epithelium and vascular endothelium.^{5,6} Because HMT is likely present in the endothelium, histamine-induced increases in microvascular permeability may also be modulated by HMT.

To test this hypothesis, we investigated the effects of HMT inhibitor SKF 91488 and diamine oxidase (DAO) inhibitor aminoguanidine on histamine- and antigen-induced increases in microvascular permeability in unsensitized and sensitized guinea pigs.

METHODS

General procedure

Male Hartley guinea pigs (Funabashi Farm, Shizuoka, Japan), weighing 400 to 500 gm, were anesthetized intraperitoneally with uretan (1 gm/kg) and pentobarbital sodium (20 mg/kg). A catheter was placed in the jugular vein for drug injection. Increases in vascular permeability were produced by intravenous injection of histamine or ovalbumin. The animals received an intravenous injection of Evans blue (EB) dye as a marker of plasma leakage. The animals were also given either the vehicle of SKF 91488 (saline solution) or SKF 91488 before the histamine or ovalbumin injection.

Measurement of vascular permeability

The magnitude of vascular permeability was quantified with a modification of the method described by Saria and Lundberg,⁷ which correlates well with extravasation of radiolabeled albumin.⁸ EB dye (30 mg/kg, 30 mg/ml in saline solution), dissolved in saline solution and filtered through a 5 μ m Millipore filter (Millipore Corp., Bedford, Mass.), was injected into a jugular vein. To determine the tissue content of EB dye after stimulation, the systemic circulation was perfused with 1% paraformaldehyde in 0.05 mol/L phosphate-buffered saline solution (pH 7.4) to wash the dye out of the vasculature. The left ventricle was incised, a blunt-ended needle was inserted into the aorta, and the ventricles were cross-clamped. Blood was expelled from the incised right atrium at a pressure of 100 mm Hg until the perfusate was clear (about 200 ml infused). The trachea, main bronchi, and a portion of nasal mucosa (3 to 5 mm by 1 to 2 mm), dissected from between the vomer and the roots of the vibrissae, were removed; and the tissues were blotted dry and weighed. To quantify the amount of extravasated EB dye, each tissue sample was immersed in 2 ml of 100% formamide for 24 hours at 50°C to extract the dye, and concentrations of dye in the solutions were determined spectrophotometrically by measuring the absorbance at 620 nm (220A spectrophotom-

eter; Hitachi Ltd., Tokyo, Japan). Tissue content (nanograms of dye per milligram of wet weight) was calculated from a standard curve of dye concentrations ranging from 0.5 to 10 μ g/ml.

Effects of SKF 91488 on histamine-induced vascular permeability

To determine dose-response effects of histamine on vascular permeability, intravenous injection of histamine (from 1 ng/kg to 100 μ g/kg) was performed in two separate groups of animals. Control animals ($n = 7$ for each concentration of histamine) received the vehicle of SKF 91488 (same amount of saline solution used for SKF 91488 solution). In the other group ($n = 7$) for each concentration of histamine SKF 91488 (20 mg/kg, 20 mg/ml in saline solution) was administered 15 minutes before the injection of EB dye. Each group received either saline solution (control) or each concentration of histamine 1 minute after the injection of EB dye (30 mg/kg, 30 mg/ml in saline solution). Five minutes later, perfusion of the circulation was started (perfusion time of approximately 3 minutes).

To determine the effects of aminoguanidine, a specific DAO inhibitor of the responsiveness to histamine, dose-response curves to histamine (from 1 ng/kg to 10 μ g/kg) on vascular permeability were obtained in animals receiving aminoguanidine (16 mg/kg, 16 mg/ml; an equimolar dose as the maximum concentration of SKF 91488) ($n = 7$ for each concentration of histamine).

To determine the dose-dependent effects of SKF 91488 on the histamine-induced increase in vascular permeability, animals received an intravenous injection of histamine (0.1 μ g/kg) 15 minutes after the administration of SKF 91488 (from 0.2 mg/kg to 40 mg/kg) ($n = 6$ for each concentration of SKF 91488).

To determine whether HMT influences vascular permeability induced by agents other than histamine, we studied the effects of SKF 91488 (20 mg/kg) after vascular permeability was induced by intravenous injection of platelet activating factor (10 ng/kg) and bradykinin (0.3 μ g/kg) ($n = 5$ for each agonist).

Effects of SKF 91488 on antigen-induced vascular permeability

Male Hartley guinea pigs, weighing 250 to 300 gm, were sensitized to ovalbumin, as described previously.⁹ Sensitization was induced on day 1 with 5 mg of ovalbumin injected intraperitoneally and 5 mg ovalbumin injected subcutaneously, each dissolved in 0.5 ml of saline solution. On day 4, an additional 5 mg of ovalbumin was injected intraperitoneally. These sensitized animals were challenged and subsequently studied at 3 to 4 weeks when they weighed 450 to 550 gm. Control animals ($n = 7$) received the vehicle of SKF 91488 15 minutes before the administration of EB dye. The EB dye (30 mg/kg) was injected into a jugular vein, followed 1 minute later by intravenously administered ovalbumin (200 μ g/kg, 200 μ g/ml in saline solution). In the other group ($n = 7$),

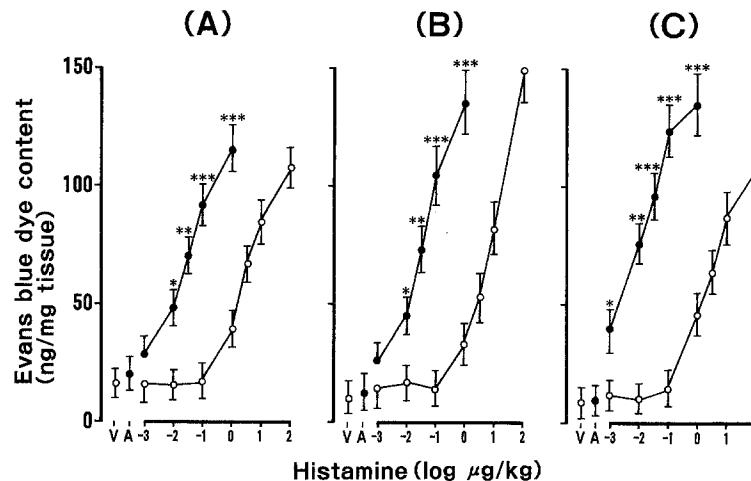


FIG. 1. Dose-response curves of the leakage of EB dye to histamine in the absence (*open circles*) or 15 minutes after the administration (*filled circles*) of SKF 91488 (20 mg/kg) in the trachea (**A**), main bronchi (**B**), and nasal mucosa (**C**). V and A indicate responses to the vehicle of SKF 91488 and SKF 91488 (20 mg/kg) without histamine, respectively. Results are reported as means $\pm$ SEM from seven animals. Significant differences between histamine with and without SKF 91488 are indicated by * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. The values at the concentration of 0.03 μ g/kg histamine with SKF 91488 were compared with those at the concentration of 0.1 μ g/kg histamine without SKF 91488.

animals received SKF 91488 (20 mg/kg) instead of the vehicle of SKF 91488, and the same procedure was performed as in the case of the control animals.

To determine whether the ovalbumin antigen-induced increase in vascular permeability involved histamine, animals received a histamine H_1 receptor blocker pyrilamine (200 mg/kg ip) and a histamine H_2 receptor blocker cimetidine (1 mg/kg ip) 45 minutes before challenge.¹⁰ We also studied the effects of SKF 91488 on vascular permeability in the presence of pyrilamine (200 mg/kg ip) and cimetidine (1 mg/kg ip) 45 minutes before the intravenous administration of SKF 91488 (20 mg/kg).

Histologic assessment of vascular permeability

To visualize vessels developing increased microvascular permeability in the airways, animals were injected intravenously with a macromolecular tracer, Monastral blue (DuPont Company, Wilmington, Del.) (30 mg/kg; 3% suspension of copper phthalocyanine blue pigment in 0.85% NaCl) in two separate groups of animals. Control animals ($n = 5$) received the vehicle of SKF 91488. In the other group SKF 91488 (20 mg/kg) was administered 15 minutes before the injection of Monastral blue. Each group received histamine (0.03 μ g/kg) 1 minute after the injection of Monastral blue. Five minutes later, perfusion of the circulation was started. After all blood was washed out, the nose, trachea, and lungs were removed and immersed in 1% paraformaldehyde for 3 days, cut into tissue blocks, and fixed again in 1% paraformaldehyde for 1 week. After fixation, the tissue blocks were sliced, dehydrated through a graded series

of ethanol, and embedded in paraffin. Tissue blocks were then cut into 4 μ m thick sections. More than three pieces of trachea, main bronchi, and nose were selected from each animal. All morphometric measurements described below were performed with a digitizer tablet coupled to a computer, with an image on a television monitor obtained directly from the light microscope (PC-9801; NEC Corp., Tokyo, Japan and LA-500; PIAS Co., Tokyo, Japan). We measured the area of vessels in which Monastral blue dye was trapped in the vascular wall and the total area of vessels in the wall as described previously.¹¹ Vessel areas in five visual fields for each section were randomly chosen and were summed for each animal. We defined the permeability index as the ratio of the area of vessels with Monastral blue to that of total vessels in each animal.¹¹

Measurements of HMT activity in nasal mucosa

Male Hartley guinea pigs, weighing 400 to 450 gm, were anesthetized intraperitoneally with pentobarbital sodium (50 mg). After the chest was opened, an incision was made on the right atrium to release blood, and a blunt-ended polyethylene tube was inserted into the left ventricle. The animal was perfused with saline solution at a pressure of 100 mm Hg to expel blood from the circulation. After the elimination of blood, the nasal mucosa (same portion as in the study of vascular permeability) was excised and homogenized in 4 vol of cold phosphate buffer (0.1 mol/L at pH 7.0 and 4°C) with a glass homogenizer. The homogenate was centrifuged at 10,000 g at 4°C, and the supernatant was used for measuring HMT activity. The supernatant was dialyzed

TABLE I. Effects of aminoguanidine on histamine-induced microvascular permeability

Histamine ($\mu\text{g/kg}$)	EB dye content (ng/mg tissue)					
	Trachea		Main bronchi		Nasal mucosa	
	Control	Inhibitor	Control	Inhibitor	Control	Inhibitor
0.001	16.3 $\pm$ 8.8	19.6 $\pm$ 6.5	15.0 $\pm$ 7.3	17.4 $\pm$ 7.3	16.1 $\pm$ 7.2	15.3 $\pm$ 6.9
0.01	16.2 $\pm$ 6.4	18.8 $\pm$ 7.1	16.9 $\pm$ 8.3	20.2 $\pm$ 7.5	15.4 $\pm$ 8.0	16.8 $\pm$ 7.1
0.1	17.5 $\pm$ 6.3	18.6 $\pm$ 6.6	15.1 $\pm$ 7.5	19.6 $\pm$ 6.4	18.3 $\pm$ 8.4	17.6 $\pm$ 7.2
1	39.4 $\pm$ 7.3	33.8 $\pm$ 9.2	33.1 $\pm$ 8.8	41.6 $\pm$ 9.2	49.1 $\pm$ 8.2	46.2 $\pm$ 9.3
10	85.0 $\pm$ 9.4	93.6 $\pm$ 8.8	82.5 $\pm$ 11.4	91.6 $\pm$ 9.8	95.1 $\pm$ 10.0	88.7 $\pm$ 9.4

Results are reported as means $\pm$ SEM from seven animals.

two times for 8 hours against 100 vol of the buffer with a cellophane membrane. To measure HMT activity, incubation was carried out at 37°C with 0.5 ml of a mixture of 0.3 ml of 0.1 mol/L sodium phosphate buffer (pH 7.4), 0.05 ml of 1 mmol/L histamine, 0.05 ml of 2.5 mmol/L S-adenosyl-L-methionine, and 0.1 ml of the supernatant for 0, 45, 60, 90, or 120 minutes in the presence of 0.2 mmol/L aminoguanidine. The product, N⁷-methylhistamine, was separated from histamine in a high-performance liquid chromatography system on a weak cation exchanger, TSK gel CM-2SW (Toyo-Soda Manufacturing Co., Tokyo, Japan), with 37.5 mmol/L citric acid, 1.25% imidazole, and 20% acetonitrile at pH 6.8 as the mobile phase at a flow rate of 1.0 ml/min and then measured fluorometrically with a postcolumn derivatization system with o-phthalaldehyde and 2-mercaptoethanol.^{12, 13} HMT activity was expressed as picomoles of N⁷-methylhistamine formed per minute per milligram of protein. Protein concentrations were measured according to the method of Lowry et al.¹⁴

Drugs

Histamine dihydrochloride, pyrilamine, aminoguanidine, ovalbumin, EB dye, Monastral blue, and formamide were from Sigma Chemical Company (St. Louis, Mo.). S-(4-(N,N-dimethyl-amino)-butyl)isothiourea (SKF 91488) and cimetidine were kindly donated by Smith Klein Company (Philadelphia, Pa.).

Statistical analysis

Values are reported as means $\pm$ SEM. For statistical analysis, we used one-way analysis of variance. Multiple comparisons between means were performed by Newman-Keuls tests. Significance was accepted at $p < 0.05$.

RESULTS

Effects of SKF 91488 on histamine-induced vascular permeability

Histamine increased microvascular permeability to EB dye in a dose-dependent fashion in the trachea, main bronchi, and nasal mucosa both with and without pretreatment with SKF 91488 (20 mg/kg iv). SKF 91488 (20 mg/kg iv) alone did not alter the leakage of EB dye from the control values

of the saline administration in all tissues studied (Fig. 1). However, SKF 91488 shifted the dose-response curves of the leakage of EB dye to histamine to the lower concentrations in all tissues (Fig. 1). In contrast to SKF 91488, pretreatment with aminoguanidine (16 mg/kg iv) did not alter histamine-induced increase in the leakage of EB dye at any concentrations in the trachea, main bronchi, and nasal mucosa ($p > 0.20$) (Table I).

In the study of dose-dependent effects of SKF 91488 on histamine-induced increases in the leakage of EB dye, histamine (0.1 $\mu\text{g/kg}$ iv) alone did not cause a significant increase in the leakage of EB dye from the control values in the trachea, main bronchi, and nasal mucosa ($p > 0.30$). SKF 91488 induced dose-dependent potentiation of the response to histamine (0.1 $\mu\text{g/kg}$ iv) with a maximal effect at the concentration of 20 mg/kg in all tissues (Fig. 2).

SKF 91488 (20 mg/kg iv) did not significantly alter the leakage of EB dye induced by platelet activating factor (10 ng/kg iv) (61.2 $\pm$ 9.3 ng/mg tissue with SKF 91488 vs 56.8 $\pm$ 8.4 ng/mg tissue without SKF 91488; $p > 0.20$, $n = 5$) and bradykinin (0.3 $\mu\text{g/kg}$ iv) (55.7 $\pm$ 7.8 ng/mg tissue with SKF 91488 vs 64.3 $\pm$ 9.0 ng/mg tissue without SKF 91488; $p > 0.10$, $n = 5$) in the trachea.

Effects of SKF 91488 on antigen-induced vascular permeability

Intravenous injection of ovalbumin (200 $\mu\text{g/kg}$) significantly increased the leakage of EB dye compared with saline control in the trachea, main bronchi, and nasal mucosa. Pretreatment with SKF 91488 (20 mg/kg iv) further potentiated an ovalbumin-induced (200 $\mu\text{g/kg}$ iv) increase in the leakage of EB dye in all tissues (Fig. 3).

Pyrilamine and cimetidine in combination significantly inhibited antigen-induced increases in microvascular leakage compared with control values in the trachea (41.3 $\pm$ 8.7 ng/mg tissue vs 20.7 $\pm$ 6.6

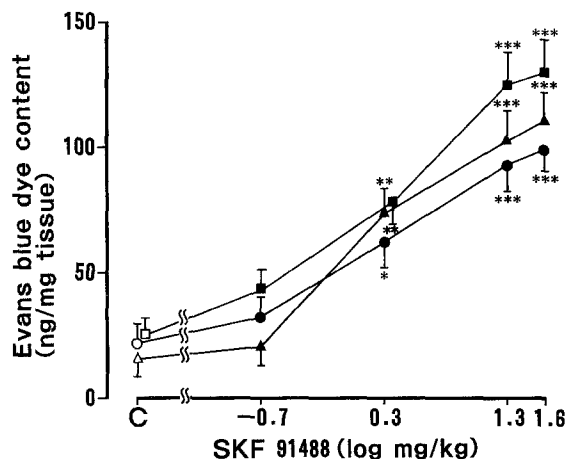


FIG. 2. Dose-response effects of SKF 91488 on histamine-induced (0.1 μ g/kg) leakage of EB dye in the trachea (circles), main bronchi (triangles), and nasal mucosa (squares). C indicates responses to histamine with the vehicle of SKF 91488. Results are reported as means $\pm$ SEM from six animals. Significant differences from the values for histamine with the vehicle are indicated by * p < 0.05, ** p < 0.01, and *** p < 0.001.

ng/mg tissue; p < 0.05, n = 7), main bronchi (56.3 ± 8.8 ng/mg tissue vs 23.1 ± 9.2 ng/mg tissue; p < 0.05, n = 7), and nasal mucosa (80.1 ± 10.0 ng/mg tissue vs 50.3 ± 9.1 ng/mg tissue; p < 0.05, n = 7). However, SKF 91488 (20 mg/kg iv) itself did not alter leakage of EB dye in the presence of pyrilamine and cimetidine (11.2 ± 6.3 ng/mg tissue in the presence of pyrilamine and cimetidine vs 10.6 ± 7.1 ng/mg tissue in the absence of them; p > 0.30, n = 4).

Histologic assessment of vascular permeability

In the absence of SKF 91488, the permeability index was zero in the trachea, main bronchi, and nasal mucosa after the administration of histamine (0.03 μ g/kg). However, SKF 91488 significantly increased the permeability index when compared with control values in the trachea ($51.0\% \pm 7.7\%$ vs $0\% \pm 0\%$; p < 0.01, n = 5), main bronchi ($56.3\% \pm 8.1\%$ vs $0\% \pm 0\%$; p < 0.01, n = 5), and nasal mucosa ($65.1\% \pm 8.0\%$ vs $0\% \pm 0\%$; p < 0.01, n = 5), respectively.

HMT activity in nasal mucosa

The nasal mucosa contained significant HMT activity (42.6 ± 4.7 pmol/min/mg protein, n = 7).

DISCUSSION

We found that SKF 91488, a selective inhibitor of HMT, potentiated the increase in microvascular permeability that was produced by histamine and

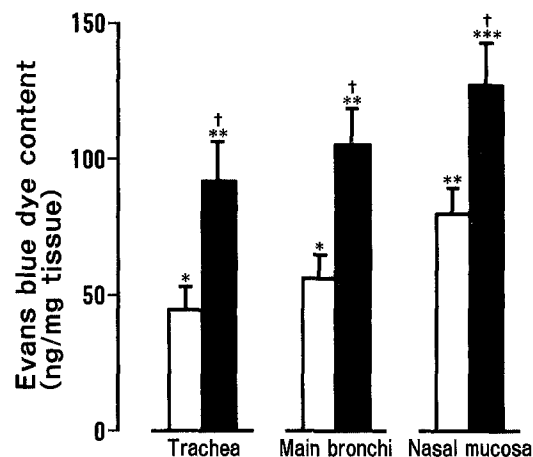


FIG. 3. Ovalbumin-induced (200 μ g/kg) leakage of EB dye in the trachea, main bronchi, and nasal mucosa in the presence (filled columns) and absence (open columns) of SKF 91488 (20 mg/kg). Results are reported as means $\pm$ SEM from seven animals. Significant differences from corresponding control values are indicated by * p < 0.05, ** p < 0.01, and *** p < 0.001 and those between columns are indicated by † p < 0.05.

antigen challenge. However, aminoguanidine, an inhibitor of DAO, was without effect on a histamine-induced increase in microvascular permeability. HMT activity was present throughout the airway of the guinea pigs,⁶ including the nasal mucosa, in this study. Furthermore, we observed partial inhibition of the increased microvascular leakage after antigen challenge by combined H_1 and H_2 receptor blockade, and increases in vascular permeability induced by other agonists, such as platelet activating factor and bradykinin, were not influenced by SKF 91488. Thus we conclude from these results that airway HMT modulates increased microvascular permeability induced by exogenous histamine and endogenous histamine released during antigen challenge.

Our results are partly in accord with those of Saria et al.¹⁵ and Evans et al.,¹⁶ who found that microvascular leakage induced by intravenous injection of ovalbumin was inhibited by antihistamines in sensitized guinea pigs. However, Saria et al.¹⁵ found a greater inhibition of ovalbumin-induced microvascular leakage of the trachea and nasal mucosa; Evans et al.¹⁶ found a smaller inhibition of vascular leakage when antihistamines were used. In our study, we used 10 times more ovalbumin than Saria et al.¹⁵ and one third of the ovalbumin used by Evans et al.¹⁶ to challenge our guinea pigs. However, this dose of ovalbumin enabled us to demonstrate the potentiation of an antigen-induced increase in microvascular perme-

ability by SKF 91488. These studies suggest the involvement of histamine in the guinea pig model of increased microvascular permeability induced by antigen challenge. Other mediators would also be significant contributors to increased microvascular permeability during antigen challenge.¹⁶

HMT catalyzes the methylation of histamine in mammalian tissues,¹⁷ resulting in the inactivation of histamine. SKF 91488 is a potent noncompetitive inhibitor of HMT with a micromolar affinity constant.^{18,19} It is a structural analog of histamine H₂-receptor agonist dimaprit,²⁰ although SKF 91488 has no histamine agonist activity.²¹ Therefore by the intravenous administration of SKF 91488, it is likely that we inhibited HMT activity in the airways. Studies of HMT activity and of cellular sites of biosynthesis of HMT by *in situ* hybridization in the guinea pig trachea⁵ indicate that HMT is likely present in the epithelium and endothelium. SKF 91488 shifted dose-response curves of vascular permeability to histamine by 2 log units in this study and those of smooth muscle contraction to histamine by 1 log unit *in vitro*⁵ and half a log unit *in vivo*.⁶ Therefore HMT may efficiently act in the proximity of cells where they are expressed, so that the location of HMT in the endothelium is ideal for limiting the effects of histamine on the endothelial cells compared with smooth muscle cells. In fact, a rapid degradation of histamine by vascular endothelial cells was reported by Haddock et al.²² They showed that cultured human vascular endothelial cells (10⁵ cells) caused metabolic conversion of 1 μ mol/L histamine to N⁷-methylhistamine for 10 minutes, and SKF 91488 completely inhibited this process. Therefore the HMT inhibitor prevents the degradation of histamine and should potentiate exogenous and endogenous histamine-induced effects on vascular responses. However, from this study it is difficult to determine the half-life of histamine in vascular tissues and the time required for histamine to interact with its receptor to induce vascular permeability. A detailed study concerning the kinetics of histamine activity in proximity to its receptor on endothelial cells is required to clarify these issues.

In contrast to the HMT inhibitor, the DAO inhibitor failed to alter the histamine-induced increase in microvascular permeability, as in the case of bronchoconstriction.^{5,6} The relative concentrations of HMT and DAO in the lung and nose vary among species. In guinea pigs HMT activity is higher than DAO activity by 13 times in the lung and by 4 times in the nasal mucosa.²³ A level of HMT activity higher than that of DAO activity is

also observed in human beings. The HMT activity is reported to be 50 times higher than the DAO activity in the human nasal mucosa.²⁴ Furthermore, the histamine content and HMT activity increased in the nasal mucosa and lungs of the toluene diisocyanate-sensitized guinea pigs, whereas the DAO activity did not.²³ Therefore HMT is highly active and more important than DAO in limiting biologic action of histamine on the airway in both human beings and guinea pigs. However, the HMT activity in the lungs was 5 times higher in guinea pigs than in human beings.^{6,25} Therefore HMT may be more important in regulating the activity of histamine in guinea pigs than in human beings.

Potential of a histamine-induced increase in microvascular permeability by SKF 91488 may not be due to increased tissue blood pool after wash-out, because we also assessed microvascular permeability qualitatively with a macromolecular tracer, Monastral blue, and observed the potentiating effects of SKF 91488 on histamine-induced increases in microvascular permeability. Monastral blue pigment does not cross the endothelium of normal blood vessels, but when microvascular permeability is increased, the pigment passes through gaps in the endothelium and becomes trapped by the basal lamina surrounding the endothelium.²⁶ As a result of this trapping of Monastral blue, the abnormally permeable blood vessels become labeled and thus can be observed in subsequent morphologic studies.

In asthmatic airways the presence of increased amounts of plasma proteins indicates increased microvascular leakage.^{27,28} The mechanisms responsible for microvascular leakage in asthma are believed to involve the autacoid- and neuropeptide-induced contraction of postcapillary venule endothelial cells, which contain both actin and myosin filaments arranged in bundles.^{29,30} In bronchial biopsy specimens obtained from asthmatic subjects, the presence of large gaps between the endothelial cells of the submucosal venules provides evidence of increased microvascular permeability in asthmatic airways.³¹ Histamine released during allergic reactions is a well known mediator of increased microvascular permeability and edema.³² Likewise, histamine is a major mediator of acute allergic rhinitis.³³ Rhinorrhea induced by increased vascular permeability and direct glandular secretion can be inhibited largely by pretreatment with histamine receptor antagonists. This study suggests that HMT in the airway, including the nasal mucosa, plays an important role in

modulating the effects of histamine released during allergic reactions on plasma extravasation.

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