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Mechanisms for histamine H_1 receptor-mediated vasodilation in isolated canine lingual arteries

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Abstract

Histamine and selective histamine receptor subtype agonists' effects on isolated and perfused canine lingual arteries were investigated with the cannula insertion method. In preparations preconstricted with phenylephrine, histamine and a selective histamine H_1 receptor agonist, 2-pyridylethylamine induced a biphasic vascular response in a dose-related manner, i.e., vasoconstriction followed by vasodilatation. The biphasic responses to histamine and 2-pyridylethylamine were inhibited by diphenhydramine, a selective histamine H_1 receptor antagonist, but were not influenced by cimetidine, a selective histamine H_2 receptor antagonist. Dimaprit, a selective histamine H_2 receptor agonist, induced only a slight vasoconstriction which was not modified by cimetidine. Dimaprit never induced vasodilation even at a large dose. A histamine H_3 receptor agonist, *R*-α-methylhistamine, did not produce any significant vascular responses. Moreover, histamine-induced vasodilation was in part inhibited by removal of the endothelium, and the vasodilation remaining was abolished by H_1 blockade. Thus, it is concluded that in canine lingual arteries there are abundant histamine H_1 receptors which mediate both vasoconstriction and vasodilation, and that the histamine-induced vasodilation is in part due to endothelium-dependent mechanisms.

Keywords: Lingual artery, dog; (Cannula insertion method); Histamine H_1 receptor; 2-Pyridylethylamine; Dimaprit

1. Introduction

The canine tongue is particularly well vascularized perhaps because of the work required for an efficient heat exchange during open-mouth panting (Pleschka, 1984). In recent years, we have attempted to clarify the pharmacologic characteristics of canine lingual arteries, and have reported that there are abundant functional α_{1A}- but no α_{1B}-adrenoceptors (Skrbic and Chiba, 1991, 1992), relatively few β-adrenoceptors (Chiba and Tsukada, 1996a), and abundant muscarinic M_3 but few M_1 receptors (Chiba and Tsukada, 1996b) in isolated and perfused lingual arteries. However, there are no available reports of a pharmacological analysis of histamine-induced vascular reactivity in the canine lingual artery. In many in vivo studies, histamine readily caused vasodilation, mediated by either histamine H_1 or H_2 receptors of peripheral resistance vessels (Flynn and Owen, 1975; Levi et al., 1982; Marshall, 1994). On the other hand, in many in vitro investigations, histamine caused vasoconstriction via H_1 receptors and vasodilation via H_2 receptors (Levi et al., 1982; Oriowo and Bevan, 1987). As recently reviewed, histamine H_1 and H_2 receptors on vascular smooth muscle generally mediate direct constriction and dilatation, respectively, whereas endothelial H_1 receptors promote vasorelaxation via release of endothelium-derived relaxing factor and/or prostacyclin (Levi et al., 1991). Previously we reported that histamine had no significant vascular action on isolated and perfused rat common carotid arteries in the non-preconstricted state (Chiba and Tsukada, 1989). However, we also showed that, in the preconstricted state, there was a histamine-induced vasodilation mediated via both H_1 and H_2 receptors which are dependent on the endothelium in rat common carotid artery (Chiba and Tsukada, 1991). The existence of a histamine H_3 receptor was confirmed and selective H_3 receptor agonists and antagonists were developed (Ishikawa and Sperelakis, 1987; Schunack and Stark, 1994; Ligneau et al., 1994).

In the present study, we made an attempt to investigate functional characteristics of canine lingual vasculature for histamine-induced vascular responses, using the cannula

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insertion method (Hongo and Chiba, 1983; Tsuji and Chiba, 1984).

2. Materials and methods

2.1. Drugs

The drugs used included histamine dihydrochloride (Wako, Tokyo, Japan), 2-pyridylethylamine dihydrochloride (kindly donated by Yamanouchi Pharmaceutical, Tokyo, Japan), dimaprit dihydrochloride (kindly donated by Yamanouchi Pharmaceutical), *R*(−)-α-methylhistamine dihydrochloride (Research Biochemicals International, Natick, MA, USA), acetylcholine chloride (ACh, Daiichi, Tokyo, Japan), phenylephrine hydrochloride (Kowa, Tokyo, Japan), diphenhydramine hydrochloride (Tokyokasei Kogyo, Tokyo, Japan), cimetidine (Fujisawa, Tokyo, Japan), 5-hydroxytryptamine creatinine sulfate (Sandoz), potassium chloride, papaverine hydrochloride (Dainippon, Tokyo, Japan) and saponin (Merck, Darmstadt, Germany).

2.2. Preparations

Thirty-two mongrel dogs of either sex, weighing 6–23 kg, were anaesthetized with sodium pentobarbital (30 mg/kg, i.v.). The animals were killed by rapid exsanguination from the right common carotid artery after treatment with sodium heparin (200 units/kg, i.v.). The tongue was cut out at the level of the papillae valatae and was immediately removed to a wet Petri dish. The lingual artery was carefully isolated and dissected into a number of segments ($n = 66$; 11 ± 0.1 mm in length and 1.6 ± 0.1 mm outer diameter). The side branches were tied with thread and surrounding connective tissues were carefully removed. Each segment was cannulated with a stainless steel cannula (22–25 gauge and 3 cm in length) from the distal to the proximal end, as described previously (Hongo and Chiba, 1983; Tsuji and Chiba, 1984). The cannula had three small holes at a distance of 3 mm from the distal blind end. The arterial segment was fixed to the cannula by means of a thin thread distal from the holes. Thus, the stream of perfusate, after passing the holes of the cannula, circulated only through the intraluminal surface of the arterial segment. The cannula with the arterial preparation was placed in an organ bath and perfused with constant flow (1.6–1.8 ml/min) by means of a roller pump (Eyela MP-3A, Tokyo, Japan). The entire system was maintained at a constant temperature of 37°C by means of a thermostat pump (Haake FE2, Karlsruhe, Germany). The perfusate contained (in mmol/l): NaCl 118; KCl 4.7: $CaCl_2$ 2.5; $MgCl_2$ 1.2; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11. It was bubbled with a mixture of 95% O_2 and 5% CO_2 to maintain the pH at 7.2–7.4.

The perfusion pressure was monitored with a pressure transducer (Nihon Kohden TR-400T, Tokyo, Japan) coupled to a recording system (Nihon Kohden WT-685GH, Tokyo, Japan). The flow rate was adjusted at the beginning of the experiment to obtain a basal perfusion pressure of 43 ± 3 mmHg ($n = 27$). Initial experiments were performed with this setup, i.e., histamine did not produce any significant vascular response in non-preconstricted preparations. Thus, subsequent experiments were performed with preconstriction produced by an infusion of phenylephrine. Phenylephrine (3 μmol/l) was added to the perfusion fluid to increase vascular tone. Once stable tone had been established (155 ± 6 mmHg, $n = 51$), the drug solution (1–10 μl) was administered with a microsyringe (Terumo Co., Tokyo, Japan) into the rubber tube connecting the cannula and perfusion system. The interval between drug administrations was more than 5 min and the injection time was approximately 3 s. Dose-response curves were obtained after the administration of increasing doses of each antagonist. The duration of the antagonistic action was monitored for approximately 30–40 min after a bolus injection. Hence, the dose-response curve for an agonist was made within 20 min after injection of each dose of antagonist. Only one antagonist was examined with each arterial preparation. To reduce endothelial function, saponin was given intraluminally as reported previously (Chiba et al., 1986; Nakane and Chiba, 1986). A dose of 0.1 μmol papaverine caused a decrease (-91 ± 8 mmHg, $n = 56$) in perfusion pressure. Following the determination of control dose-response curves, a single saponin injection (1 mg/0.01 ml) was made into the rubber tube connecting the cannula; transient increases and sustained decreases in perfusion pressure were then usually observed. The time allowed for the preparation to equilibrate was more than 30 min.

Results are expressed as means ± S.E.M. For statistical evaluation, two analyses of variance and a paired or an unpaired Student's *t*-test were used.

3. Results

3.1. Vascular responses to vasoactive substances of isolated and perfused canine lingual arteries in non-constricted state

When norepinephrine and phenylephrine were given intraluminally as bolus even to an unconstricted, isolated, lingual artery, strong vasoconstriction was consistently induced in a dose-related manner as reported previously (Skrbic and Chiba, 1991, 1992). Under the same conditions, 5-hydroxytryptamine (5-HT) produced greater vasoconstriction than did norepinephrine or phenylephrine. A receptor-independent substance, KCl, induced strong vasoconstriction only at a dose higher than 10 μmol. On the other hand, histamine never induced any significant vascular responses in 8 non-constricted preparations of lingual

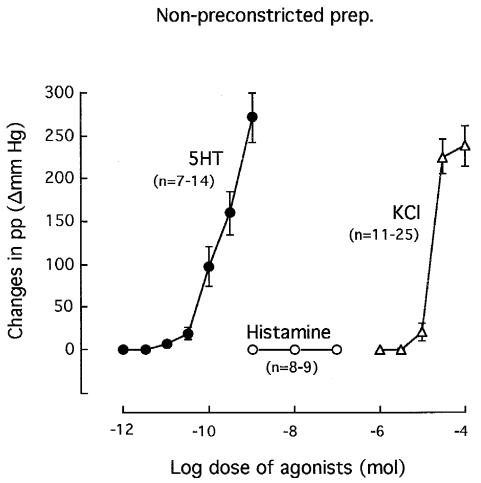


Fig. 1. Vascular responses to increasing doses of 5-HT, histamine and KCl in isolated and perfused canine lingual arteries in the non-preconstricted state. PP, perfusion pressure.

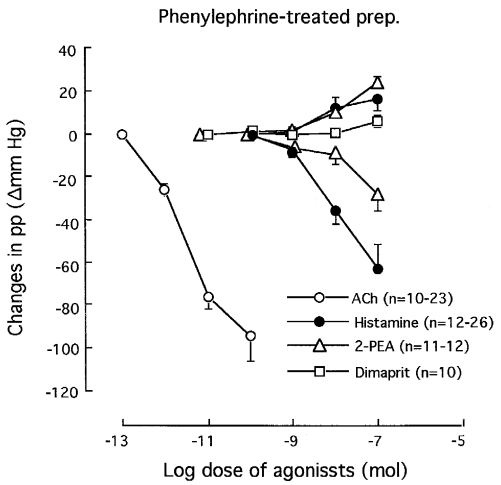


Fig. 3. Vascular responses to acetylcholine (ACh) and histamine-related compounds of isolated lingual arteries as phenylephrine-treated preparations. PP, perfusion pressure.

arteries. Fig. 1 shows vascular responses to 5-HT, KCl and histamine in non-constricted lingual arteries.

3.2. Vascular effects of histamine-related agonists in preconstricted preparations

In preparations which were preconstricted with phenylephrine, ACh readily caused clear vasodilation in a dose-related manner, but isoproterenol caused only slight vasodilatation as reported previously (Chiba and Tsukada, 1996a,b).

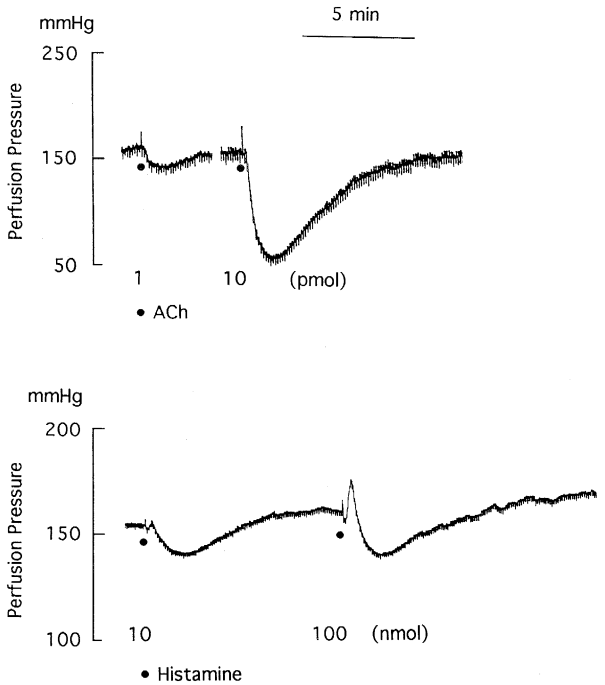


Fig. 2. Typical tracings of effects of acetylcholine (ACh) and histamine on a canine lingual artery preconstricted by treatment with phenylephrine.

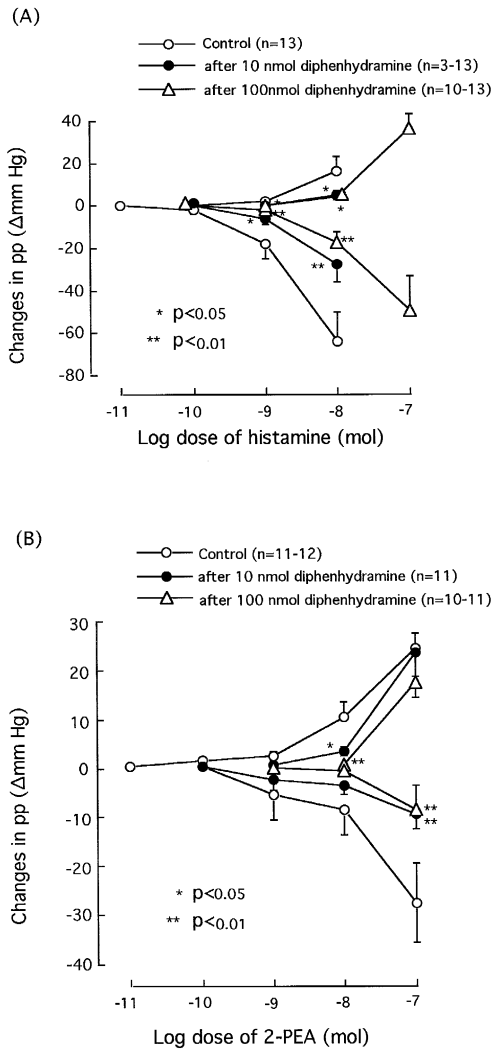


Fig. 4. (A) Effects of diphenhydramine on histamine-induced vascular responses of phenylephrine-treated preparations. (B) Effects of diphenhydramine on 2-pyridylethylamine (2-PEA)-induced vascular responses in phenylephrine-treated preparations. PP, perfusion pressure.

Histamine readily caused not only vasodilation but also vasoconstriction of arteries preconstricted with phenylephrine as shown in Fig. 2. 2-Pyridylethylamine (a selective histamine H_1 receptor agonist) also caused a biphasic response. On the other hand, dimaprit, a selective histamine H_2 receptor agonist, induced only slight vasoconstriction at a relatively high dose, 10–1000 nmol in all preparations tested ($n = 8$). A selective histamine H_3 receptor agonist, $R(-)$-α-methylhistamine, produced no vascular responses even at the high dose of 100 nmol ($n = 4$).

Summarized data for acetylcholine and three histamine-related compounds are shown in Fig. 3.

3.3. Effects of diphenhydramine on histamine- and 2-pyridylethylamine-induced vascular responses

Both histamine-induced vasoconstrictor and dilatator effects were significantly inhibited by treatment with diphenhydramine, a selective histamine H_1 receptor antagonist. As shown in Fig. 4A, histamine-induced dose-response curves were shifted parallel to the right by treatment with 100 nmol of diphenhydramine. 2-Pyridylethylamine-induced dose-response curves were also shifted to the right by treatment with 100 nmol of diphenhydramine, as shown in Fig. 4B.

3.4. Absence of blocking effects of cimetidine on histamine- and dimaprit-induced vascular responses

Histamine-induced biphasic vascular responses were not significantly influenced by treatment with a relatively high dose of cimetidine, 1000 nmol (a selective histamine H_2 receptor antagonist). The summarized data are shown in Fig. 5. Relatively large doses of dimaprit (10 and 100 nmol) produced only slight vasoconstriction but never induced any vasodilator effect. These vasoconstrictor responses to dimaprit were not modified by a high dose, 1000 nmol, of cimetidine ($n = 9$) (data not shown).

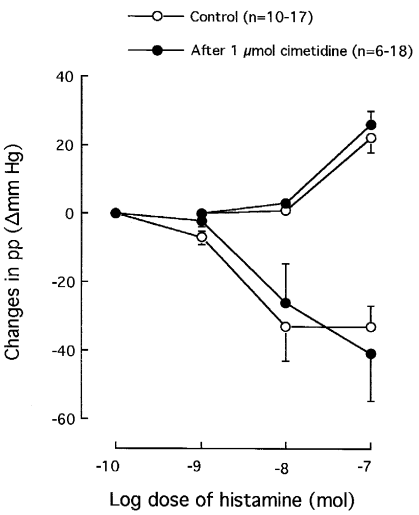
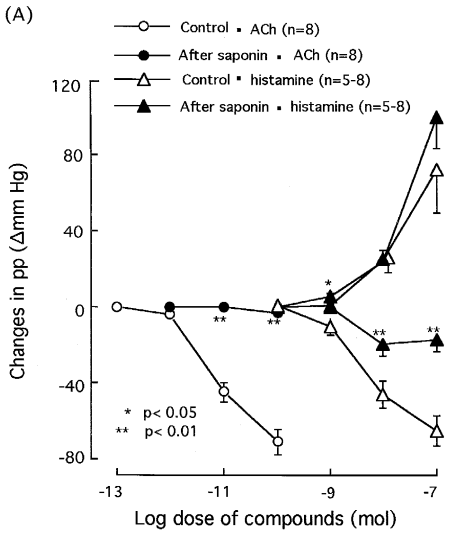


Fig. 5. Absence of blocking effects of cimetidine on histamine-induced vascular responses of phenylephrine-treated preparations. PP, perfusion pressure.



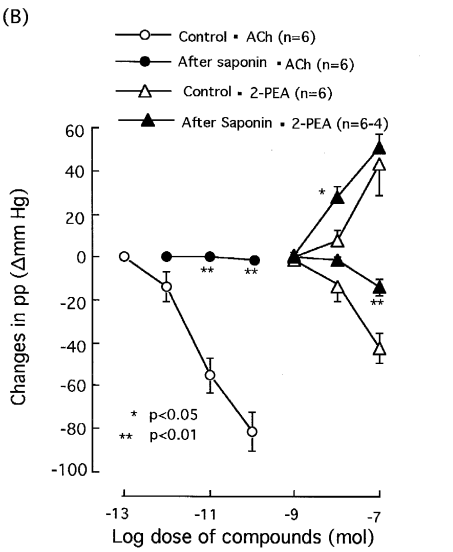


Fig. 6. (A) Comparison of vascular responses to acetylcholine (ACh) and histamine before and after removal of the endothelium in canine lingual arteries. (B) Comparison of vascular responses to ACh and 2-pyridylethylamine (2-PEA) before and after removal of the endothelium in canine lingual arteries. PP, perfusion pressure.

3.5. Effects of endothelial removal on histamine- and 2-pyridylethylamine-induced vascular responses

When 1 mg of saponin was given intraluminally into the isolated lingual artery, the perfusion pressure was initially increased and returned to the control level within 30–60 min. After saponin treatment, acetylcholine-induced vasodilation was strongly suppressed in all preparations,

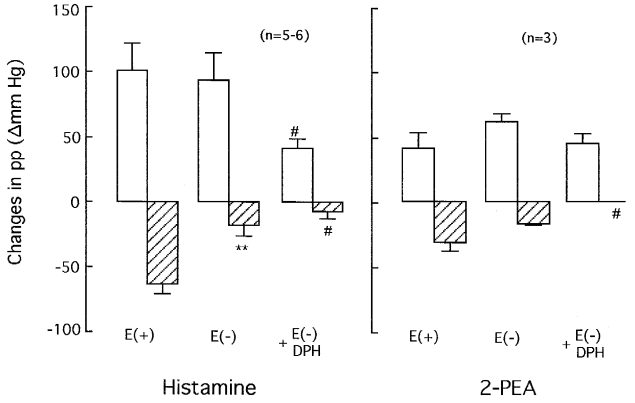


Fig. 7. Effects of endothelium removal and 100 nmol diphenhydramine (DPH) on 100 nmol histamine- and 100 nmol 2-pyridylethylamine (2-PEA)-induced vascular responses. PP, perfusion pressure. E(+), endothelium-intact preparations; E(−), endothelium-removal preparations. $^{**}P < 0.01$ vs. E(+), $^{\#}P < 0.05$ vs. E(−).

showing that the endothelium had disappeared. After removal of the endothelium, histamine-induced vasodilation was greatly and significantly inhibited but the effect was not completely different from the results for acetylcholine-induced responses. On the other hand, histamine-induced vasoconstriction was not blocked but was slightly potentiated instead, although not significantly so. Summarized data are shown in Fig. 6A.

2-Pyridylethylamine-induced vasodilatation was also significantly inhibited by treatment with 1 mg of saponin, when acetylcholine-induced vasodilation was completely inhibited. 2-Pyridylethylamine-induced vasoconstriction was enhanced by removal of the endothelium. Summarized data are shown in Fig. 6B.

In the presence of the endothelium, 100 nmol of histamine and 2-pyridylethylamine induced biphasic vascular responses. After removal of the endothelium by intraluminal saponin treatment, histamine- and 2-pyridylethylamine-induced vasodilation was inhibited but not completely so. However, the histamine- and 2-pyridylethylamine-induced vasodilation remaining after removal of the endothelium was strongly and significantly suppressed by treatment with 100 nmol diphenhydramine, as shown in Fig. 7.

4. Discussion

In the present experiments, we demonstrated that histamine has no vascular action in non-preconstricted preparations, although norepinephrine, phenylephrine, 5-HT and KCl readily caused strong vasoconstriction. Changes in the blood vessel tone level would be expected to qualitatively and quantitatively influence the response to histamine, although changes in intraluminal flow can alter vascular smooth muscle tone through a local mechanism (Bevan and Henrion, 1994). Thus, in this study we used phenylephrine-preconstricted preparations for investigating histamine-induced actions. Since the vascular walls had their in vivo tonicity maintained, the preconstricted state may be physiologically suitable to investigate drug actions. Differing from the isolated lingual artery, but with the same perfusion technique, histamine readily caused vasoconstriction in isolated canine femoral arteries even in the non-preconstricted state (Kawai and Chiba, 1989). In canine coronary arteries in the non-preconstricted state histamine readily caused strong vasodilation following an initial brief vasoconstriction in the non-preconstricted state (Nakane and Chiba, 1987). These authors reported that the histamine-induced vasodilation was due to activation of histamine H_2 receptors because of its blockade by a histamine H_2 receptor antagonist. Likewise, the histamine-induced constriction was due to activation of histamine H_1 receptors because of its blockade by a selective histamine H_1 receptor antagonist, chlorpheniramine. They also showed that histamine H_1 receptors might not participate in the production of vasodilation in the dog coronary artery (Nakane and Chiba, 1987). Moreover, the same authors demonstrated that histamine H_2 receptor-mediated vasodilation was independent of the endothelium, because removal of the endothelium with intraluminal saponin did not modify the histamine H_2 receptor-mediated vasodilatations in canine coronary arteries. In the rat common carotid arteries, histamine induced vasodilation which was mediated by histamine H_1 and H_2 receptors and dependent on the endothelium (Chiba and Tsukada, 1991).

In the present study, histamine induced vasodilation which was mediated by histamine H_1 but not by histamine H_2 receptors, as shown by the fact that a selective histamine H_2 receptor agonist, dimaprit, did not produce dilatation, and histamine-induced vasodilation was significantly inhibited by histamine H_1 receptor blockade but not by H_2 receptor blockade. A selective histamine H_3 agonist, $R(-)$-α-methylhistamine, did not produce any vascular responses, indicating that there is no participation of histamine H_3 receptors in histamine-induced vascular responses.

Furchgott and co-workers (Furchgott and Zawadzki, 1980; Furchgott, 1983, 1984) showed that acetylcholine relaxed isolated arteries by releasing endothelium-derived relaxing factor (EDRF) from endothelial cells. It has been reported that histamine induces vasodilation through the release of EDRF and that this release is mediated by histamine H_1 receptors in rat thoracic aorta and mesenteric arteries (Van de Voore and Leusen, 1983; Carrier et al., 1984; Moritoki et al., 1986) and guinea-pig pulmonary arteries (Satoh and Inui, 1984). In the present study with canine lingual artery, histamine-induced vasodilation was significantly but not completely decreased by treatment with intraluminal saponin, although acetylcholine-induced vasodilation was completely suppressed after removal of the endothelium. Moreover, the dilatator responses to histamine and 2-pyridylethylamine remaining after removal

of the endothelium were strongly suppressed by treatment with diphenhydramine. Thus, it seems that histamine H_1 receptors exist both in the endothelium which releases the EDRF and in vascular smooth muscle which causes a relaxation in the canine lingual artery. On the other hand, there are no functional histamine H_2 receptors, because vascular responses to the histamine-related agonists were not influenced by cimetidine, a potent histamine H_2 receptor antagonist.

From these results, it is concluded that in isolated canine lingual arteries there are abundant histamine H_1 but not H_2, or H_3 receptors, and that vasodilator H_1 receptors might exist in both endothelium and vascular smooth muscle.

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