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In vitro relaxation of dog cerebral veins in response to histamine is mediated by histamine H_2 receptors

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Abstract

There is little information on the histamine receptor mechanisms involved in cerebral venodilation, thus the role of histamine present in human cerebrospinal fluid is difficult to assess. In isolated canine pial veins, concentration–response curves to histamine (10^{-7}–10^{-3} M), the histamine H_1 receptor agonist, 2-pyridylethylamine (10^{-6}–10^{-2} M), the histamine H_2 receptor agonist, dimaprit (*S*-(3-dimethylaminopropyl) isothiourea dihydrochloride, 10^{-6}–10^{-2} M), and the histamine H_3 receptor agonist, imetit (*S*-[2-(1 midazol-4-yl)ethyl]isothiourea dihydrobromide, 10^{-7}–10^{-3} M) were isometrically determined. In resting veins, histamine, 2-pyridylethylamine and dimaprit had no significant effect, whereas in endothelin-1-precontracted veins, these drugs produced concentration-dependent relaxation (E_{max} in % of active tone and pD_2 were: for histamine, 72 ± 6 and 5.36 ± 0.09; for 2-pyridylethylamine, 59 ± 5 and 3.28 ± 0.05; for dimaprit, 65 ± 7 and 4.81 ± 0.10, respectively). The relaxations in response to histamine and dimaprit were competitively antagonized by the histamine H_2 receptor antagonist, cimetidine (3×10^{-6}–10^{-4} M) ($pA_2 = 6.07 \pm 0.03$ for histamine, and 6.09 ± 0.07 for dimaprit), but were not affected by the histamine H_1 receptor antagonist, chlorpheniramine (10^{-6} M) or the histamine H_3 receptor antagonist, thioperamide (*N*-cyclohexyl-4-(1-H-imidazol-4-yl)-1-piperidine-carbothioamide maleate, 10^{-6} M). The relaxation in response to 2-pyridylethylamine was inhibited by cimetidine (10^{-5} M), but not by chlorpheniramine (10^{-6} M). Imetit produced a small contraction in resting veins (14 ± 4 mg) and precontracted veins (20 ± 3 mg), which was not modified by thioperamide (10^{-6} M). The relaxation of veins in response to histamine was not modified by endothelium removal, nor by the inhibitor of nitric oxide synthase, N^G-nitro-L-arginine methyl ester (10^{-4} M), or the cyclooxygenase inhibitor, meclofenamate (10^{-5} M). Therefore, in pial veins: (1) histamine produces relaxation by activation of histamine H_2 receptors, probably located in the smooth musculature, with no participation of histamine H_1 and H_3 receptors, and (2) endothelium, nitric oxide and prostanoids are probably not involved in the relaxation in response to histamine.

Keywords: Cerebral vein; Histamine H_2 receptor; Venodilation; Endothelium; Nitric oxide (NO); Prostanoid

1. Introduction

Histamine is an endogenous substance with marked vascular effects. In vivo this amine produces vasodilation, but in isolated blood vessels it produces contraction or relaxation depending upon the type of vessel and the species, and this variation may be derived from the ability of histamine to activate the different subtypes of histamine receptors (H_1, H_2 and H_3) (Garrison, 1990). It has been observed that in non-cerebral veins this amine produces relaxation (Schoeffter and Godfraind, 1989; Matsuki and Ohhashi, 1990; Yamazaki and Toda, 1992) and contraction (Bergner et al., 1988; Schoeffter and Godfraind, 1989).

In the cerebral circulation, it appears that histamine has a pronounced effect both in vivo and in vitro, but analysis of the cerebrovascular effects of this amine may be complex as experimental evidence suggests that they depend on the species, the location of the vessel studied, the presence or absence of endothelium, and other experimental conditions such as precontraction, or prior blockade of the contractile response (Edvinsson et al., 1993). Histamine produces cerebral vasodilation in vivo (Anderson and Kubicek, 1971; Tindall and Greenfield, 1973) by activating histamine H_2 receptors (Lord et al., 1981; Edvinsson et al., 1983), whereas in isolated cerebral arteries it produces either contraction by activating histamine H_1 receptors located in the vascular smooth muscle (Toda, 1990) or dilation by activating histamine H_1, H_2 or H_3 receptors located in the endothelium (Toda, 1990; Bened-

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ito et al., 1991; Ea Kim et al., 1992) and by activating histamine H_2 receptors located in the vascular smooth muscle (Toda, 1990; Benedito et al., 1991). Therefore, whether histamine dilates or contracts cerebral blood vessels may also depend, in part, on the relative concentration of histamine H_1, H_2 and H_3 receptors in the vessels as well as on the role played by the endothelium in these effects.

Most of the studies analyzing the cerebrovascular effects of histamine have been performed in arteries, but very few have involved veins (Hardebo et al., 1987). These authors reported that histamine produces no effect or a small relaxation of precontracted human pial veins. Reactivity of cerebral veins to vasoactive stimuli in general has received little attention, but deserves interest because these vessels play an important role in the regulation of intracranial blood volume and pressure by being encased within the cranial cavity (Auer and MacKenzie, 1984). Histamine is present in intracranial tissues and has several potential sources of synthesis, storage and release near the cerebral vasculature. This amine can be released from nerve terminals (Schwartz et al., 1980), mast cells (Edvinsson et al., 1977) and non-mast cells (El-Ackad and Brody, 1975), and human cerebrospinal fluid contains significant amounts of histamine despite quite low concentrations in plasma and other body fluids (Khandelwal et al., 1982).

In the present study we have determined the in vitro response of canine pial veins to histamine, analyzing the receptor subtypes and some of the mechanisms that might be involved.

2. Materials and methods

2.1. Tissue preparation

Twenty four mongrel dogs of either sex, weighing 15–23 kg, provided by the Centro de Protección Animal (Ayuntamiento de Madrid, Spain), were anaesthetized by i.v. injection of sodium pentobarbital (50 mg/kg body weigh) and killed by intracardiac injection of suxamethonium chloride (10 mg/kg). The brain was removed and placed into isotonic saline (NaCl 0.9%) on ice, and both brain basalis veins (pial veins), carefully dissected out, were cut into cylindrical segments 5 mm in length and about 1 mm in external diameter. Each vein segment was prepared for isometric tension recording in a 4 ml organ bath containing modified Krebs–Henseleit solution with the following composition (millimolar): NaCl, 115; KCl, 4.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25; glucose, 11.1. The solution was equilibrated with 95% oxygen and 5% carbon dioxide to give a pH of 7.3–7.4, and temperature was held at 37°C. Briefly, the method consists of passing two fine, stainless steel pins, diameter 150 μm, through the lumen of the vein segment. One pin was fixed to the organ bath wall while the other was connected to a strain gauge, permitting the application of passive tension in a plane perpendicular to the long axis of the vascular cylinder. The recording system included a Universal Transducing Cell UC3 (Statham Instruments), a Statham Microscale Accessory UL5 (Statham Instruments) and a Beckman Type RS Recorder (model R-411, Beckman Instruments). A resting tension of 150 mg was applied and the venous segments were allowed to equilibrate for 40–60 min before any drugs were added.

In this study, a total of 158 vein segments were used as follows: 25 segments were examined under resting tension, 127 segments were examined in the presence of an active tone induced with 10^{-9} M endothelin-1, and the remaining 6 segments were used as control preparations with active tone also induced with 10^{-9} M endothelin-1. Endothelin-1 contracted the vein segments, and this contraction reached a plateau, the magnitude of which ranged from 50 to 160 mg (mean $\pm$ S.E.M. = 88 $\pm$ 3 mg). Each concentration–response curve for the agonists lasted about 30 min, and in veins with active tone the agonists were applied 5–10 min after the veins had reached a steady plateau. In the 6 veins used as control preparations with active tone the plateau achieved with 10^{-9} M endothelin-1 was maintained for at least 90 min, without application of any other drug.

Each vein segment was used for only one concentration–response curve for the agonists.

2.2. Experimental protocol

The response of venous segments to histamine (10^{-7}–10^{-3} M), the histamine H_1 receptor agonist, 2-pyridylethylamine (10^{-6}–10^{-2} M), the histamine H_2 receptor agonist, dimaprit (10^{-6}–10^{-2} M), and the histamine H_3 receptor agonist, imetit (10^{-7}–10^{-3} M), was determined in a cumulative manner. Both veins under resting tension and veins with an extrinsic active tone induced by 10^{-9} M endothelin-1 were used. The relaxation of the veins with active tone in response to the agonists used was evaluated as percentage of the contraction obtained with endothelin-1.

As the histamine receptor agonists used had no significant effects on the resting veins, only the relaxation found in the veins with active tone was studied. This was done with veins not treated (control) or pre-treated with the histamine H_1 receptor antagonist, chlorpheniramine (10^{-6} M), the histamine H_2 receptor antagonist, cimetidine (3×10^{-6}–10^{-4} M), the histamine H_3 receptor antagonist, thioperamide (10^{-6} M), the inhibitor of nitric oxide synthase, N^G-nitro-L-arginine methyl ester (L-NAME, 10^{-4} M), or the inhibitor of cyclooxygenase, meclofenamate (10^{-5} M).

The histamine receptor antagonists used, L-NAME or meclofenamate, were added to the organ bath 15–20 min before the agonists were applied to the tissues.

In another group of experiments the response to histamine was recorded in endothelin-1-precontracted veins where the endothelium had been previously removed by

gently rubbing their luminal surface. Morphological examination at the end of the experiments by direct observation after en face silver staining of the luminal surface revealed than these rubbed veins had less than 5% of their intima covered with endothelium. Using this morphological technique, we also found that at the end of the experiments the veins considered as controls had more than 50% of their intima covered with endothelium.

All drugs used in this study were prepared in physiological saline solution, except sodium meclofenamate which was dissolved in a solution of 25 mM sodium bicarbonate.

2.3. Data analysis

The concentration of histamine receptor agonist causing 50% of its own maximal response (EC_{50}) was calculated by non-linear regression analysis for each segment, and pD_2 ($-\log EC_{50}$) was calculated for each group of experiments. pA_2 values for cimetidine were determined by Schild analysis (Arunlakshana and Schild, 1959). The data, expressed as means ± S.E.M., were evaluated with an analysis of variance followed by Dunnett's test to compare each set of experimental conditions with its control. In each case, $P < 0.05$ was considered statistically significant.

2.4. Chemicals

Drugs used were: endothelin-1 (human, porcine) from Peninsula Laboratories Europe; histamine dihydrochloride, and N^G-nitro-L-arginine methyl ester (L-NAME) from Sigma; 2-pyridylethylamine was kindly donated by Smith Kline Beecham Pharmaceuticals (Worthing, West Sussex, UK); dimaprit dihydrochloride (*S*-(3-dimethylaminopropyl) isothiourea dihydrochloride), imetit dihydrobromide (*S*-[2-(1-midazol-4-yl)ethyl]isothiourea dihydrobromide) and thioperamide maleate (*N*-cyclohexil-4-(1-H-imidazol-4-yl)-1-piperidine-carbothioamide maleate) from Research Biochemicals; cimetidine hydrochloride (Tagamet®) from Smith Kline and French; *d*-chlorpheniramine maleate (Polaramine®) from Schering-Plough; sodium meclofenamate from Parke Davis.

3. Results

3.1. Control conditions

Under resting tension, histamine (10^{-7}–10^{-3} M, $n = 6$), 2-pyridylethylamine (10^{-6}–10^{-2} M, $n = 4$) and dimaprit (10^{-6}–10^{-2} M, $n = 4$) had no appreciable effect. Only imetit produced a very small contraction in 3 of 6 vein segments when the higher concentrations, 10^{-4} and 10^{-3} M, were applied (no effect with 10^{-7}–10^{-5} M); the maximal contraction for these 3 vein segments averaged 14 ± 4 mg.

In the vein segments precontracted with endothelin-1, histamine produced concentration-dependent relaxation (maximal relaxation, $E_{max} = 72 \pm 6\%$ of the active tone; $pD_2 = 5.36 \pm 0.09$ for 12 vein segments) (Table 1). 2-pyridylethylamine (10^{-6}–10^{-2} M) and dimaprit (10^{-6}–10^{-2} M) also produced concentration-dependent relaxation of the vein segments an active tone (for 2-pyridylethylamine, $E_{max} = 59 \pm 5\%$ of the active tone, $pD_2 = 3.28 \pm 0.05$, for 7 vein segments; for dimaprit, $E_{max} = 65 \pm 7\%$ of the active tone, $pD_2 = 4.81 \pm 0.10$, for 4 vein segments) (Table 1). Fig. 1(A, B and C) shows actual recordings of histamine-, 2-pyridylethylamine- and dimaprit-induced relaxations in pial veins precontracted with endothelin-1.

In 6 precontracted veins, imetit (10^{-7}–10^{-3} M) had no relaxant effect, and at higher concentrations (10^{-4}–10^{-3}

Table 1
Summary of the effects of histamine, 2-pyridylethylamine, dimaprit and imetit on canine pial veins with active tone induced with 10^{-9} M endothelin-1, which were obtained in the absence (control) or in the presence of chlorpheniramine, cimetidine or thioperamide

Agonist	Conditions	Tone (mg)	Relaxation (−, % of tone) or contraction (+, mg)	pD_2 ($-\log EC_{50}$)	*n*
Histamine	control	90 ± 8	−72 ± 6	5.36 ± 0.09	12
	chlorpheniramine 10^{-6} M	88 ± 12	−75 ± 8	5.47 ± 0.08	8
	cimetidine 10^{-5} M	87 ± 15	−67 ± 10	4.25 ± 0.09 [a]	6
	thioperamide 10^{-6} M	87 ± 20	−74 ± 3	5.35 ± 0.13	8
2-Pyridyl–ethylamine	control	92 ± 12	−59 ± 5	3.28 ± 0.05	7
	chlorpheniramine 10^{-6} M	83 ± 14	−59 ± 9	3.26 ± 0.09	6
	cimetidine 10^{-5} M	84 ± 13	−52 ± 6	2.82 ± 0.08 [a]	7
Dimaprit	control	83 ± 6	−65 ± 7	4.81 ± 0.10	4
	cimetidine 10^{-5} M	64 ± 9	−69 ± 9	3.75 ± 0.16 [a]	4
Imetit	control	97 ± 17	+20 ± 3		6
	thioperamide 10^{-6} M	78 ± 23	+21 ± 5		4
	cimetidine 10^{-5} M	75 ± 14	+21 ± 5		4

Values are means ± S.E.M.; *n* = number of venous segments.
[a] Statistically significant ($P < 0.01$) compared with its control.

M) it induced a further small contraction (Fig. 1D and Table 1).

3.2. Effects of histamine receptor antagonists

In resting veins, thioperamide (10^{-6} M) by itself had no effect and did not affect the response to imetit as compared to control conditions. In the presence of thioperamide, imetit produced a small contraction in 3 of 5 segments ($E_{max} = 15 \pm 3$ mg).

In precontracted veins, chlorpheniramine (10^{-6} M) by itself affected neither the venous tone, nor the pD_2 values or the maximal relaxation of the concentration–response curve for histamine (8 vein segments) and for 2-pyridylethylamine (6 vein segments) (Table 1).

Cimetidine (3×10^{-6}–10^{-4} M) by itself did not alter venous tone, but produced a concentration-dependent, rightward, parallel displacement of the concentration–response curve to histamine and dimaprit in precontracted veins (Fig. 2 and Table 1). Schild analysis of cimetidine antagonism yielded a pA_2 value of 6.07 ± 0.03 and a slope of 1.11 ± 0.09 against histamine ($n = 6$), and a pA_2 value of 6.09 ± 0.07 and a slope of 0.89 ± 0.03 against dimaprit ($n = 4$). In both cases, analysis of the regression lines showed that the slope values were not significantly different from unity. Cimetidine (10^{-5} M) also produced a

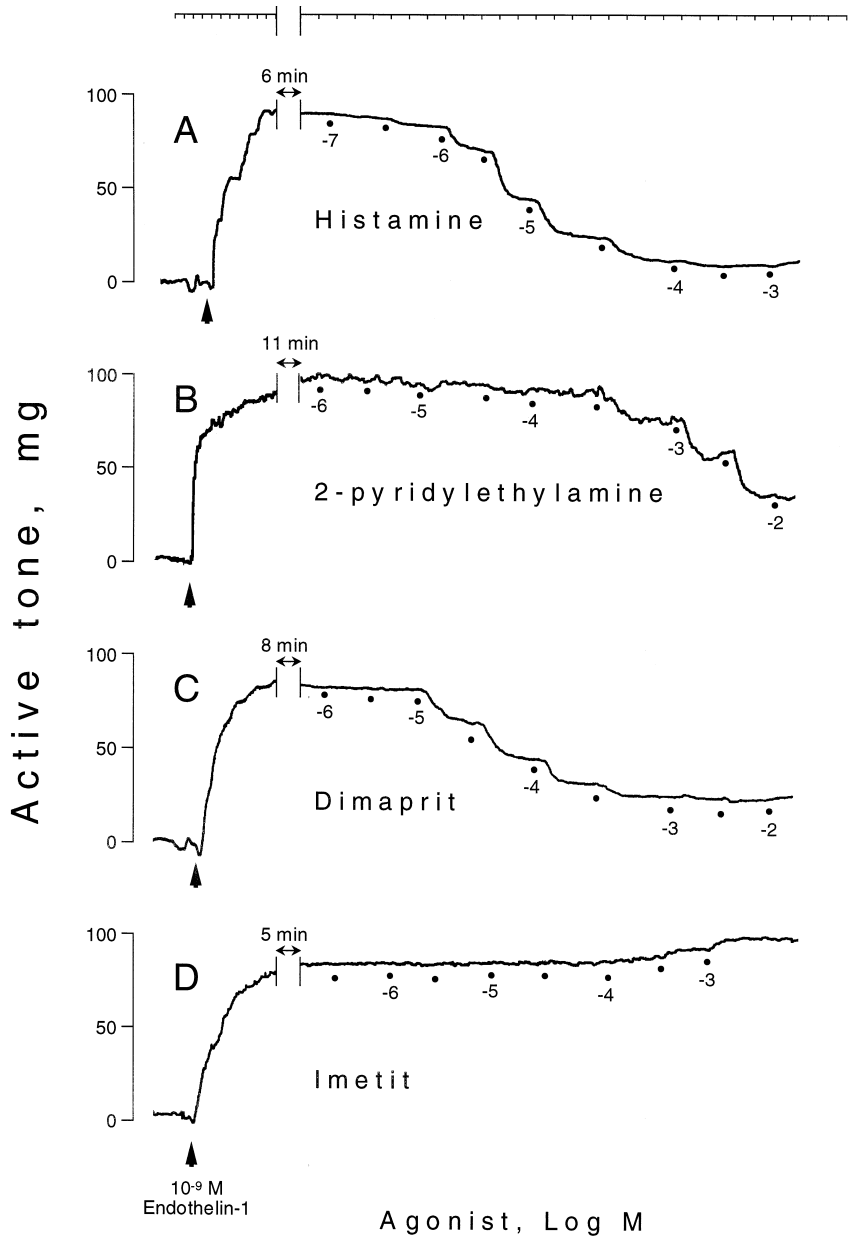

Fig. 1. Representative tracings showing the effects produced by histamine (A), 2-pyridylethylamine (B), dimaprit (C), and imetit (D), in the absence of histaminergic antagonists, on canine pial veins precontracted with 10^{-9} M endothelin-1. Upper, time recording, each mark = 1 min.

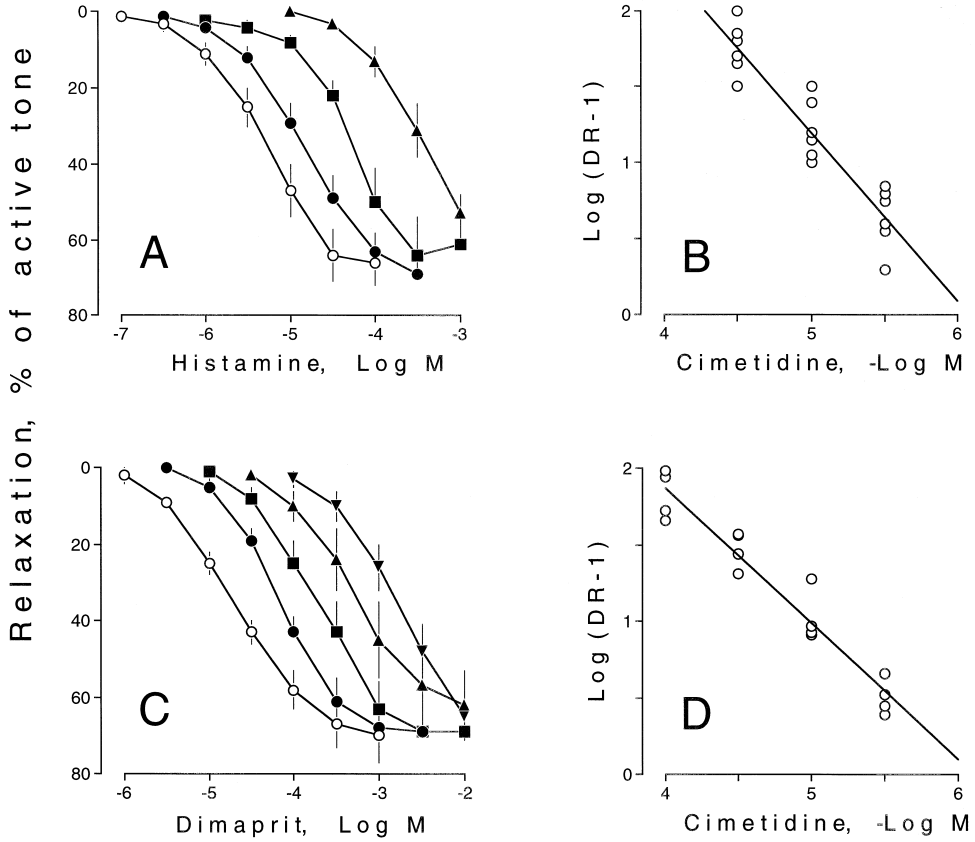

Fig. 2. (A) Concentration–response curves for histamine obtained in canine pial veins with active tone under control conditions (○) or treated with cimetidine at concentrations of 3×10^{-6} M (●), 10^{-5} M (■) and 3×10^{-5} M (▲), using 6 vein segments in each case. (B) Schild plot of the antagonism of histamine-induced relaxation of canine pial veins by cimetidine. The slope of the regression line was 1.11 ± 0.09 ($r=0.93$, $P<0.01$); each point represents data from one vein segment. (C) Concentration–response curves for dimaprit in canine pial veins with active tone under control conditions (○) or treated with cimetidine at concentrations of 3×10^{-6} M (●), 10^{-5} M (■), 3×10^{-5} M (▲) and 10^{-4} M (▼), using 4 vein segments in each case. (D) Schild plot of the antagonism of dimaprit-induced relaxation of canine pial veins by cimetidine. The slope of the regression line was 0.89 ± 0.03 ($r=0.97$, $P<0.01$); each point represents data from one vein segment.

rightward parallel displacement (about 3 times) of the concentration–response curve to 2-pyridylethylamine in 7 precontracted veins, but had no effect on the weak contractile response to imetit in 4 precontracted vein segments (Table 1).

Thioperamide (10^{-6} M) did not itself affect the tone of veins or the response of precontracted veins to histamine and imetit (Table 1).

Table 2
Histamine-induced relaxation of canine pial veins precontracted with 10^{-9} M endothelin-1, in the absence (control) and in the presence of L-NAME or meclofenamate, and after endothelium removal

Conditions	Tone (mg)	Relaxation (% of tone)	pD_2 ($-\log EC_{50}$)	n
Control	106±14	70±7	5.38±0.09	9
L-NAME 10^{-4} M	82±12	63±3	5.35±0.10	6
Meclofenamate 10^{-5} M	83±18	74±3	5.46±0.14	6
Without endothelium	78±12	72±7	5.44±0.14	6

Values are means±S.E.M. n = number of venous segments.

3.3. Effects of L-NAME, meclofenamate and endothelium removal

Addition of L-NAME (10^{-4} M), or meclofenamate (10^{-5} M) to precontracted vein segments did not alter the tone and the concentration–response curve for histamine as compared to that obtained with the control, non-treated veins (Table 2).

In veins deprived of endothelium and precontracted with endothelin-1, the relaxation in response to histamine was not significantly different from those obtained in precontracted, intact veins (Table 2).

4. Discussion

There are only a few studies of the reactivity of cerebral veins to vasoactive stimuli. The issue, however, deserves attention because these vessels, encased within the cranial cavity, play an important role in controlling intracranial blood volume and pressure (Auer and MacKenzie, 1984).

Cerebral veins contract in response to cervical sympathetic stimulation in vivo (Auer and Johansson, 1983) and to norepinephrine and vasopressin in vitro (Diéguez et al., 1983). Cerebral venoconstriction in response to sympathetic stimulation may be of significance in the control of cerebral blood volume at normal and increased intracranial pressure (Auer et al., 1983).

The present results showed that canine pial veins under resting tension are unresponsive to histamine, but when they have an active tone they respond with relaxation. It is interesting that concentrations of histamine near to those occurring physiologically in cerebrospinal fluid of humans (4×10^{-7} M) (Gross, 1982) produce relaxation of isolated pial veins with active tone. Therefore, histamine mainly produces cerebral venodilation and might be involved under physiological circumstances in the regulation of intracranial blood volume and pressure by affecting the calibre of cerebral veins. This role may become more relevant in the pathophysiology of some cerebrovascular alterations in which histamine release is increased, such as inflammation and anaphylaxis.

In pial veins under resting tension, 2-pyridylethylamine and dimaprit did not cause any appreciable effect, and only imetit was able to induce a small contraction in some of the veins tested when relatively high concentrations were applied. This contraction in response to imetit, however, was not inhibited by thioperamide, suggesting that the contraction may be mediated by receptors other than histamine H_3 receptors, such as serotonin 5-HT_3 receptors (Leurs et al., 1995).

With regard to histamine receptors involved in the relaxation of precontracted pial veins, we observed that the relaxation to histamine was competitively blocked by cimetidine, and was not affected by chlorpheniramine or by thioperamide. These findings suggest that the relaxation of pial veins induced by histamine is mainly mediated by activation of histamine H_2 receptors, with no participation of histamine H_1 and H_3 receptors. We also found that the relaxation induced by 2-pyridylethylamine was not modified by chlorpheniramine, but was blocked by cimetidine, and that the relaxation with dimaprit was competitively blocked by cimetidine, suggesting that the relaxation caused by both 2-pyridylethylamine and dimaprit is also mediated by histamine H_2 receptors. The pA_2 value for cimetidine against histamine in canine pial veins was 6.07, which was similar to that found against dimaprit (6.09). These values are comparable to that reported for histamine in rat cerebral arteries in vitro (Benedito et al., 1991). Like that in pial veins under resting tension, the small contraction produced by imetit in pial veins with an active tone was not affected by thioperamide. Therefore, the present results for canine pial veins suggest that H_2 receptors are the histamine receptors of functional significance for mediating venodilation, and that histamine H_1 and H_3 receptors, if they are present, are not of functional significance for mediating responses of cerebral veins to histamine.

Data in the literature about the effects of histamine on cerebral veins are very sparse and, to our knowledge, only Hardebo et al. (1987) using a single dose (3×10^{-5} M), have reported that histamine produces no effect, or a slight relaxation, in precontracted human pial veins. Studies with non-cerebral veins show that histamine induces relaxation of precontracted monkey pulmonary veins via histamine H_2 receptors located in smooth muscle and histamine H_1 receptors located in the endothelium (Matsuki and Ohhashi, 1990), contraction of porcine coronary veins (Bergner et al., 1988) and human saphenous vein (Schoeffter and Godfraind, 1989) via histamine H_1 receptors located in smooth muscle, and relaxation of dog mesenteric veins (Yamazaki and Toda, 1992) and human saphenous veins (Schoeffter and Godfraind, 1989) through histamine H_2 receptors located in smooth muscle.

More data about the effects of histamine on cerebral arteries in vivo and in vitro are available (see Section 1). Although it is difficult to compare results for cerebral arteries with ours obtained with canine pial veins, it seems that at least some of the cerebral arteries examined (Lord et al., 1981; Edvinsson et al., 1983; Toda, 1990; Benedito et al., 1991) also exhibit relaxation in response to histamine and mediated by histamine H_2 receptors as occurs in pial veins (present results). According to the pD_2 values, the sensitivity of the histamine-induced relaxation of canine cerebral veins with active tone we now found was similar to that found by Toda et al. (1985) with precontracted canine cerebral arteries. The maximal relaxation in response to this amine found by us in veins (about 75% of active tone) was however higher than that found by Toda et al. (1985) in arteries (about 45% of active tone).

The role of the endothelium in the histaminergic response of cerebral vessels is not well established. In cerebral arteries of humans and monkeys, the relaxation induced by histamine may be mediated by endothelial histamine H_1 receptors, in addition to histamine H_2 receptors located on the smooth musculature (Toda, 1990). In cerebral arteries of rats, histamine H_2 receptors located both on endothelial cells and on smooth muscle cells may be involved (the former by releasing nitric oxide) (Benedito et al., 1991), while in rabbits endothelial histamine H_3 receptors are involved (Ea Kim et al., 1992).

Our results with pial veins show that endothelium removal, and treatment with the inhibitor of nitric oxide synthesis, L-NAME, or with the inhibitor of cyclooxygenase, meclofenamate, did not affect the reactivity to histamine. This suggests that the endothelium, nitric oxide and prostaglandins may not be involved in the relaxation of pial veins in response to histamine, and that the histamine H_2 receptors that mediate this relaxation may be located in the venous smooth musculature. We have not found any report concerning a possible role of the endothelium, nitric oxide or prostaglandin in the histaminergic response of cerebral veins. Our present results are in line

with previous findings suggesting that the venous endothelium has little ability to produce relaxing factors, although it can produce contracting factors (García-Villalón et al., 1993). However, results of studies with dog mesenteric veins (Yamazaki and Toda, 1992) and human saphenous veins (Yang et al., 1991) suggest that the relaxation of these veins in response to histamine may be mediated by the release of nitric oxide.

In summary, the present results with canine pial veins suggest that: (1) histamine mainly produces cerebral venodilation by activation of histamine H_2 receptors, which may be located in venous smooth muscle; (2) H_2 receptors may be the histaminergic receptors of functional significance, whereas histamine H_1 and H_3 receptors, if they are present, are not of functional significance for mediating the effects of cerebral veins to histamine and (3) the endothelium, nitric oxide and prostaglandins may not be involved in the cerebral venodilation induced by histamine.

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