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Mucosal blood flow in the human nose following local challenge with histamine

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Nasal blood flow was measured using the ^{133}Xe wash-out method in 10 non-allergic subjects and 13 asymptomatic hay fever patients. Determinations were made before and 15 min after challenge with diluent, 0.13 mg, 1.3 mg and 13 mg of histamine/nasal cavity. Nasal symptom scores were recorded. The nasal inspiratory peak flow was determined simultaneously in the hay fever patients. No differences in blood flow or symptom score recordings were found between the normal subjects and allergic patients under basal conditions or after histamine challenge. The nasal blood flow increased after challenge with the highest histamine dose. The increase was 34% ($P < 0.05$) from baseline in normals and 47% ($P < 0.05$) in allergics. There was a dose-dependent increase in nasal symptom scores following histamine challenge, again with no difference between normal and allergic subjects. The nasal peak flow decreased in a similar manner with a maximum decrease of 74% ($P < 0.001$). The present study gives further support to the notion that histamine is not the only mediator involved in vascular reactions during allergic rhinitis.

Key words: allergic rhinitis; blood flow; histamine; nasal mucosa.

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CLINICAL ASPECTS

Nasal challenges with histamine have previously been used to study the pathophysiology of allergic reactions of the upper airways and clinically to demonstrate the presence of hyperreactivity. Using ^{133}Xe wash-out technique and measurements of nasal airway resistance simultaneously, it was in the present study possible to demonstrate that histamine in certain aspects appears to differ from allergen when it comes to the influence on the tone of the resistance vessels. Whether such differences are of importance for the clinical understanding of nasal allergic reactions *in vivo* is still unknown.

Histamine, which is synthetized from the amino acid histidine, is the most well-known mediator of nasal allergy (19, 20). When given as a local challenge intranasally histamine produces all the typical symptoms of nasal allergy, such as itching, sneezing, hypersecretion and blockage, even in normal subjects (23, 26, 31). Further, antihistamines given systemically as well as topically inhibit allergen-induced nasal symptoms (9, 17) and are widely used clinically for hay fever treatment (15, 19, 28). Thus, the reaction of the capacitance vessels during the allergic reaction may apparently be explained by the actions of histamine. It is unclear, however, whether the reactions of the resistance vessels can also be explained by histamine (21). In a previous study we found that the blood flow decreased in a dose-dependent manner after allergen provocation (14), whereas histamine increases the blood flow in many tissues.

The aim of the present investigation was therefore to study changes in nasal mucosal blood flow after challenge with histamine in

patients with asymptomatic allergic rhinitis and in healthy controls.

MATERIAL AND METHODS

Subjects

A total of 23 subjects (12 males and 11 females) participated in the study. Details are presented in Table 1. The healthy volunteers lacked any history of allergic conditions, had no clinical signs of allergy and produced a demonstrated negative skin test to a standard allergen panel. The allergic patients had a strictly seasonal history of allergic rhinitis due to birch and/or grass pollen. Their allergy was verified by a positive skin prick test. None of the subjects were smokers and none used any medication apart from oral contraceptives. All of the subjects had normal findings at anterior rhinoscopy. None of the subjects had any acute nasal disease, such as a cold, during the study. The trial was carried out during pollen-free autumn months. All subjects gave their informed consent to participate in the study, which was approved by the Ethics and Isotope Committees of the University of Göteborg.

Nasal histamine challenge

The subjects were in the upright position at administration of the histamine solutions. At least 1 week elapsed between each challenge. The histamine-hydrochloride solutions were prepared at the pharmacy of the Sahlgrenska Hospital. Buffered saline solutions of 1 mg/ml, 10 mg/ml or 100 mg/ml of histamine-hydrochloride were used (pH 7.4). The diluent alone (pH 7.4) was used as a control solution. The solutions were administered to the nasal cavity with the help of a mechanical pump spray commercially available for delivering DSCG solution (Lomudal Nasal™, Fisons Ltd, Loughborough, UK). Each spray delivers 0.13 ml of fluid and yields a widespread distribution in the nasal cavity (22). Both nasal cavities were challenged except for the highest dose. After bilateral challenge with the highest dose of histamine the first non-allergic subject had general symptoms such as severe flush and tachycardia. It was then decided to challenge only unilaterally with the highest histamine dose in the same nasal cavity where blood flow was determined.

Table 1

Study subjects

	Normals	Allergics
Number	10	13
Males/Females	4/6	8/5
Age (years)		
mean	21.4	24.2
range	19–28	20–33

Determination of blood flow

All blood flow determinations were carried out with the subjects in the supine position. The nasal mucosal blood flow was determined using a ^{133}Xenon wash-out method described by Bende et al. (3). In short, 0.1 ml of ^{133}Xenon containing 1–10 Millibequerel (MBq) in an isotonic saline solution was injected with a sterile 1 ml syringe (Microfine III; outer diameter: 0.36 mm) into the mucosa of the inferior turbinate. The disappearance of the isotope was followed by a single scintillation detector (Nukab, Gammaspectrometer 9700) placed in a circular collimator (36 mm inside diameter) positioned as close to the nose of the subject as possible. Pen recordings (KA series, Rikadenki) were coded and blood flow was calculated from the slope of the disappearance of the isotope by an independent investigator. The wash-out curve was assumed to be mono-exponential. Only the portion of the curve from 0.5 min to 5 min was considered for the calculation of the slope. The mucosal blood flow was determined in $ml \cdot min^{-1} \cdot (100\ g)^{-1}$ according to the formula presented by Lassen et al. (18):

$$f = \frac{\ln 2 \cdot lambda \cdot 100 \cdot 60}{T1/2}$$

where T1/2 is the halftime of elimination of ^{133}Xe in seconds, ln 2 is the natural logarithm of 2, lambda represents the partition coefficient of

^{133}Xe between blood and tissue and was taken at 0.7. The ^{133}Xenon was supplied by Mallinckrodt Diagnostica (Petten, Holland) and delivered through the Department of Radiophysics at Sahlgrenska Hospital in sterile, isotonic saline solution.

Determination of symptom score

Throughout the study nasal symptoms were recorded 15 min after each challenge using a scoring technique. Sneezes were counted and transformed on a 0–3 scale: 0 = 0 sneezes, 1 = 1–4 sneezes, 2 = 5–9 sneezes and 3 = ⩾ 10 sneezes. Nasal blockage, secretion and itching were also rated on a 0–3 scale with: 0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe symptoms. A composite nasal symptom score was then calculated. The nasal mucosa was also inspected for colour, thickness and secretion every time a blood flow measurement was made.

Determination of nasal peak inspiration flow

All of the allergic subjects were tested before and 10 min after challenge with a Wright inspiratory nasal peak flow meter after clearing their noses of any nasal secretion, as described by Youlten et al. (32). Subjects were standing in an upright position when tested. Three peak flow determinations were obtained each time and the highest value was used in the subsequent evaluation.

Statistics

Changes in blood flow after histamine challenge in relation to baseline were analysed by means of Wilcoxon's signed rank sum test utilizing a statistical software package (Statview 512$^+$, Abacus Concept, Inc., Calabasas, CA) on a microcomputer (Macintosh, Apple Computer, Cupertino, CA). A two-tailed test was used. A P-value of < 0.05 was regarded as significant.

RESULTS

The mean of the baseline blood flow values of the non-allergic individuals was 62.3±5.9 (mean±SEM) and of the allergic individuals 64.1±3.1 (mean±SEM) ml·min^{-1}·(100 g)$^{-1}$. The intraindividual (within subject) coefficient of variation as determined by the prechallenge values on the different days (4 determinations) was 17% (range 9 to 40%) for the normal subjects and 29% (range 6 to 47%) for the allergic subjects. The interindividual (between subjects) coefficient of variation of the first baseline determination in 23 subjects was 23%. The blood flow values before and 15 min after challenge with placebo and histamine are presented in Table 2. All the determinations of blood flow after challenge were compared to the baseline values of the corresponding days. Fig. 1 shows these comparisons expressed as a percentage change in the baseline for the non-allergic individuals, and Fig. 2 shows the corresponding values for the allergic subjects. As shown, challenge with control solution alone did not induce any change in blood flow, whereas there was an increase in blood flow after the highest dose of histamine of 34% ($P < 0.05$) and 47% ($P < 0.05$) for the normal and allergic subjects, respectively. A dose-dependent decrease in nasal inspiratory peak flow was found after the histamine challenge as shown in Fig. 3. The histamine challenge induced almost immediate sneezing followed by hypersecretion and nasal blockage. The symptom scores are

Table 2

Nasal mucosal blood flow (ml·min^{-1}·(100 g)$^{-1}$) before and 15 min after challenge with diluent and histamine (mean±SEM)

Subjects	Challenge dose/cavity	Blood flow (ml·min^{-1}·(100 g)$^{-1}$) baseline	15 min
Normals			
(n = 10)	diluent (mg)	57.2(±7.4)	61.8(±7.0)
	0.13	60.8(±4.8)	53.2(±2.6)
	1.3	63.1(±5.0)	62.0(±3.8)
	13	59.5(±5.8)	74.1(±6.5)*
Allergics			
(n = 13)	diluent (mg)	60.3(±4.3)	62.9(±4.5)
	0.13	63.5(±4.3)	61.2(±6.2)
	1.3	65.3(±4.8)	64.7(±4.6)
	13	60.5(±5.4)	74.6(±5.7)*

*$P < 0.05$.

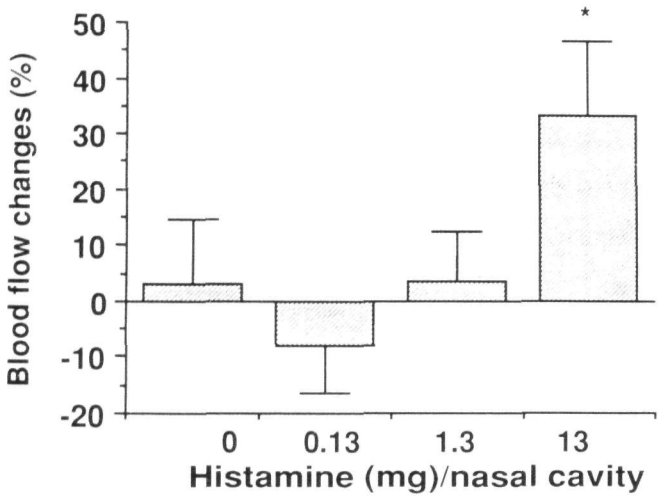

Fig. 1. Change in mucosal blood flow compared with baseline 15 min after challenge with diluent (= 0 mg histamine) and increasing doses of histamine (mean±SEM). Normal subjects (n = 10). The increase after 13 mg is statistically significant ($^*P < 0.05$).

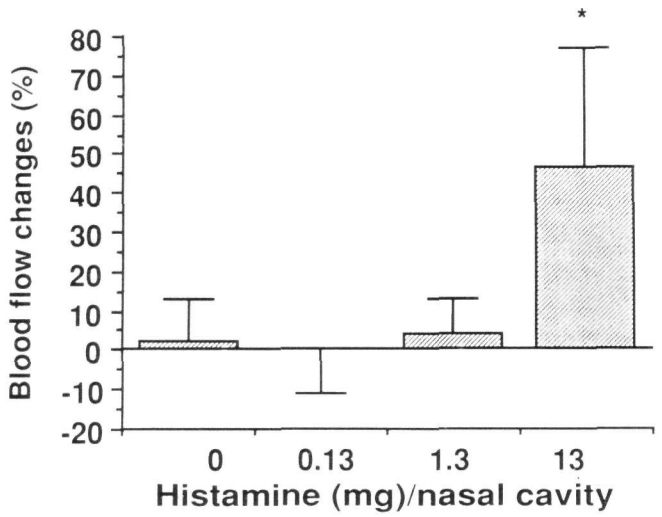

Fig. 2. Change in mucosal blood flow compared with baseline 15 min after challenge with diluent (= 0 mg histamine) and increasing doses of histamine (mean±SEM). Allergic patients (n = 13). The increase after 13 mg is statistically 1 ($^*P < 0.05$).

given in Table 3. On anterior rhinoscopy carried out before each blood flow determination it was noted that the colour of the mucosa was unchanged or a little more reddish after challenge with histamine. In no case was the mucosa pale-bluish which could be seen after allergen challenge. Every subject had a severe flush after the high histamine dose which started within 1 min of challenge and lasted for about 3 min. On three occasions the Xenon injection failed after the highest histamine dose due to severe hypersecretion. In two subjects the determinations were successfully repeated on another day, while the third individual refused to repeat the highest histamine challenge. Occasionally there was a minimal bleeding after the injection, but only after histamine challenge. Nobody started bleeding before they blew their nose, none of the bleeding incidences called for any special treatment and nobody had to withdraw from the determination of blood flow.

DISCUSSION

In the present study we found that a high topical dose of histamine induced an increase in nasal mucosal blood flow. Normal, healthy volunteers and patients with asymptomatic allergic rhinitis were found to have similar basal resting blood flow in agreement with a previous report (4); they were also found to react almost identically to the histamine provocations.

The amount of histamine which reaches the histamine receptors responsible for the nasal symptoms is not known. The doses of histamine administered intranasally in this study might not be physiological at the mucosal site. Nevertheless, it was a special interest to study whether topically administered histamine *per se* would change the mucosal blood flow and, if so, whether the Xenon wash-out method could determine this change. The highest dose of histamine was chosen to give severe symptoms, such as nasal hypersecretion and blockage, in all of the subjects. As mentioned above, challenge bilaterally in one of the non-allergic subjects induced general and severe local symptoms. Subsequently, the highest histamine dose was given only unilaterally. In spite of this, there was an oedema of the soft palate in two normal subjects and one of the allergic subjects. The lowest dose was chosen to produce no symptoms at all in some of the subjects. The range of histamine doses was 100-fold.

Histamine has previously been shown to induce an increase in blood flow in a variety of tissues including nasal mucosa (4, 7). However,

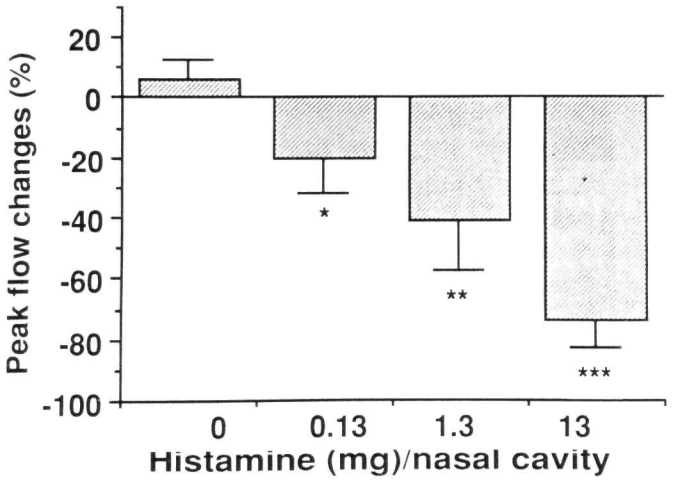

Fig. 3. Increase in inspiratory nasal peak flow 10 min after challenge with diluent (= 0 mg histamine) and increasing doses of histamine. Allergic patients (n = 13). $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

this could not be taken for granted since it has been reported that there is a difference in nasal reactions to histamine depending on the mode of distribution. It has thus been shown that the local injection of histamine into the nasal mucosa only gives rise to a local swelling, while a local challenge with histamine produces all the symptoms of nasal allergic reaction (23). The present study is in agreement with a previous preliminary report using the laser-doppler technique where an increase in blood flow was reported after local histamine challenge (24).

The present findings show that resistance vessels are affected only after a very large dose of locally administered histamine. However, in smaller doses the nasal mucosal blood flow is not affected in non-allergic or in allergic subjects.

Although a local histamine challenge in the nose can stimulate all the symptoms of nasal allergy there are differences between allergen- and histamine-induced changes in the nasal mucosa. Allergen challenge is followed by local eosinophilia and increased nasal reactivity which is not seen after histamine challenge (1, 2, 8, 10, 11, 12, 27). There is also a difference in the biochemical composition of nasal secretions harvested after allergen as compared to histamine challenge (6). Further, the increased nasal airway resistance after histamine challenge cannot be completely prevented by H_1 and H_2 receptor antagonists (29). The present findings of the behaviour of the resistance vessels after histamine challenge are in contrast to previous findings where allergen challenge in the nose produces a dose-dependent decrease in blood flow (14). Thus, histamine challenge affects the nasal mucosal blood flow slightly or contrarily compared with allergen challenge.

The validity of the Xenon wash-out method in tissue with severe congestion, such as in the allergic reaction, has been discussed in a previous report (14). When measured using the laser-doppler method topical histamine caused a dose-dependent increase in the blood flow in the superficial layer of the nasal mucosa (5). The Xenon wash-out technique determines the mean nasal mucosal blood flow, i.e. the blood flow in a deeper compartment of the mucosa. However, we found an increased blood flow, although laser-doppler flowmetry has shown that the injection trauma itself, which lasts for 2 min, gives rise to a decrease followed immediately by an increase in blood flow in the superficial layer of the nasal mucosa (21). After challenge with the highest dose of histamine there was a severe oedema with severe hypersecretion in the same nasal cavity where the blood flow was determined. In contrast to challenge after a very high dose of allergen, the colour of the mucosa was now reddish and not pale. This clinical sign would agree with an increase in blood flow as shown by the Xenon wash-out method in the present study. As discussed in a previous report (14), the Xenon wash-out method seems able to reveal contrary

Table 3

Composite nasal symptom score 15 min after challenge with diluent and histamine (mean±SEM)

Challenge dose/cavity	Composite nasal symptom score	
	Normals (n = 10)	Allergics (n = 13)
Diluent (mg)	0.1(±0.1)	0.0(±0.0)
0.13	2.0(±0.3)**	2.5(±0.3)***
1.3	4.3(±0.4)**	4.8(±0.5)***
13	7.9(±0.4)**	7.2(±0.5)***

$**P < 0.01$, $***P < 0.001$, change in relation to baseline.

changes in blood flow in the nasal mucosa in spite of the presence of severe congestion.

Histamine acts on the tissue in two ways (19). Firstly, it acts indirectly via reflexes which cause sneezing and hypersecretion, secondly it acts directly on cellular histamine receptors causing oedema and persistent blockage. Histamine also increases epithelial permeability. Whether the increase in blood flow is reflex-mediated like sneezing (23), or is a direct effect of histamine receptors acting on blood vessels like oedema formation (23), cannot be concluded from the present study. Neither can we conclude whether the effects are mainly H_1 receptor-mediated, like the effects on the capacitance vessels (13, 16, 17) or whether a major involvement of H_2 receptors is present. Regardless of this, it becomes more apparent that the capacitance vessels and the resistance vessels in the nose seem to be independently regulated, as has been previously suggested (25).

In the present study histamine increased blood flow only after challenge with a very large dose. This could be explained by the fact that the topically administered histamine of the two lower doses only reached the surface of the mucosa (and the capacitance vessels). The Xe wash-out method, however, determines the blood flow in a deeper part of the mucosa. The highest dose might have penetrated the mucosa to the point where the Xenon measures blood flow. However, another possible explanation could be that histamine opens the A-V shunts and a histamine-induced increase in blood flow by-passing the capillary bed after the two smaller histamine doses might not be detected by the Xenon wash-out technique (30). A third possibility is of course that histamine in the two smaller doses did not actually affect the resistance vessels.

The amplitudes and forms of the Xenon wash-out curves after the two lower doses of histamine did not differ from the baseline curves, and there were no other signs that the radioisotope disappeared immediately or before the final point of the determinations.

In conclusion, histamine acted on the capacitance vessels with the expected results but had a slight or opposite effect on the resistance vessels compared to challenge with allergen. Thus, mediators other than histamine, or reflexes elicited by means other than histamine, are apparently involved in the allergic reaction.

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