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Possible role of histamine (H_1- and H_2-) receptors in the regulation of meningeal blood flow

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1 Vasodilatation in the dura mater has been suggested to play an important role in the pathophysiology of vascular headaches. Histamine may contribute to these vascular changes. The aim of the present study was to examine the role of different histamine receptors in histamine-induced meningeal hyperperfusion using laser Doppler flowmetry.

2 The blood flow in the medial meningeal artery was monitored in the exposed parietal dura mater encephali of barbiturate anaesthetized rats. Local application of histamine (10^{-5} and 10^{-4} M) onto the dura caused increases in flow to 114.2 ± 9.6 and $135.1 \pm 19.1\%$, respectively, of the basal flow.

3 Flow increases induced by topical application of histamine (10^{-4} M) were reduced by local pretreatment with the H_2-receptor antagonist cimetidine (0.4 and 4 mM) to 63.4 ± 17 and $37.8 \pm 18.8\%$, respectively. Systemic pre-administration of cimetidine (5 mg kg^{-1} i.v.) did not change histamine-induced flow increases.

4 Local pretreatment with the H_1-receptor antagonist cetirizine (2 μM) further increased the flow evoked by topical histamine administration (10^{-4} M) to $123.5 \pm 14.7\%$ of the histamine control.

5 Increases in blood flow induced by i.v. administration of histamine (10 μg kg^{-1}) were reduced by i.v. pre-injection of cetirizine (50 μg kg^{-1}) to $31.9 \pm 9\%$ but not by i.v. cimetidine (5 mg kg^{-1}).

6 We conclude that histamine-induced relaxation of dural arterial vessels is mediated by H_2-receptors, most likely located on vascular smooth muscle cells, and by endothelial H_1-receptors. In addition, H_1-receptors on smooth muscle cells may mediate vasoconstriction.

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Abbreviations: ANOVA, analysis of variance; CET, cetirizine; CGRP, calcitonin gene-related peptide; CIM, cimetidine; HA, histamine; LSD test, least significance difference test; NO, nitric oxide

Introduction

Clinical and experimental data suggest that blood vessels in the dura mater encephali are involved in meningeal nociception and the pathogenesis of headaches (Davis & Dostrovsky, 1988; Wirth & Van Buren, 1971). The dura mater is the major pain-sensitive intracranial structure (Ray & Wolff, 1940), and experimental neurogenic inflammation of dural blood vessels – characterized by increased blood flow, plasma extravasation, aggregation and adhesion of platelets and activation of mast cells – has led to the neurovascular hypothesis of migraine pain as proposed by Moskowitz (1993). Although an important role of neurogenic inflammation in migraine is now doubtful, increased plasma levels of calcitonin gene-related peptide (CGRP) and histamine in migraine patients indicate that specific inflammatory processes may contribute to this disease (Goadsby *et al*., 1990; Heatley *et al*., 1982). CGRP and histamine as well as nitric oxide (NO) are powerful mediators of meningeal and intracerebral vasodilatation and increased blood flow (Iadecola *et al*., 1994; Kurosawa *et al*., 1995; Martins *et al*., 1980; Messlinger *et al*., 2000b; Suzuki *et al*., 1999). The vascular effects of histamine may partly be caused by endogenous formation of NO in cranial blood vessels (Schmetterer *et al*., 1997). Possible sources of NO in meningeal tissues are endothelial cells, perivascular nerve fibres and immunocompetent cells (Berger *et al*., 1994; Korytko & Boje, 1996), while histamine is likely to be stored in dural mast cells, which are closely associated with sensory nerve fibres and blood vessels (Dimlich *et al*., 1991). A bidirectional communication between sensory nerve fibres and dural mast cells may be involved in neurogenic inflammatory processes (Dimitriadou *et al*., 1990; 1991). Finally, it is long known that both histamine and NO liberating nitrovasodilators induce headaches preferentially in migraineurs, which may suggest a common mechanism linking the effect of histamine to NO (Clark *et al*., 1936; Pickering, 1933; Krabbe & Olesen, 1980; Thomsen, 1997; Thomsen *et al*., 1994).

Most of the experimental and clinical studies addressing vascular changes relevant for the pathophysiology of headaches have focused on intracerebral blood vessels, while little attention has been paid to the specifically pain sensitive structures of the dura mater. In the present study we examined the effects of histamine on the meningeal blood flow in an *in vivo* preparation of the rat dura mater. We intended to find out which subtypes of histamine-receptors

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are involved in vascular responses to histamine. For this purpose we tested the effects of the H_1-receptor antagonist cetirizine and the H_2-receptor antagonist cimetidine on local histamine-induced dural blood flow changes. Additionally, endothelium-dependent mechanisms possibly involved in responses to intravenous or topical applications of histamine were examined by i.v. pre-administration of cetirizine or cimetidine.

Methods

Anaesthesia and general preparation

All experimental procedures were performed in accordance with the regulations and ethical issues for animal care and treatment and received institutional approval by the local district government. Male Wistar rats weighing 300–400 g were anaesthetized by an initial intraperitoneal (i.p.) dose of thiopentone (150 mg kg^{-1}, Trapanal, Byk Gulden, Germany). Additional doses of thiopentone (25 mg kg^{-1} i.p.) were used to hold the anaesthesia at a level in which noxious stimuli (pinching the earlobes) failed to elicit nociceptive motor reflexes or changes of the systemic blood pressure. A catheter was inserted into the right femoral vein for the infusion of solutions. Systemic blood pressure was recorded with a pressure transducer *via* a catheter in the right femoral artery. The body temperature was maintained at 37–37.5°C with a heating plate. The animals were tracheotomized and breathed spontaneously. The room air was enriched with oxygen at the opening of the tracheal tube. This was sufficient to hold ventilation and circulation parameters (inspiration frequency, systemic blood pressure) constant during the whole experiment. The parietal dura mater of the animals was exposed by trepanizing the skull. The head was fixed in a stereotaxic frame, the scalp was incised in the midline and the parietal bone was exposed at one side. A cranial window of 4×6 mm was drilled into the parietal bone to expose the underlying dura mater. To avoid thermal lesions of the dura mater during this phase of preparation, the bone was continuously cooled with cold saline. Needle type probes of a laser Doppler flowmeter (Moore Instruments, U.K.) were oriented with their tips towards branches of the medial meningeal artery. To minimize flow signals from the cortical surface, recording sites were selected along the medial meningeal artery which were distant from cortical blood vessels (visible through the dura mater). On this condition the blood flow signal derived nearly exclusively from dural blood vessels. This has been shown in previous experiments by optical isolation of the dura from the underlying cortex (see Figure 5 in Kurosawa *et al*., 1995). Blood flow was on-line recorded with a time constant of 1 s; the data were stored and processed with the DRTsoft program (Moore Instruments).

Drug administration

All drugs were dissolved in saline. For topical application of substances, the cranial window was filled with 50 μl of solution using an Eppendorf pipette. Histamine (10^{-5} and 10^{-4} M, Sigma) was applied for 5 min. Following each histamine application the dura was washed and covered with saline to restore the basal flow, which was reached within 10 min after washing. In some experiments the effect of repeated histamine application (10^{-5} and 10^{-4} M) was tested.

To determine the receptors involved in the histamine effect, solutions (50 μl) of cetirizine (2, 20, 40 μM, Zyrtec®, UCB, Pharma, Germany) or cimetidine (0.04, 0.4, 4 mM, Sigma) were locally applied to the exposed dura. Three minutes later the antagonist was carefully removed prior to the test application of histamine (10^{-4} M, 5 min). In this way cetirizine or cimetidine was pre-applied at increasing concentrations followed by same doses of histamine. For intravenous (i.v.) administration, drugs were diluted with saline to a 0.3 ml final volume and slowly injected into the femoral vein. Histamine (10 μg kg^{-1}) was injected or locally applied to the dura mater as described above. Then cetirizine (50 μg kg^{-1} i.v.) or cimetidine (5 mg kg^{-1}, i.v.) was pre-administered prior to i.v. or local application of histamine 5–10 min later.

Measuring and evaluation of data

Data were not collected unless the unstimulated dural blood flow (basal flow) was stable. The basal flow is constant as far as the systemic arterial pressure does not change significantly. The arterial pressure is stable both in ventilated animals, in which the end-expiratory CO_2 is monitored and held in a normal range (data from previous experiments), as well as in spontaneously breathing animals like in the present study. Control flow values were obtained by measuring the mean flow within 5 min after local application of 50 μl saline (vehicle) to the dura or i.v. injection of 0.3 ml saline, respectively. Changes in flow induced by local application of histamine or by histamine receptor antagonists were determined as mean flow values (in per cent) within the respective application period (5 or 3 min) relative to the control after saline application (basal flow). Changes in flow induced by i.v. histamine application were determined as mean flow within a period of 90 s, which represents the first phase of the histamine-evoked flow response (see Figure 4), relative to the control after saline (in per cent). For examination of receptor antagonist effects on the histamine-induced flow, histamine-induced increases in flow before and after cetirizine or cimetidine, respectively, were compared, the initial histamine-induced flow increase defined as 100%. Basal flow values were always determined prior to histamine receptor antagonists. To statistically test effects of antagonists and to compare histamine effects before and after antagonists, one-way analysis of variance (ANOVA) with repeated measurements was applied followed by the *post hoc* least significance difference test (LSD test) or the *t*-test for dependent samples. For groups with sample sizes $n < 8$, the Wilcoxon's matched pairs test was additionally used. Significance was assessed at the 5% level. All flow values are listed as mean $\pm$ s.e.mean.

Results

Effect of local application of histamine

Without any drug application the meningeal blood flow was constant. Local application of saline to the dura mater

(control) induced no significant changes in flow (mean 96.9±3.1%). Local application of histamine to the dura caused immediate increases in blood flow which reached a plateau within 60 s (Figure 1). These increases were dose-dependent and reproducible in size: three consecutive applications of 50 μl of 10^{-5} M histamine solution (separated by wash-out phases) induced flow increases to 114.2±9.6, 116.7±9.9 and 113.2±4.8% ($n=6$), respectively, and repeated applications at 10^{-4} M increased the flow to 135.1±19.1, 137.6±20.3 and 137.8±12% ($n=9$) compared to saline (control). Local application of histamine had no effect on the systemic arterial pressure.

Effect of local cetirizine on the histamine-induced flow

In 11 experiments, the H_1-receptor antagonist cetirizine was applied to the dura mater prior to histamine. Cetirizine at a concentration of 2 μM did not influence the blood flow. Application of 20 μM cetirizine induced a transient reduction in flow in some experiments. Ceterizine at the highest concentration (40 μM) lowered the basal blood flow significantly (Table 1). After pre-application of 2 and 20 μM cetirizine, an increase in histamine-induced blood flow was observed, which was significant after 2 μM cetirizine (123.5±14.7%; $n=7$) but no longer significant after 20 μM cetirizine (128.2±31.2%; $n=9$) due to the high variation of data (Figure 2). After 40 μM cetirizine, the histamine-induced blood flow was not changed on average (105.8±24%; $n=7$), although in single experiments both clear increases and decreases were observed.

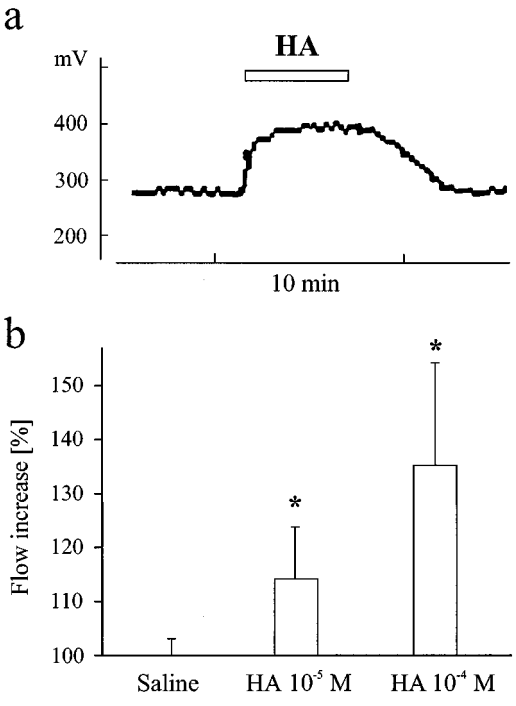

Figure 1 Effect of topical histamine application on the meningeal blood flow. (a) Original recording, histamine (HA, 50 μl, 10^{-4} M) applied to the dura. (b) Mean effects of HA at doses of 10^{-5} (*n*:6) and 10^{-4} M ($n=9$) compared with saline application. Error bars show s.e.mean; *$P<0.05$.

Table 1 Effects of topical application of cetirizine and cimetidine on the basal blood flow

Antagonist	*Concentration*	*Changes in blood flow* (%)
Cetirizine	2 μM	100.1±1.5 ($n=7$)
	20 μM	98.8±6.1 ($n=9$)
	40 μM	80.4±12.9* ($n=7$)
Cimetidine	0.04 mM	100.2±2.3 ($n=7$)
	0.4 mM	103.7±2.5 ($n=8$)
	4 mM	106.5±13.7 ($n=7$)

Values indicate mean±s.e.mean, measured within the 3 min application period, relative to the control (in %); *significant difference to saline ($P<0.05$).

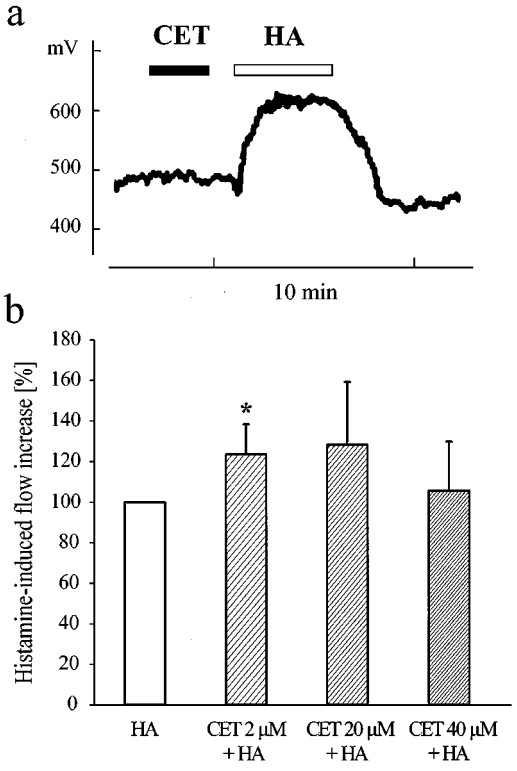

Figure 2 Effect of cetirizine on the increase of meningeal blood flow induced by local histamine application. (a) Original recording, cetirizine (CET, 20 μM) and histamine (HA, 10^{-4} M) applied to the dura. (b) Mean effects of cetirizine at three doses on the flow induced by histamine (10^{-4} M). Error bars show s.e.mean; *$P<0.05$.

Effect of local cimetidine on the histamine-induced flow

In 11 experiments, the H_2-receptor antagonist cimetidine was applied to the dura mater. Within the whole range of doses (0.04–4 mM) cimetidine did not change the blood flow (Table 1). After pre-application of cimetidine, histamine-induced flow increases were dose-dependently inhibited: 0.04, 0.4 and 4 mM cimetidine reduced the histamine-induced flow to 80.1±21.4 ($n=7$), 63.4±17 ($n=8$) and 37.8±18.8% ($n=7$), respectively; this effect was significant at the two higher doses (Figure 3).

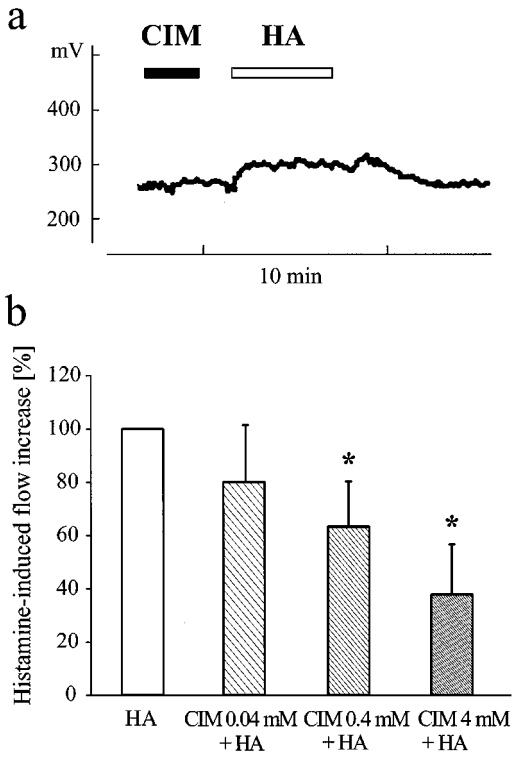

Figure 3 Effect of cimetidine on the increase of meningeal blood flow induced by local histamine application. (a) Original recording, cimetidine (CIM, 0.4 mM) and histamine (HA, 10^{-4} M) applied to the dura. (b) Mean effects of cimetidine at three doses on the flow induced by histamine (10^{-4} M). Error bars show s.e.mean; $*P<0.05$.

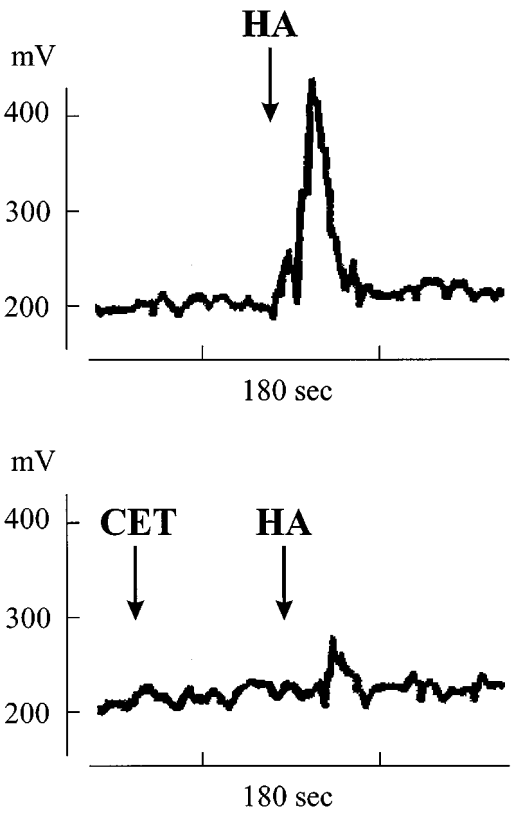

Figure 4 Original recording of the meningeal blood flow in one experiment; effect of i.v. histamine administration (HA, 10 μg kg^{-1}) and i.v. cetirizine (CET, 50 μg kg^{-1}) on the blood flow induced by i.v. histamine (arrows).

Effect of i.v. administration of histamine on dural blood flow

Injection of 0.3 ml saline had no effect on the blood flow ($101.2\pm2.6\%$) and served as a control in these experiments. Injection of 10 μg kg^{-1} histamine ($n=8$) induced a rapid and transient drop of the systemic blood pressure by 20–40 mmHg, which was normalized within 2 min. With a latency of 40–60 s after the histamine injection, increases in blood flow followed showing two phases. In the first phase lasting up to 90 s, the flow formed a peak, in a second phase it stabilized at a slightly higher level compared with the baseline (Figure 4, top). The mean increase in flow of the first phase was $121.5\pm12.4\%$ ($n=14$), which was significantly different from control values (saline injection).

Effect of i.v. cetirizine on the flow induced by i.v. or local histamine

In 10 experiments, cetirizine (50 μg kg^{-1}) was administered i.v. prior to i.v. histamine injection (10 μg kg^{-1}) or local application of histamine (10^{-4} M) to the dura mater. Cetirizine administration did not change the basal flow values ($103.9\pm5.5\%$; $n=10$) and the flow increases induced by topical histamine application ($105.4\pm14.6\%$; $n=8$). Flow increases induced by i.v. histamine administration were significantly reduced by cetirizine pretreatment to $31.9\pm9\%$ ($n=5$) of the histamine-induced response before cetirizine (Figures 4 and 5a). Systemic blood pressure was not influenced by cetirizine administration.

Effect of i.v. cimetidine on the flow induced by i.v. or local histamine

Cimetidine i.v. administration (5 mg kg^{-1} i.v.) did not change the basal flow ($106.2\pm8\%$; $n=12$) and the systemic blood pressure. Neither the flow increases induced by local histamine application ($68.8\pm30.9\%$; $n=5$) nor the increases induced by i.v. histamine injection ($116\pm31.2\%$; $n=9$) were significantly changed by cimetidine i.v. preadministration, due to the high variation of values (Figure 5b).

Discussion

Effect of histamine

In the present study we have used laser Doppler flowmetry to measure histamine-induced blood flow changes in dural arteries. Histamine was applied locally at same concentrations as used in a mixture of different mediators that liberated CGRP and prostaglandin E_2 in an *in vitro* preparation of the dura mater (Ebersberger *et al*., 1999). For systemic administration, histamine was injected intravenously at a concentration that has been shown to cause

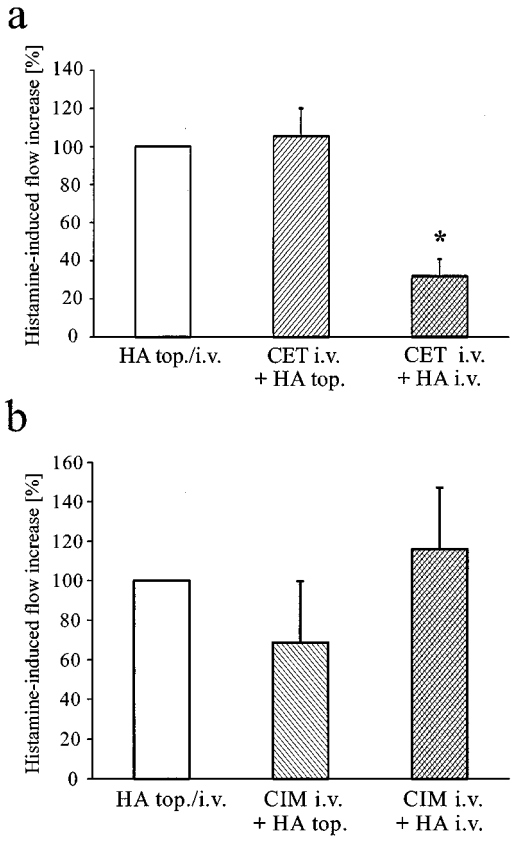

Figure 5 Mean effects of i.v. injection of (a) cetirizine (CET, 50 μg kg^{-1}) and (b) cimetidine (CIM, 5 mg kg^{-1}) on the flow increases induced by topical (10^{-4} M) and i.v. (10 μg kg^{-1}) administration of histamine (HA). Error bars show s.e.mean; $^*P<0.05$.

experimental headache in humans when infused over 20 min (Lassen *et al*., 1995). Topical application of histamine induced a dose-dependent, significant blood flow increase in the medial meningeal artery. Injection of histamine was less effective under these experimental conditions, which may be explained by lower local histamine concentrations accumulating in the dura mater and by the rapid elimination of circulating histamine. Since the effect of identical concentrations of histamine was not different after repeated applications and was also stable after wash-out periods between the applications of different antagonists, changes of histamine receptor sensitivity during the experiments can be excluded. The results suggest the presence of different histamine receptors on meningeal arteries. Histamine-induced relaxation of these blood vessels seems to be mediated partially by H_1-receptors, present on the endothelium, and partially by H_2-receptors, most likely located on smooth muscle cells. In addition, H_1-receptors mediating vasoconstriction may be present in smooth muscle cells. These conclusions are derived from the differential effects of cimetidine and cetirizine applied topically and i.v., respectively, on the histamine evoked dural blood flow. Since neither systemic blood pressure nor breathing frequency was influenced by i.v. administration of these antagonists, the changes in histamine-evoked blood flow are most likely due to local effects. Although i.v. administration of histamine induced a transient decrease in systemic blood pressure, a decrease in dural blood flow was not observed. Thus we suppose that changes in homeostatic parameters after i.v. administration of substances did not significantly influence the dural blood flow.

Histamine receptors mediating vasodilatation are generally considered to be coupled to different second messenger systems. H_1-receptors have been shown to be coupled to the phospholipase C system increasing the inositol-1,4,5-triphosphate and diacylgylcerol formation. H_2-receptors activate the adenylyl cyclase system resulting in increased levels of cyclic 3′,5′-adenosine monophosphate (Johnson, 1992).

Effects of cetirizine

The H_1-receptor antagonist cetirizine was pre-applied to the dura mater or intravenously pre-administered at concentrations that have been shown to result in an effective plasma and tissue concentration inhibiting histamine-induced wheal and flare reaction in the human skin after oral administration (Petersen *et al*., 1999). Topical application of cetirizine at a low concentration (2 μM) increased the histamine-evoked flow. This effect of H_1-receptor blockade supports earlier observations on the presence of vasoconstrictory histamine receptors in cranial human arteries (Jansen-Olesen *et al*., 1997). Intravenous application of cetirizine, on the other hand, reduced the flow increase evoked by i.v. histamine injection. This effect indicates a role of H_1-receptors in endothelial vasodilatory mechanisms. The remaining vasodilatory effect of i.v. histamine after i.v. cetirizine injection can be explained by the penetration of histamine through the endothelium and the action on smooth muscle H_2-receptors. In some additional experiments (not included in this paper) we applied cimetidine topically and cetirizine intravenously prior to i.v. histamine administration. The histamine-induced blood flow increase that was left after i.v. cetirizine was abolished by cimetidine pre-application. Histamine and cetirizine at high concentrations may also be able to penetrate the dural vascular system in the opposite direction, e.g. by diffusion into postcapillary venules, to reach the arterial endothelium through the circulation. In this way, the vasodilatory effect of endothelial H_1-receptor activation may partly counteract the vasoconstrictory effect of smooth muscle H_1-receptor activation. This is a possible explanation for the lack of effects of topically applied cetirizine at higher concentrations (20 and 40 μM) on the histamine-induced blood flow increase, assuming that part of the cetirizine has reached the endothelial histamine receptors and dose-dependently blocked the endothelial component of the histamine-induced flow increase.

Effects of cimetidine

The H_2-receptor antagonist cimetidine was applied at concentrations that have been shown to inhibit histamine-induced dilatation in precontracted isolated human middle meningeal arteries (Ottosson *et al*., 1991). The inhibitory effect of topical cimetidine on the flow increase induced by local application of histamine supports earlier observations on isolated cerebral and meningeal arteries about the significance of H_2-receptor-mediated vasodilatation in the

vascular smooth muscles (Jansen-Olesen *et al*., 1997). Cimetidine seems not to cross the blood vessel wall, since neither local nor i.v. histamine-induced flow increases were significantly changed by the i.v. pre-administration of the drug. Besides, since i.v. cimetidine did not influence the effect of i.v. histamine injection, the presence of H_2-receptors on the endothelial cells is not very likely.

Relevance for the pathophysiology of headaches?

Recent studies have shown the presence of H_1- and H_2-receptors located on the human middle meningeal artery by *in vitro* pharmacology and reverse transcriptase-polymerase chain reaction (Jansen-Olesen *et al*., 1997). The present study has shown that both receptor types are functionally active and can contribute to the control of meningeal blood flow when histamine is released from dural mast cells. So far there is no evidence for postjunctional H_3-receptors mediating relaxation of intracranial blood vessels (Benedito *et al*., 1991), but prejunctionally localized H_3-receptors, the activation of which may inhibit neuropeptide release, may exist in sensory nerve fibres of the dura mater (Matsubara *et al*., 1992).

Although the role of histamine in different types of headaches is not clear, experimental headache induced by the infusion of histamine is similar to the pulsating headache in migraine (Krabbe & Olesen, 1980). In migraine patients immediate and delayed headache, induced by i.v. histamine was abolished by H_1-receptor antagonist pretreatment (Lassen *et al*., 1995). Some clinical studies indicate the role of histamine in cluster headache attacks, since treatment of patients with the combination of H_1- and H_2-receptor antagonists effectively reduced the intensity and duration of symptoms, but H_2-receptor antagonist pretreatment alone was ineffective (Cuypers *et al*., 1979). Other clinical studies could not support the beneficial effect of H_1- and H_2-receptor antagonist pretreatment in cluster headache patients (Russel, 1979) indicating the complex character of pain generation. The close association of sensory nerve fibres, blood vessels and mast cells in meningeal tissues support the view that these structures within the dura mater can communicate. Histamine-induced headache depends in part on the formation of NO (Lassen *et al*., 1995). NO causes vasodilatation by relaxing the vascular smooth muscle cells but there is recent evidence that NO stimulates also the release of CGRP from perivascular nerve fibres in the dura mater (Messlinger *et al*., 2000a). CGRP in turn causes vasodilatation and increased blood flow in meningeal blood vessels. In rats CGRP may also degranulate mast cells, which liberate histamine and possibly NO. This additional effect may also be considered as part of the interactions involved in the pathophysiology of headaches, although it could not be shown in human mast cells possibly due to methodological difficulties (Ottosson & Edvinsson, 1997). Experimental (antidromic) stimulation of meningeal afferents has been shown to degranulate dural mast cells (Dimitriadou *et al*., 1991). Thus these interactions, reminiscent of a vicious circle, could trigger inflammatory reactions and suggest a role for histamine released by dural mast cells in pathological conditions contributing to the development of vascular headaches.

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