Characteristics of Histamine Receptors in Human Cerebral Arteries

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Abstract

Histamine and 2,2-pyridylethylamine, an H_1 -receptor agonist, (both 10^{-8} – 10^{-3} M) caused contraction of human cerebral artery preparations in the absence of active tension, while dimaprit, an H_2 -receptor agonist, caused vasorelaxation. The histamine-induced vasoconstriction was blocked non-competitively by tripeleennamine, an H_1 -receptor antagonist. In the presence of cimetidine, an H_2 -receptor antagonist, histamine-induced contraction was enhanced. The histamine-induced contraction was not affected by phentolamine or propranolol, but abolished by nifedipine. In prostaglandin $F_{2\alpha}$ -precontracted arteries, histamine and dimaprit caused relaxation, while 2,2-pyridylethylamine had no apparent effect. Histamine-induced relaxation was much greater in the presence than in the absence of an H_1 -antagonist. The vasorelaxation induced by histamine in the presence of an H_1 -antagonist was also inhibited by an H_2 -antagonist. Histamine caused no apparent relaxation in precontracted preparations without endothelium. The present results provide further evidence that histamine causes either vasoconstriction or vasodilation in human cerebral arteries, and suggest that vasoconstriction and vasorelaxation are due to the activation of H_1 - and H_2 -receptors, respectively. The relaxation induced by histamine may also be related to the endothelium-derived relaxing factors released from endothelial cells.

Key words: human cerebral arteries, histamine response, histamine receptors, endothelium

Introduction

Histamine is synthesized, stored and released at several locations near the cerebral vessels. The vascular responsiveness to histamine of the cerebral blood vessels is still unclear. Histamine acts as a potent cerebral vasodilator *in vivo*.^{3,27,29,33,34} *In vivo* experiments have shown that stimulation of histamine receptors with specific H_1 - and H_2 -receptor agonists causes dilation of pial cerebral arteries.^{11,12} However, histamine usually causes contraction of the cerebral arteries in different experimental animals, such as the cat,^{19,20} dog,^{2,17} goat,³¹ cow,⁷ and in man.²⁵

Animal experiments have indicated the existence of both H_1 (constrictor) and H_2 (dilator) histamine receptors in the cerebral vascular system.^{9,13,31} The response of *in vitro* human cerebral arteries to

vasoactive agents is often different compared to cerebral arteries from experimental animals. This study investigated the responsiveness to histamine of human cerebral arteries *in vitro*.

Materials and Methods

Human cerebral arteries (M_2 portions of the middle cerebral arteries) were obtained at autopsy within 8 hours after death from 20 male and female patients, 60–85 years of age, who died from respiratory failure (pneumonia) or cancer of the stomach. The arteries were kept in a cold Krebs-Ringer solution for 30 minutes before arrival in the laboratory. All these patients demonstrated arteriosclerotic changes in most of the vasculature.

Helical strips (2.5 cm in length and 2.5 mm in width) from the cerebral arteries were prepared eliminating as much of the lesions as possible, and mounted vertically in a tissue bath containing 20 ml Krebs-Ringer solution with the composition (mM):

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NaCl, 120.3; KCl, 4.8; CaCl₂, 1.2; MgSO₄·7H₂O, 1.3; NaHCO₃, 24.2; and glucose, 5.5. A gas mixture of 95% O₂ and 5% CO₂ was passed through the solution maintained at 37 ± 1°C, pH 7.3. In most experiments, a resting tension of 1 g was initially applied to the strips and maintained throughout the experiment. The preparations were allowed to equilibrate for 60 minutes in the bath before the experiment commenced. Isometric tension changes were measured by a force-displacement transducer (TB-612T; Nihon Kohden, Tokyo), connected to a minipolygraph (CP-602G; Nihon Kohden).

The following agents were used: histamine dihydrochloride (Katayama Chemical Co., Osaka); H₁-agonist, 2,2-pyridylethylamine (2-PEA) (Aldrich Chemical Co., Milwaukee, Wis., U.S.A.); H₂-agonist, dimaprit (Fujisawa Co., Osaka); H₁-antagonist, tripeleminamine (Sigma Chemical Co., St. Louis, Mo., U.S.A.); H₂-antagonist, cimetidine (Smith Klein & French Lab., Philadelphia, Pa., U.S.A.); Ca-antagonist, nifedipine (Bayer Co., Leverkusen, Germany); α -adrenoceptor-blocking agent, phentolamine (Ciba-Geigy Co., Basel, Switzerland); and β -adrenoceptor-blocking agent, propranolol (Sigma Chemical Co.).

Histamine, H₁- or H₂-agonists were added to the bath to obtain a cumulative concentration-response curve. Antagonists were added to the bath 20 minutes before addition of the agonists. The responses to histamine were also examined in cerebral arteries precontracted with 5 × 10⁻⁶ M prostaglandin F_{2 α} (PGF_{2 α}) (Sigma Chemical Co.). Concentration-response curves for histamine were obtained in the absence and presence of antagonists.

Endothelium was removed from some preparations by rubbing the intimal surface with a steel spatula. The procedure was considered successful if relaxation with acetylcholine chloride (Sigma Chemical Co.) was less than 5% of the control level.

The data are presented as means ± SE. Statistical analysis used the Student's *t*-test or analysis of variance followed by Dunnett's test. Significant differences between control and test groups were evaluated using *p* < 0.05 as the significance level. The competitive relationship between agonists and antagonists was calculated using the method of Arunlakshana and Schild.⁴⁾

Results

I. Effects of histamine on preparations without active tension

Histamine at 10⁻⁸–10⁻³ M and 2-PEA at 10⁻⁸–10⁻³ M both caused concentration-dependent contraction of human cerebral arteries without tone (Fig. 1).

Fig. 1 Effects of histamine with (○) or without (●) cimetidine (10⁻⁵ M), 2-PEA (△) and dimaprit (□) on isolated human cerebral arteries in the absence of active tension. Each point represents the mean ± SE of six values. *Significantly different (*p* < 0.05) from histamine response.

Fig. 2 Representative traces of the response to histamine in isolated human cerebral arteries in the presence (left) or absence (right) of cimetidine (10⁻⁵ M, arrow). upper: Typical response to histamine. lower: Atypical response to histamine.

The contractile effect of histamine was greater than that of 2-PEA. The potency (50% effective dose: ED₅₀) of histamine also was greater than that of 2-PEA. Dimaprit at 10⁻⁷–10⁻³ M caused concentra-

tion-dependent vasorelaxation.

In the presence of cimetidine (10^{-5} M), the concentration-response curve for histamine shifted to the greater response side of the control curve with an increase in maximum tension, as shown by Figs. 1 and 2 *upper*. In two of 10 preparations, histamine at low concentrations (10^{-7} – 10^{-5} M) caused slight relaxation, while histamine at high concentrations (10^{-4} and 10^{-3} M) produced contraction. The relaxation was inhibited by cimetidine (Fig. 2 *lower*). This effect, however, was not observed in the response to 2-PEA.

Tripeleennamine at 3×10^{-9} , 10^{-8} and 3×10^{-8} M in the presence of cimetidine (10^{-5} M) shifted the concentration-response curve for histamine to the lower response side of the control curve without affecting the maximum contraction (Fig. 3). Inhibition due to tripeleennamine was not competitive, since the slope of the regression line in Schild plots of the response to histamine was less than unity (0.78 ± 0.10).

In the presence of cimetidine (10^{-5} M), both phenolamine and propranolol (both 10^{-6} M) did not affect the histamine-induced contraction, ED_{50} (M) and maximum contraction (g) were: $3.8 \pm 0.2 \times 10^{-6}$ and 1.10 ± 0.2 for the control; $4.0 \pm 0.3 \times 10^{-6}$ and 1.16 ± 0.2 for phenolamine; and $4.2 \pm 0.3 \times 10^{-6}$ and 1.14 ± 0.2 for propranolol ($n = 4$).

Fig. 3 Inhibitory effect of tripeleennamine ($\circ$: 3×10^{-9} M, $\triangle$: 10^{-8} M, $\blacktriangle$: 3×10^{-8} M) on contractile responses to histamine in isolated human cerebral arteries in the absence of active tension. Tissues pretreated with cimetidine (10^{-5} M). Each point represents the mean $\pm$ SE of seven experiments. Maximum contraction induced by 10^{-3} M histamine is expressed as 100% of maximum developed tension. *Significantly different ($p < 0.05$) from control ($\bullet$).

Fig. 4 Representative traces of the inhibitory effect of cimetidine (arrow) on dimaprit-induced relaxation in isolated human cerebral arteries in the absence of active tone.

Fig. 5 Representative traces of the inhibitory effect of nifedipine (arrow) on histamine-induced contraction in isolated human cerebral arteries in the presence of cimetidine (10^{-5} M).

Dimaprit at 10^{-7} – 10^{-4} M induced relaxation in the arteries without tone ($n = 3$), which was almost completely inhibited by pretreatment with cimetidine at 10^{-5} M, but at a high concentration (10^{-3} M) dimaprit still caused relaxation (Fig. 4).

Nifedipine (10^{-6} M) caused the resting tension of arteries to decrease, and subsequent addition of histamine (10^{-7} – 10^{-3} M) caused no contraction (Fig. 5).

II. Effect of histamine on preparations with active tension

In tissues pretreated with $PGF_{2\alpha}$ (5×10^{-6} M), histamine at low concentrations (10^{-8} – 10^{-5} M) caused concentration-dependent relaxation, but high concentrations (10^{-4} M) caused only slight contraction in the absence of tripeleennamine (Fig. 6). 2-PEA (10^{-8} – 10^{-4} M) had no apparent effect in pre-contracted arteries, while dimaprit (10^{-8} – 10^{-4} M) caused concentration-dependent relaxation. Histamine (10^{-5} M) and dimaprit (10^{-4} M) decreased the $PGF_{2\alpha}$ -induced contraction by 36 ± 1.1 and $30 \pm$

Fig. 6 Representative traces of the response to histamine (*upper*), 2-PEA (*middle*) and dimaprit (*lower*) in cerebral arteries precontracted with $\text{PGF}_{2\alpha}$ (5×10^{-6} M, *arrow*).

Fig. 7 Inhibitory effect of cimetidine ($\circ$: 3×10^{-7} M, $\triangle$: 10^{-6} M, $\blacktriangle$: 3×10^{-6} M, $\square$: 10^{-5} M) on relaxation response to histamine in cerebral arteries precontracted with $\text{PGF}_{2\alpha}$ (5×10^{-6} M). Each point represents the mean $\pm$ SE for five experiments. Complete relaxation induced by 10^{-5} M histamine in the presence of tripeleennamine (10^{-6} M) is expressed as 100% of maximum relaxation. *Significantly different ($p < 0.05$) from control ($\bullet$).

Fig. 8 Representative traces of histamine-induced relaxation in normal (*upper*) and rubbed (*lower*) cerebral arteries precontracted with $\text{PGF}_{2\alpha}$ (5×10^{-6} M, *arrow*). The tissues were pretreated with tripeleennamine (10^{-6} M).

1.4% ($n = 5$), respectively. Cimetidine (10^{-5} M) completely blocked the relaxation in both cases (data not shown).

Histamine (10^{-7} – 10^{-4} M) caused much greater relaxation in the presence of tripeleennamine (10^{-6} M) than in its absence (Fig. 7), and a similar effect was observed for chlorphenylamine (10^{-6} M), also an H_1 -antagonist (data not shown). Histamine (10^{-5} and 10^{-4} M) completely relaxed the precontracted arteries. Pretreatment with cimetidine (3×10^{-7} – 10^{-5} M) inhibited the concentration-dependent relaxation induced by histamine (10^{-7} – 10^{-4} M), and the highest cimetidine concentration (10^{-5} M) nearly abolished the responses completely (pD'_2 , 5.99 ± 0.15).

Precontracted arteries without endothelium ($n = 3$) showed no histamine (10^{-8} – 10^{-5} M) relaxation and a high concentration (10^{-5} M) caused little contraction (Fig. 8). Normal precontracted arteries relaxed in response to acetylcholine at 10^{-6} M, but the preparations without endothelium did not. However, the amplitude of contraction induced by $\text{PGF}_{2\alpha}$ (5×10^{-6} M) in the endothelium-free arteries was the same as in normal preparations (maximum contraction, 0.94 ± 0.1 g for normal arteries and 1.02 ± 0.2 g for rubbed arteries; $n = 3$).

Discussion

Our experiments on human cerebral arteries

demonstrated that histamine and 2-PEA (an H_1 -agonist) caused concentration-dependent contraction in the absence of active tension, while dimaprit (an H_2 -agonist) produced concentration-dependent vasorelaxation. The results of our earlier study were similar, *i.e.* histamine produced contraction in human cerebral arteries in the absence of active tension.²⁶⁾ Tripeleennamine (an H_1 -antagonist) inhibited histamine-induced contraction and cimetidine (an H_2 -antagonist) blocked dimaprit-induced relaxation.

Animal experiments using dog and cow showed that cerebral arteries have only contractile responses to histamine at various concentrations (10^{-8} – 10^{-4} M) in the absence of active tension.^{7,17,25)} Histamine at lower concentrations caused vasodilation in cat cerebral arteries without active tension, while higher concentrations induced vasoconstriction.²⁰⁾ The vasodilation and vasoconstriction were blocked by H_2 - and H_1 -receptor antagonists, respectively. *In vitro* experiments showed that histamine and 2-PEA caused contraction of resting cat cerebral arteries, while impromidine (an H_2 -agonist) had no effect.¹⁰⁾

In cat arteries precontracted with $PGF_{2\alpha}$, histamine, 2-PEA and impromidine caused vascular relaxation which was reduced by the H_2 -antagonists. Edvinsson *et al.*¹⁰⁾ pointed out that the relaxation caused by histamine could only be seen when the vessel segments were first contracted in *in vitro* studies. The present experiments demonstrated that in $PGF_{2\alpha}$ -precontracted arteries, histamine (10^{-8} – 10^{-5} M) caused vasorelaxation, except at high concentrations (10^{-4} M) which caused contraction, although 2-PEA had no apparent effect. Dimaprit, however, caused relaxation, as in arteries without tone. Furthermore, histamine- and dimaprit-induced vasorelaxation was blocked by H_2 -antagonists in $PGF_{2\alpha}$ -precontracted arteries. These results suggest that histamine-induced relaxation may be mediated by H_2 -receptors in human cerebral arteries, as in experimental animals. The vasomotor actions of histamine in human cerebral arteries are known to be generally somewhat similar to those in the corresponding arteries of experimental animals.

Rabbit cerebral arteries *in vitro* only show a contraction response to histamine, but the receptors have not been identified.^{5,8,21,28)} The contraction of pial arteries *in vitro* occurs *via* interaction of histamine with non-specific sites, since histamine-induced contraction was inhibited in a non-competitive manner by an H_1 -antagonist.^{9,10)} Similarly, these experiments on human cerebral arteries have shown that the vasoconstriction and vasorelaxation induced by histamine are non-specific, since they are not blocked competitively by classical histamine receptor

antagonists. The vasoconstriction action of histamine may be partly indirect, in addition to the direct effect on histamine receptors. The present study also demonstrated that nifedipine completely blocked the contractile response to histamine. Thus, the activation of H_1 -receptors by histamine may increase Ca^{2+} influx through nifedipine-sensitive Ca^{2+} channels, resulting in the contraction of human cerebral arteries.

Histamine provokes the release of contraction-producing substances such as norepinephrine from the sympathetic innervation in human and cat cerebral arteries without tone *in vitro*.^{14,15)} Presumably an indirect adrenergic component may participate in the vasoconstriction induced by histamine in human cerebral arteries. The present results suggest that this is most unlikely, since α - and β -adrenoceptor-blocking agents had no effect on the vasomotor actions of histamine. Sercombe *et al.*²³⁾ also suggested that an indirect adrenergic component does not participate in the vasoconstriction action of histamine in rabbit cerebral arteries. The non-competitive inhibitory action of an H_1 -receptor antagonist against the contractile response to histamine may not involve H_2 -receptors, since this type of inhibition was observed in the presence of an H_2 -antagonist.

Our study raises the basic question of why the blocking action of a classical histamine antagonist on the histamine-induced contraction is not competitive in human cerebral arteries. Since the human cerebral arteries used in this experiment were obtained from autopsy of patients with systemic diseases, the non-specific type of histamine-induced contraction may be related to the pathological condition of the preparation.

Histamine may induce vasodilation by releasing the endothelium-derived relaxing factor (EDRF), as mediated by H_1 -receptors in rat thoracic aorta and mesenteric arteries,^{6,16,32)} and guinea-pig pulmonary arteries.^{1,22)} Nakane and Chiba¹⁸⁾ reported that endothelium removal did not affect the vascular response to histamine in canine coronary arteries. Toda³⁰⁾ showed that histamine-induced vasodilation was endothelium-dependent in monkey coronary arteries, but not in dog coronary arteries. Therefore, histamine-induced relaxation is not always endothelium-dependent, and differs between preparations and species of experimental animals. Sercombe *et al.*²⁴⁾ demonstrated that H_2 -agonist-induced vasorelaxation in rabbit middle cerebral arteries was reduced in rubbed arteries and suggested that H_2 dilatory receptors are situated on the endothelial cells. Our experiments on rubbed human arteries

precontracted with $\text{PGF}_{2\alpha}$ (5×10^{-7} M) showed histamine did not induce relaxation, suggesting that histamine-induced relaxation is endothelium-dependent. However, $\text{PGF}_{2\alpha}$ -induced contraction was the same in normal and rubbed cerebral arteries.

This study of human cerebral arteries demonstrated that histamine causes vasoconstriction in the absence of active tension, but vasorelaxation in the presence of active tension. An H_1 -agonist produced contraction in the absence of active tension, but had no apparent effect in its presence. An H_2 -agonist, however, consistently caused vasorelaxation in both the absence and presence of active tension. The vasoconstricting and vasorelaxing effects of histamine in human cerebral arteries were inhibited by H_1 - and H_2 -antagonists, respectively. Therefore, histamine-induced contraction and relaxation may be mediated mainly through H_1 and H_2 types of receptors, respectively. Histamine may also induce vasodilation by releasing EDRF, mediated by H_2 -receptors, but this requires direct confirmation. The possible localization and functional importance of histamine receptors in cerebral arteries still require further evaluation.

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