

Effect of Platelet Activating Factor on the Human Nasal Mucosa

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In order to determine the effect of PAF-acether on the vascular bed in the human nose, 11 healthy volunteers were studied. Rhinomanometry was performed to determine the effect on the capacitance vessels, and the ^{133}Xe wash-out method enabled determination of the mucosal blood flow, regulated mainly by the resistance vessels. These measurements were made before and after topical administration of PAF-acether in three different doses; 0.26 μg , 2.6 μg and 26 μg per nostril. The results indicate that PAF-acether induces a dose-dependent vasoconstriction of the capacitance vessels and a reduction in mucosal blood flow. That PAF-acether should be a principal mediator in the allergic reaction in the human nose is not supported by these findings.

Key words: allergic mediator; capacitance vessels; nasal allergy; PAF-acether; resistance vessels.

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Histamine is considered to be the main mediator involved in the human nasal allergic reaction (8). This view is mainly based on the findings that histamine can mimic all the symptoms elicited in the nasal allergic reaction (1) and that anti-histamines are effective in the treatment of patients with allergic rhinitis. The role of other mediators in the human nose is unknown. This includes mediators such as neutrophil chemotactic factor (NCF), eosinophil chemotactic factor of anaphylaxis (ECF-A), platelet activating factor (PAF) as well as the membrane-derived mediators: leukotrienes and prostaglandins (7).

PAF-acether was initially described as a product of antigen-induced degranulation of basophils. However, with the elucidation of its chemical structure it has been established that in addition to basophils, thrombocytes, neutrophils and macrophages can also generate PAF-acether (12). In animal experiments several symptoms associated with acute and chronic inflammatory reactions have been shown to occur following administration of PAF-acether,

both intravenously and intratracheally (10). In the human skin, reactions similar to the wheal and flare reaction induced by allergens has been shown to occur after injection of 30–100 ng of PAF-acether, and, in addition to this acute reaction, a late reaction (hyperalgesia) was also identified (2). The reaction of the human airways to PAF-acether is not known.

The object of this study was to investigate the effect of topically administered PAF-acether on the vascular bed of the human nose.

MATERIAL AND METHODS

Experimental design

Since to our knowledge this was the first human airway challenge study with PAF, and not knowing what reactions to expect, the study was designed to be open, with rhinomanometric measurements before and after intranasal challenge with placebo and different doses of PAF-acether. In addition, nasal

mucosal blood flow determinations with a ^{133}Xe wash-out method were made before and after challenge with placebo and the same doses of PAF-acether used in the rhinomanometric measurements.

Subjects

The trial comprised 11 healthy volunteers (5 females and 6 males) between 19 and 40 years of age (mean age 32.0), none of whom had ever had any symptoms of allergic rhinitis. Five of the 11 individuals participated in both the rhinomanometric determinations and the blood flow measurements. Of the remaining six subjects, three participated in the rhinomanometric determination and three in the blood flow measurements, thus a total of eight subjects participated in both the rhinomanometric measurements and the blood flow determinations. They were free from nasal symptoms at the time of the trial and were taking no medication. Each individual was fully informed of the methods and objectives of the trial, and informed consent was obtained from each participant. Before entering the trial each subject was interviewed and subjected to a routine ENT examination. The study was approved by the Ethical Committee at the University of Göteborg.

Nasal challenge

The nasal cavity was challenged with a technique previously used for challenge with allergens and histamine (11). Using a nasal pump spray commercially available for delivering disodium-cromoglycate (DSCG) solution, a total of 0.26 ml was administered to each nostril. PAF-acether was dissolved in a stock solution of 70% ethanol. Dilutions were made with 0.9% NaCl containing 0.25% human serum albumin (pH 4.8). The placebo preparation was identical to the diluent used for the PAF-acether solutions. After a pilot study and guided by previous results from skin tests with PAF-acether (2) the following dilutions were used for challenge: 1 $\mu\text{g/ml}$, 10 $\mu\text{g/ml}$ and 100 $\mu\text{g/ml}$. These dilutions gave a total of 0.26 μg , 2.6 μg and 26 μg of PAF-acether into each nostril. Both nasal cavi-

ties were challenged in the rhinomanometric determinations.

To test the biological activity of the PAF-acether and to test the subjects' skin reactivity, intracutaneous injections of placebo or 30 ng of PAF-acether were given. These solutions were taken from the same bottles as the nasal challenges and the injection were made on the same day as the rhinomanometric determinations. Two perpendicular diameters of the induced wheal were measured 15 min after injection.

Rhinomanometry

In order to evaluate the nasal patency, posterior rhinomanometric determinations were made (Rhinoma XI, Dr Ing. Heinz Gohlke, 8251 Kirchdorf ü Dorfen, West Germany). The airflow at a pressure-drop of 1.5 cm H_2O over the nose was recorded and the nasal airway resistance was calculated. After adaptation to the testing room a baseline value was determined. A nasal challenge was made with either placebo or PAF-acether solution. The nasal patency was recorded at intervals for 180 min, or until the nasal patency had returned to the base level. At least 60 min was recorded at each challenge.

Blood flow determinations

For determinations of the nasal mucosal blood flow a recently described ^{133}Xe wash-out method was used (3). After an adaptation period, 0.1 ml of a saline solution of ^{133}Xe was injected into the nasal mucosa of the lower turbinate in one of the nasal cavities. The disappearance of the isotope was followed externally with a scintillation detector. The blood flow was then calculated from the rate of disappearance of the isotope. These measurements were made before and 15 min after challenge with either placebo or the PAF-acether solution. In four patients these measurements were also made before and 15 min after administration of 0.3 ml oximetazoline solution per nostril (1 mg/ml).

Statistical methods

For evaluation of the changes in nasal airway resistance after challenge the paired t-test was used. Wilcoxon's signed rank sum test was used for evaluation of the changes in blood flow.

RESULTS

No subjective symptoms similar to allergic nasal reactions (i.e. sneezing, nasal secretion, nasal

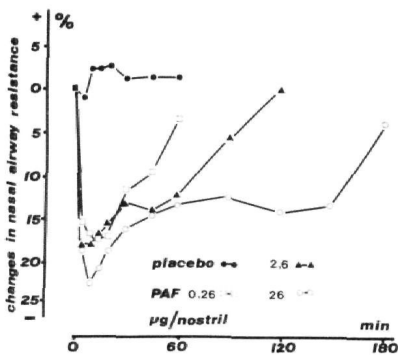


Fig. 1. Changes in nasal airway resistance after challenge with PAF-catheter and placebo. The figure shows the change in percentage of prechallenge nasal airway resistance.

Table 1

Changes in nasal airway resistance in percent from baseline following aerosol administration of PAF acether in both nostrils. Mean $\pm$ SEM

Time (min)	Placebo	0.26 µg/ nostril	2.6 µg/ nostril	26 µg/ nostril
5	-1 $\pm$ 1	-16 $\pm$ 3**	-18 $\pm$ 5**	-19 $\pm$ 5**
10	+2 $\pm$ 2	-17 $\pm$ 2**	-18 $\pm$ 5**	-23 $\pm$ 4***
15	+2 $\pm$ 1	-18 $\pm$ 4**	-17 $\pm$ 4**	-21 $\pm$ 5**
20	+2 $\pm$ 2	-17 $\pm$ 4**	-13 $\pm$ 6**	-19 $\pm$ 5*
30	-1 $\pm$ 2	-12 $\pm$ 4*	-14 $\pm$ 6*	-16 $\pm$ 5*
45	-1 $\pm$ 2	-10 $\pm$ 3*	-14 $\pm$ 5*	-15 $\pm$ 6*
60	-1 $\pm$ 1	-4 $\pm$ 3	-12 $\pm$ 6	-14 $\pm$ 6
90			-6 $\pm$ 3	-13 $\pm$ 6
120			0 $\pm$ 1	-14 $\pm$ 6*
150				-13 $\pm$ 6
180				-4 $\pm$ 2

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

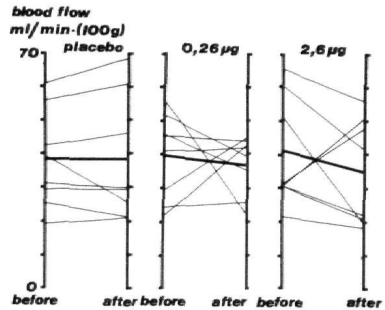


Fig. 2. Mucosal blood flow before and after challenge with placebo and two doses of PAF-acether.

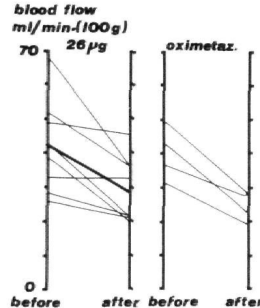


Fig. 3. Mucosal blood flow before and after challenge with 26 µg of PAF-acether and oximetazoline.

itching or nasal blockage) were experienced by any of the subjects after challenge with the PAF-acether solution.

The mean results from the rhinomanometric determinations are given in Fig. 1 and Table 1. No reaction was obtained after challenge with placebo solution. The PAF-acether solutions induced a decrease in NAR that had a tendency to be dose-dependent but no statistically significant differences were obtained between the different doses of PAF-acether. However, there were statistically significant differences from baseline values as shown in Table 1. The changes in blood flow after challenge are presented in Figs. 2 and 3. PAF-acether in the highest dose used (26 µg/nostril) gave a 25% reduction of mucosal blood flow. Oximetazoline resulted in a 50%

reduction in the blood flow, which is consistent with a previous report (3). The reduction of blood flow was statistically significant for 26 μg of PAF-acether ($P < 0.05$).

Skin injections of placebo gave no reaction. The area of the wheal obtained after PAF-acether injections as calculated from two perpendicular diameters was $64.8 \pm 7.4 \text{ mm}^2$ (mean $\pm$ SEM).

DISCUSSION

The role of different mediators in allergic reactions in the nose are not clear, except in the case of histamine. It has been suggested that PAF-acether is a mediator of acute allergic reactions (4). The basis for this suggestion is the abundant evidence from animal studies (see 4 for references) showing release of PAF-acether in allergic processes and also that PAF-acether can induce symptoms similar to those in an acute IgE-mediated reaction (10). Furthermore, it has been shown that intratracheal administration of PAF-acether in baboons (60 $\mu\text{g}/\text{kg}$) can produce a bronchoconstriction similar to an asthmatic bronchoconstriction (4).

Our findings with intracutaneously injected PAF-acether are consistent with previous findings (2, 9). However, intranasally administered PAF-acether did not produce the expected mucosal swelling. On the contrary, NAR and the mucosal blood flow decreased with increasing dose. The observed decrease in NAR differs from that found after nasal allergen challenge, when an increase in NAR is obtained (11). On the other hand, the decrease in mucosal blood flow observed is consistent with the findings of Bende (3) that there was a decrease in mucosal blood flow 15 min after allergen challenge in the nose. Reduction of mucosal blood flow in the nose after allergen challenge was previously suggested by Ingelstedt & Rundcrantz (6). They based their suggestion on indirect evidence. They found that treatment with low molecular weight dextran (Rheomacrodex®) decreased the allergen-induced congestion of the nasal mucosa.

The present finding of a decrease in NAR conflicts with the findings in the lower airway

of baboons, where intratracheal administration of PAF-acether induced an acute bronchoconstriction (4). Changes in bronchial airway resistance may involve changes in the tone of the bronchial smooth muscle as well as in the state of congestion of the bronchial mucosa. These two components cannot be separated as it is the sum of the changes which is measured. If an increase in tone is obtained in both these muscular components (bronchus and vascular wall), in theory all possible reactions can be obtained, i.e. an increased, decreased or unchanged airway resistance. In nasal challenge only the mucosal reaction is tested. This circumstance might be one explanation for the different findings in this study compared with bronchoconstriction in baboons (5). Another possibility is that the reactions are species dependent.

The dosage of PAF-acether may also be an important consideration. Up to now the amount of PAF-acether elicited at antigen challenge in humans is unknown. Thus, the doses used in the present study may be totally unrelated to the physiological concentrations. However, in a pilot study with a limited number of patients lower doses of PAF-acether, from 0.26 ng up to 26 ng produced no change in NAR. For histamine it has been shown that a dose 100 times that which produce a wheal and flare reaction when administered subcutaneously, produces a marked increase in NAR, as well as the other symptoms associated with nasal allergy when given intranasally (1). The doses used in the present study for intranasal challenge with PAF-acether were about 10, 100 and 1000 times the dose shown to produce a wheal and flare reaction in the human skin.

This study does not support PAF-acether as being a major mediator in the acute inflammatory reaction, as challenge with PAF-acether produced a decrease in NAR and mucosal blood flow in the nose and no symptoms similar to those following allergen challenge.

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