

Nasal Challenge with Serotonin and Histamine in Normal Persons

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In order to study the nasal response to serotonin, 14 normal persons, in a double-blind study, were provoked in the nose with serotonin and histamine. Itching and the number of sneezes were noted, the amount of secretion measured, and nasal airway resistance recorded by active posterior rhinomanometry. Serotonin induced significant nasal itching, sneezing and hypersecretion, similar to the effects of histamine. The effect of serotonin on nasal airway resistance, on the other hand, was slight (+10 %) and insignificant in contrast to that of histamine in equipotent doses (+48 %) ($P < 0.001$). In conclusion, we have shown that serotonin provocation can induce a rhinitis response in the human nose. The nasal symptoms suggest an effect on sensory nerves with reflex-induced sneezing and hypersecretion, while there appears to be little direct effect on capacitance vessels. The possible role of serotonin as a mediator of rhinitis remains speculative.

Key words: histamine; rhinitis; serotonin.

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The role of serotonin in asthma and rhinitis is largely unknown. Some investigators have reported a moderate fall in lung function parameters after inhalation of serotonin in asthmatic subjects (1, 5), while others have been unable to confirm this observation (6, 7). In a recent study we did not find any significant change in FEV₁ and FVC in 23 asthmatic patients after inhalation of 20 mg serotonin (11). It was noted, however, that a number of the patients sneezed and produced nasal discharge after inhalation of serotonin from a face mask. The aim of the present study is to confirm this observation in a controlled setting and to compare the effect of serotonin with that of histamine in the normal human nose.

MATERIAL AND METHODS

Volunteers

Fourteen normal volunteers participated in the study. The mean age was 28.7 years (range, 16-

46); 7 were males and 7 females. None had a history of atopic disease, perennial rhinitis or chronic symptoms from the airways, neither had they had a common cold during the last 2 weeks. They did not use any medicine. Six were light smokers (mean: 5 cigarettes, range: 1-8 daily).

Provoking agents

Histamine chloride (histamine) (MW 184) in a phosphate buffer was used in three concentrations, 0.1 mg/ml, 0.5 mg/ml and 2.5 mg/ml; pH was measured to 7.34, 7.33 and 7.01, respectively, and the osmolarity calculated to 269, 276 and 304 mOsm.

Serotonin creatinine sulphate (serotonin) (MW 380) (Sigma Chemicals) in a phosphate buffer was used in three concentrations, 0.8 mg/ml, 4 mg/ml and 20 mg/ml; pH was measured to 7.34, 7.08 and 5.82, respectively, and the osmolarity calculated to 240 mOsm for all dilutions.

The dilutions were made immediately before the trial and stored at 5°C during the 8 days' study period. In an earlier study we found no loss of serotonin activity over a 1-week period (11). Preservatives were not used. The solutions were filtered through a Millipore filter before use.

The solutions for nasal provocation were filled on metered-dose pump sprays, which delivered 0.075 ml per actuation (Glaxo, Ware, UK). All sprays were coded by a person who did not participate in the trial, which was undertaken with a double-blind design.

Nasal challenge

The two provocation tests were carried out at the same time of the day with 1 week's interval. Serotonin and histamine were used in a randomized order. Each provocation was started with a phosphate buffer (pH 7.41; 240 mOsm), one puff into each nostril. Increasing doses of serotonin or histamine were then given with 15 min interval, one puff into each nostril. The amounts of serotonin used for the provocation test were calculated to 120 µg, 600 µg and 3,000 µg, and those of histamine to 15 µg, 75 µg and 375 µg.

To measure the nasal airway resistance (NAR) we used a standard method of active posterior rhinomanometry, as described earlier (2, 10). A computer was added to calculate the mean NAR of five consecutive respiration curves (10). Measurement of NAR was performed in duplicate immediately before, 5 and 15 min after the provocation. The mean of two tests was used. In a 5-min period just after provocation the patient bent his head forward, and after 5 min blew his nose into a funnel, to collect the secretions. The amount of secretions were measured (mg). In the 5-min period after provocation the patient scored itching in the nose on a 10 cm visual analogue scale and counted the number of sneezes. After each period the patient was asked about heating, flushing, headache, and other adverse symptoms.

Statistical methods

Wilcoxon's sign rank test for paired data was used for itching score, number of sneezes and

amount of secretion. A paired t-test was used for changes in NAR, because these values appeared to be approximated to a normal distribution.

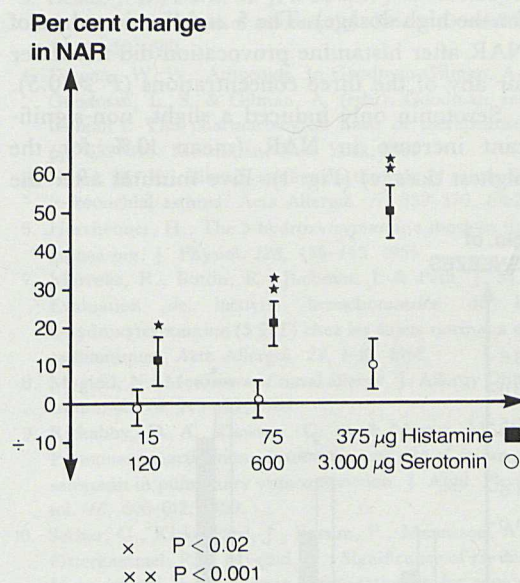


Fig. 1. Mean per cent changes in nasal airway resistance (NAR) in 14 normal persons after serotonin and histamine nasal provocation ($\bar{x} \pm \text{SEM}$).

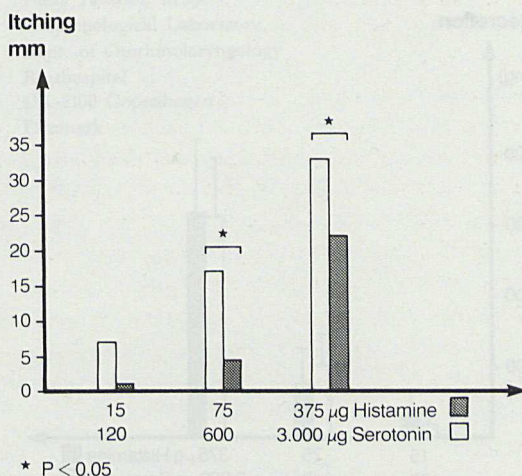


Fig. 2. Mean itching score in mm in 14 normal persons after serotonin and histamine nasal provocation.

RESULTS

The post-saline baseline NAR values before histamine and serotonin provocation were similar (29.6 ± 6.8 and 30.2 ± 5.7 , mean $\pm$ SD). There was a dose-dependent increase in NAR after histamine provocation (mean 48 % for the high dosage). The 5 and 15 min values of NAR after histamine provocation did not differ for any of the three concentrations ($P > 0.5$).

Serotonin only induced a slight, non-significant increase in NAR (mean 10 % for the highest dosage) (Fig. 1). Five minutes after the

highest serotonin concentration was given four patients had a transient mean increase in NAR of 38 %, but the 15-min values showed only an increase in NAR of 18 %.

Itching and sneezing occurred within seconds following both histamine and serotonin challenge. Fig. 2 shows that these symptoms increased in a dose-dependent manner.

All patients produced measurable amounts of secretions after serotonin challenge, while three patients had none after histamine challenge. The amounts of nasal secretions after these two types of challenge were not significantly different (Fig. 3).

By using linear regression analysis we have calculated the line of identity between the response to histamine and to serotonin provocation. The response to 100 μ g histamine is equipotent to 791, 629 and 518 μ g serotonin with regard to secretion, itching and sneezing. When the above doses are given as equimolar doses, the difference in response between histamine and serotonin is reduced from 5.2–7.9 times to 2.5–3.8 times.

Concerning side effects, two persons felt a slight sensation of heat in the face and two others had a headache after 375 μ g histamine. After 3,000 μ g serotonin three felt a pulsating sensation inside the nose and three others got headache. Some of the volunteers stated that itching was felt more "irritating" after serotonin as compared with histamine.

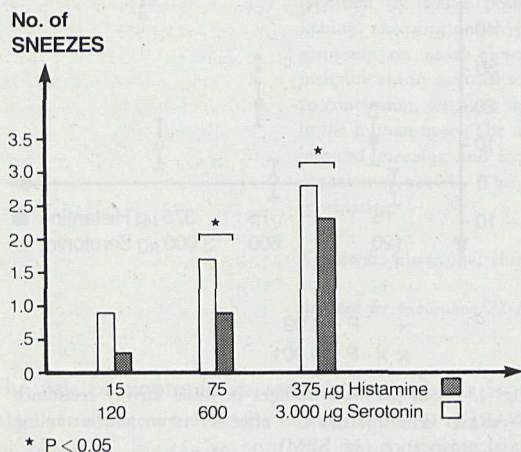


Fig. 3. Mean number of sneezes in 14 normal persons after serotonin and histamine nasal provocation.

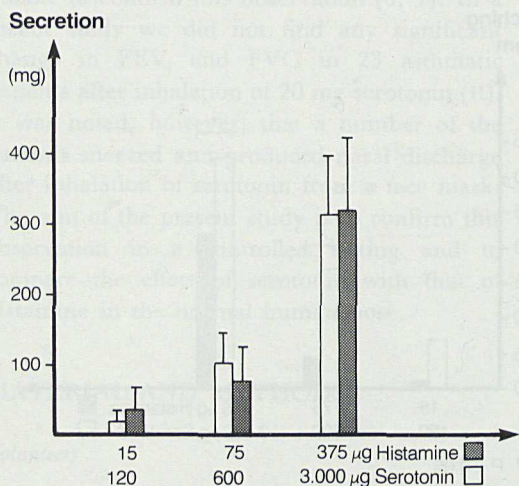


Fig. 4. Mean secretory response in mg after histamine and serotonin nasal provocation in 14 normal persons ($\bar{x} \pm$ SEM).

DISCUSSION

Our preliminary observation (11) that serotonin can produce rhinitis symptoms has been confirmed in the present controlled study. The effect of equipotent doses of serotonin and histamine applied in the nose seems to produce itching, sneezing and hypersecretion in largely similar proportions, while only histamine induces a significant increase in NAR. The mode of action of serotonin in the nose could be through the sensory nerve endings, because itching, sneezing and hypersecretion are the typically reflex-mediated nasal symptoms. The prompt reaction after serotonin application also points to a reflex effect. It has been

proposed that the histamine-induced reflex-mediated symptoms from the nose are through specific H_1 -receptors associated with the sensory nerve endings, because the effect can be blocked by a topical H_1 -antihistamine (10). Because serotonin produced almost the same reflex-mediated symptoms as histamine, it is possible that serotonin acts on the H_1 -receptors, or in a more unspecific way on the nerve endings. Another purely hypothetical possibility is the presence of serotonin receptors in the nose.

The maximal doses of both histamine and serotonin used in this study are supraphysiological, and one has to be careful, when considering any pathophysiological significance of serotonin in rhinitis. Serotonin has a well-known effect on blood vessels (4), usually it constricts veins (3, 9) but its effect depends on the concentration and on the type of blood vessel and organ studied (4). Because the NAR did not change significantly after serotonin in the nose, a direct effect on the capacitance vessels (venoles, veins and cavernous sinusoids) seems unlikely.

In contrast to the present findings in the nose we observed no change in lung function nor in subjective symptoms after bronchial challenge with serotonin (20 mg) in asthmatics (11). This could point to a difference between the bronchi and nose regarding irritant receptors, and the role of reflexes (8).

In conclusion, our study has shown that serotonin induces rhinitis symptoms suggesting stimulation of irritant receptors in the nose. Further studies are in progress concerning the possible pathophysiological role of serotonin in rhinitis.

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