

Short communication

Plasma histamine and bronchial reactivity in allergic asthma

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Histamine is an important mediator of allergic inflammation and bronchial hyperresponsiveness (BHR), a hallmark of asthma. Studies on the relationship between plasma histamine and BHR in allergic asthmatic patients have yielded controversial results. We therefore measured plasma histamine and bronchial reactivity in 30 nonsmoker volunteers taking no medication. Eleven were normal subjects; 19 were stable, mildly allergic asthmatic patients. Venous blood was taken to measure blood cells and basal plasma histamine by radioimmunoassay. After blood sampling, all subjects underwent a measurement of PC₂₀M (concentration of methacholine causing a 20% fall in FEV₁). Mean plasma histamine levels were 0.21 ± 0.1 ng/ml and 0.44 ± 0.3 ng/ml in normal and asthmatic subjects, respectively ($P < 0.05$). We found a significant increase of blood eosinophils and basophils in asthmatic patients, and a positive correlation between plasma histamine and circulating basophils. PC₂₀M was greater than 16 mg in normal volunteers, and mean PC₂₀M was 2.1 ± 2 mg/ml in asthmatic patients. PC₂₀M did not correlate with plasma histamine levels, but it did so negatively with blood eosinophils. The increased plasma histamine concentration in mildly atopic asthmatic patients might be a consequence of the high basophil releasability of atopics and the higher basophil counts in allergic asthma. Plasma histamine is thus unlikely to be a determinant of BHR in asthma.

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Histamine is a major mediator of allergic inflammation and bronchial hyperresponsiveness (BHR), a common hallmark of asthma. An increase of plasma histamine has been found in diseases associated with a degranulation of mast cells or basophils. Stable asthmatic patients are found to have higher histamine plasma levels than nonasthmatic control subjects (1, 8).

Studies on the relationship between plasma histamine and BHR in allergic asthma have yielded controversial results. Howarth et al., using a radioenzymatic assay, showed a relationship between nonspecific airway reactivity and resting plasma histamine levels in allergic asthmatic patients (5). In contrast, Phillips et al., using the same method, did not find a significant correlation between these two indicators (10). However, fluorometric or radioenzymatic methods of histamine determination are tedious and time-consuming, and they do not always

give reproducible results among laboratories. A sensitive and specific method of histamine determination based on a radioimmunologic assay with monoclonal antibodies (7, 8) has recently become available.

The purpose of this study was to reevaluate by this new method the relationship between plasma histamine and airway reactivity in stable, mildly allergic asthmatic patients.

Subjects and methods

Thirty nonsmoker subjects (7 women, 23 men), aged 17-46 years (mean $\pm$ SD: 25.8 ± 6.2 years), volunteered for this study. Nineteen were stable, mildly allergic asthmatic patients (mean age $\pm$ SD: 27.4 ± 6.8 years) requiring no medication. They were atopic by history and had positive skin tests and RAST. Their base-line FEV₁ were within normal

limits with a mean value ($\pm$ SD) of $100.5(\pm 8.4)\%$ of predicted values. Eleven healthy subjects (mean age $\pm$ SD: 24 ± 2.8 years) served as controls. They had normal pulmonary function and no allergic background on the basis of history and negative skin tests for a battery of the most common inhalant allergens.

The subjects attended the laboratory on one occasion at the same time of the day (0900), outside the pollen season. An intravenous cannula was inserted into the brachial vein for blood sampling, and the patients were then allowed to rest for 30 min. Venous blood (10 ml) was collected before methacholine challenge in two cold tubes containing EDTA. The first tube was immediately centrifuged (1500 g) at 4°C for 10 min, and the upper part of the plasma supernatant was carefully collected and stored at -20°C until analysis. Histamine was measured by a specific and sensitive radioimmunoassay (Immunotech, Marseille, France) (7, 8). Its sensitivity was 0.1 ng/ml, with, in our hands, intra- and interassay coefficients of variation of 7% and 11%, respectively. The second blood sample served for cell counts (total and differential) by an automatic hemacytometer (Technicon HI).

Bronchial reactivity was measured by the method described by Cockcroft et al. except that methacholine was used instead of histamine (3). Aerosols of methacholine in phosphate-buffered saline (from 0.032 to 16 mg/ml) were generated by a Hudson's nebulizer (airflow 8 l/min, output 0.3 l/min). The provocative concentration (PC_{20}M) required to produce a fall in FEV_1 of 20% from the base-line value was calculated by linear interpolation on the dose-response curve.

Results are given as mean $\pm$ standard deviation (SD). We used a logarithmic transformation (base 10) of the PC_{20}M to account for the abnormal distribution of this measure. Regression analysis and unpaired Student's *t* test were used. Any value of $P < 0.05$ was considered to be significant.

Results

As shown in Table 1, mean plasma histamine levels were, respectively, 0.21 ± 0.1 ng/ml and

Table 1. Basal plasma histamine, blood eosinophil and basophil counts, and PC_{20}M in normal and mildly allergic asthmatic subjects

	Normal (<i>n</i> = 11)	Asthmatic (<i>n</i> = 19)
Histamine (ng/ml)	0.21 ± 0.1	$0.44 \pm 0.3^*$
Eosinophils (/mm ³)	93.6 ± 61.2	$395.7 \pm 238.6^{**}$
Basophils (/mm ³)	32.9 ± 11.6	$60.6 \pm 29.3^{**}$
PC_{20}M (mg/ml)	> 16	2.1 ± 2

* $P < 0.05$; ** $P < 0.01$.

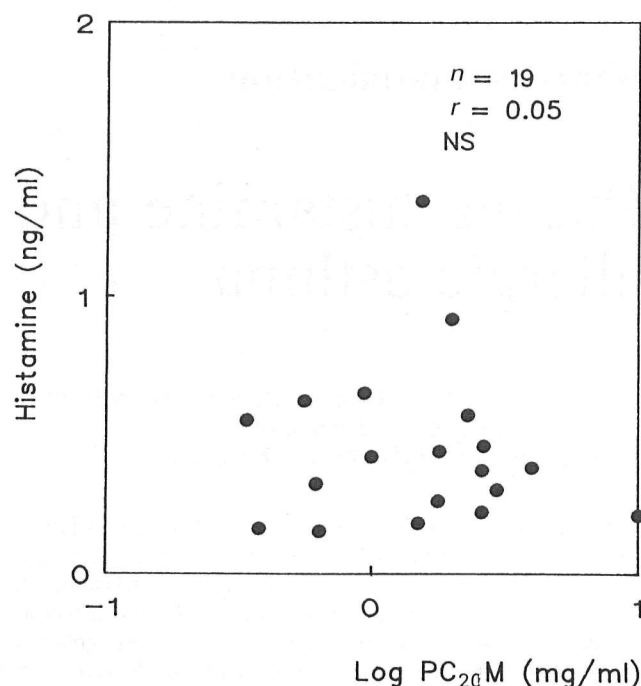


Fig. 1. Basal plasma histamine and bronchial hyperresponsiveness (log PC_{20}M) in 19 allergic asthmatic patients.

0.44 ± 0.3 ng/ml in normal subjects and allergic asthmatic patients ($P < 0.05$). As expected, we found a significant increase of blood eosinophils and basophils in asthmatic patients, as compared with normal subjects (Table 1). There was a significant positive quadratic relationship between base-line plasma histamine and circulating basophils ($r = 0.53$; $P < 0.01$).

PC_{20}M was greater than 16 mg in all normal volunteers and was, on average, 2.1 ± 2 mg/ml in asthmatic patients. As shown in Fig. 1, there was no correlation between log PC_{20}M and basal plasma histamine levels in the 19 allergic asthmatic patients studied. In contrast, we found in this group of patients a significant inverse linear correlation between blood eosinophil counts and log PC_{20}M ($r = -0.48$; $P < 0.05$).

Discussion

Our results showing an increased plasma histamine and a positive correlation with blood basophil counts in mildly allergic asthmatic patients with normal ventilatory function confirm previous data (1, 2, 8). It has been reported that circulating blood basophils of asthmatic patients release more histamine than those of normal subjects with or without immunologic stimulation (4, 6, 9). It can therefore be speculated that the higher basal plasma histamine in mildly allergic asthmatic patients could be the consequence of an increase in releasability and number of basophils.

This study is the first of its kind to investigate the correlation of plasma histamine and BHR by a sensitive and specific radioimmunologic method of histamine determination. Our results showing no correlation between BHR and basal plasma histamine agree with another study which was performed by the radioenzymatic method (10), but they contrast with yet another study (5) in which many patients were symptomatic and required regular medication. Subject differences could account for the differences between these studies.

The lack of correlation between plasma histamine and BHR is not surprising, because it is commonly admitted that the causality underlying BHR is multifactorial. In conclusion, our results suggest that basal plasma histamine is unlikely to be a determinant of bronchial hyperresponsiveness in asthma.

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