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# Nasal reactivity to histamine and methacholine: Two different forms of upper airway responsiveness*

R. Gerth van Wijk, P.H. Dieges

Department of Allergology, University Hospital, Rotterdam, The Netherlands

SUMMARY

*In 44 subjects (healthy controls and patients with allergic, non-allergic or infectious rhinitis) we compared nasal histamine and methacholine responsiveness. A weak correlation between histamine- and methacholine-induced secretion was found ($r=0.34$; $p=0.02$), in contrast to the highly significant asssociation between secretion and sneezes induced by histamine ($r=0.78$; $p<0.0001$). Our observations suggest that histamine and methacholine responsiveness represent different forms of upper airway hyperreactivity. The contribution of glandular responsiveness as measured by methacholine challenge and the involvement of irritant receptors or reflexes as measured by histamine provocation may vary between individuals.*

*Key words: allergic rhinitis, histamine, methacholine, nasal challenge*

## INTRODUCTION

Nasal challenge tests with histamine and methacholine have been performed in patients with allergic (Britton et al., 1978; Okuda et al., 1983; Asakura et al., 1984; Druce et al., 1985; Doyle et al., 1990) and non-allergic rhinitis (Borum 1979; Clement et al., 1985). In analogy to bronchial asthma rhinitis patients may have an increased responsiveness to non-specific stimuli compared with normal subjects, although a considerable overlap in responsiveness to histamine and methacholine limits the diagnostic value of these tests (Pipkorn 1989).

It is well known that histamine and methacholine may have different effects on the nose. Histamine leads to vasodilation and increased vasopermeability resulting in nasal congestion (Britton et al., 1978; Doyle et al., 1990). Histamine-induced nasal discharge is believed to be caused by both transudation and glandular secretion (Raphael et al., 1989). This glandular secretion may involve direct stimulation of histamine receptors and indirect stimulation via a nasonasal reflex. The involvement of reflexes is also demonstrated by the induction of sneezes after histamine application (Okuda et al., 1983; Doyle et al., 1990). Methacholine has a direct effect on glands only (Borum 1979, Raphael et al., 1988).

In the past few years, we have investigated the effect of non-specific stimuli on the nasal mucosa in a series of studies (Gerth van Wijk et al., 1987, 1989, 1991). In a number of patients and healthy subjects both histamine and methacholine challenges were performed, so we were able to compare nasal responsiveness to both agents.

Comparison of histamine and methacholine responsiveness may yield information on the pathophysiological background of nasal hyperreactivity because of the different sites in the nasal mucosa (i.e. nasal glands, irritant receptors and nasal vasculature) on which histamine and methacholine have an effect.

## MATERIAL AND METHODS

### *Subjects*

In earlier studies healthy subjects, allergic and non-allergic rhinitis patients were compared with respect to responsiveness to non-specific stimuli (Gerth van Wijk et al., 1987, 1991). The data obtained from 17 healthy controls (9 males and 8 females; median age and range: 25 and 19-31 years, respectively), 11 patients with allergic perennial rhinitis (6 males and 5 females; median age and range: 25 and 21-35 years, respectively), 15 patients with chronic or recurrent infectious rhinitis (5 males and 10 females; median age and range: 31 and 20-54 years, respectively) and 17 patients with non-allergic perennial rhinitis (10 males and 7 females; median age and range: 33 and 11-55 years, respectively) were re-analysed. All healthy subjects, 10 allergic rhinitis patients, 8 subjects with non-allergic rhinitis and 9 patients with infectious rhinitis had ondergone a histamine and methacholine challenge test as well. The reason why not all patients were tested with both histamine

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and methacholine was that some subjects were not able to undergo the two tests because of lack of time.

The selection of the subjects has been described in earlier reports (Gerth van Wijk et al., 1987, 1991). Healthy subjects were characterized by the absence of nasal symptoms and skin reactions to a panel of intradermal skin tests with aero-allergens (i.e. pollen, mites, animal dander and moulds).

Selection of patients with allergic perennial rhinitis was based upon a history of long-standing nasal symptoms such as sneezing, rhinorrhoea and nasal blockage. Moreover, they showed skin reactions to a low concentration (1 Noon unit/ml) of house dust mite extract (Diephuis, Groningen, the Netherlands). Allergen-specific IgE (RAST class 3 or 4; Phadebas RAST, Pharmacia, Sweden) to house dust mites could be found in serum.

Patients with non-allergic perennial rhinitis also had long-standing nasal symptoms, the symptoms having been present for at least one year. All patients were negative to a panel of routine skin tests.

The selection of patients with recurrent or chronic infections was based upon their history: they all experienced episodes of purulent discharge. The diagnosis of recurrent or chronic infections was mostly made by referring ENT specialists. According to a symptom score used in the week before the tests a majority of patients had a period of nasal purulent discharge in this period. None of the patients had skin tests positive to a routine series of inhalant allergenic extracts.

The studies were approved by the Ethical Committee of the University Hospital and Medical Faculty, Erasmus University, Rotterdam. All participants gave their informed consent before taking part in the study.

*Agents*

Histamine phosphate was used in the following concentrations: 0.25, 0.5, 1, 2, and 4 mg/ml. Methacholine bromide was used in the concentrations of 8, 16, 32, and 64 mg/ml.

*Nasal provocation tests*

Nasal challenge tests were performed as described previously (Gerth van Wijk et al., 1987, 1991). In the case of the patients, medication was withheld for 2 days before the test. Topical corticosteroids or long-lasting antihistamines had not been used. Except for the patients with infectious rhinitis, airway infections during the 2 weeks preceding the tests had been excluded.

On each occasion subjects waited 30 min before the test to allow the nasal mucosa to become acclimatized. After rhinoscopy a control solution (phosphate-buffered saline containing 0.03% human serum albumin and 0.05% benzalkonium chloride) was sprayed into the nostrils with a nasal pump spray delivering a fixed dose of approximately 0.125 ml of the solution. After provocation with the control solution, increasing doses of histamine phosphate or methacholine were applied in both nostrils. The interval between each dose was 5 min during the histamine challenge tests and 15 min during the provocation with methacholine. The interval between histamine and methacholine challenge was one day.

After each provocation with histamine the subject was asked to bend forward and to collect secretion in a syringe-equiped funnel, using the method introduced by Borum (1979). Sneezes were counted and just before the next provocation the NAR was measured using a passive anterior rhinomanometer (Heyer PAR).

When methacholine was used, secretion only was collected. The area under the curve (AUC) of histamine and methacholine response relationships were chosen as primary response variables of these tests. In an earlier study (Gerth van Wijk et al., 1989) it was demonstrated that the total amount of secretion or the number of sneezes (i.e. the AUC) induced by histamine was highly reproducible. Also, challenges with methacholine as described by Borum (1979) yielded a good reproducibility.

*Statistical analysis*

All calculations were made with a commercially available statistical package (STATA). For comparison of response variables a Spearman rank correlation was computed, evaluated at $p < 0.05$.

## RESULTS

In 44 subjects both histamine and methacholine challenges were performed. The secretory response to both agents appeared to be significantly associated (overall $r=0.34$, $p=0.02$; Figure 1). However, when subjects were divided into healthy controls, patients with allergic, non-allergic, and infectious rhinitis, the secretory response to histamine and methacholine was significantly correlated in the healthy subject group only (Table 1). In contrast to these weak or absent correlations, the secretory response to histamine was highly correlated with the

Table 1. Comparison between the secretory response to methacholine and histamine (Spearman's rank correlation).

| group | r | p | n |
|---|---|---|---|
| all subjects | 0.34 | 0.02 | 44 |
| healthy controls | 0.66 | 0.004 | 17 |
| allergic rhinitis | 0.05 | 0.88 | 10 |
| non-allergic rhinitis | -0.19 | 0.66 | 8 |
| infectious rhinitis | 0.52 | 0.15 | 9 |

Table 2. Comparison between the summed amount of secretion and the number of sneezes and the summed NAR generated by histamine (Spearman's rank correlation coefficient with p-value between parentheses).

| group | secretion and sneezes | secretion and NAR | sneezes and NAR |
|---|---|---|---|
| all subjects (n=60) | 0.78 ($p<0.0001$) | 0.14 ($p=0.14$) | 0.12 ($p=0.34$) |
| healthy controls (n=17) | 0.72 ($p=0.002$) | 0.29 ($p=0.27$) | 0.08 ($p=0.77$) |
| allergic rhinitis (n=11) | 0.58 ($p=0.06$) | -0.17 ($p=0.61$) | 0.18 ($p=0.60$) |
| non-allergic rhinitis (n=17) | 0.90 ($p<0.00001$) | 0.23 ($p=0.37$) | 0.19 ($p=0.46$) |
| infectious rhinitis (n=15) | 0.55 ($p=0.04$) | 0.21 ($p=0.21$) | -0.19 ($p=0.5$) |

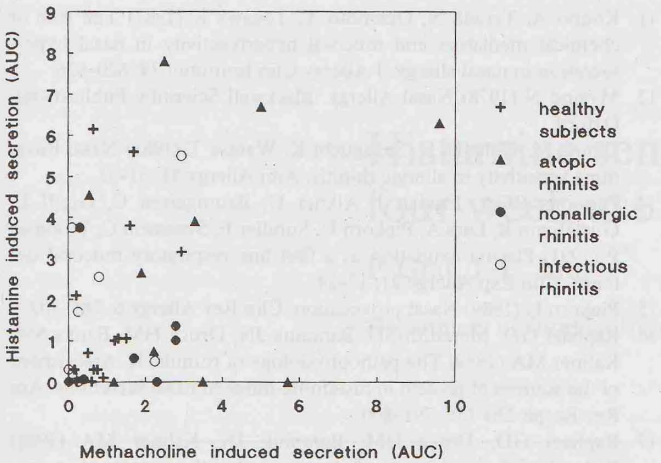


Figure 1. Comparison of total amounts of secretion (in ml; AUC or area under the dose-response curves) generated by methacholine and histamine, respectively ($r=0.34$; $p=0.02$; $n=44$).

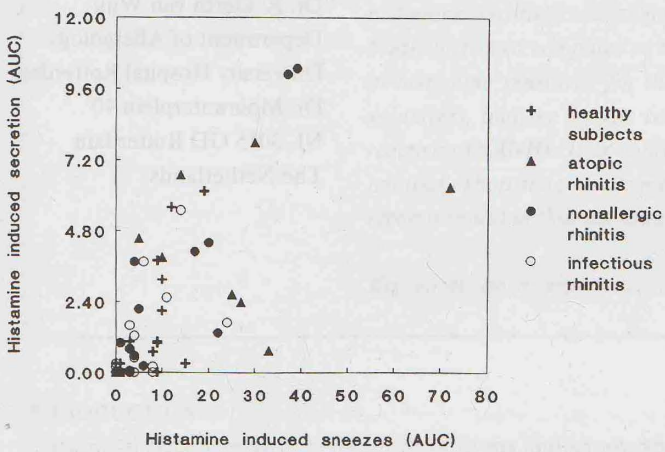


Figure 2. Comparison of total amount of secretion (in ml) and number of sneezes induced by histamine ($r=0.78$; $p<0.00001$; $n=60$).

number of sneezes elicited by histamine in the pooled groups ($r=0.78$, $p<0.00001$; Figure 2) and in the separated groups (Table 2). This correlation was not seen, when the AUC of NAR/dose-response relationships were compared with the number of sneezes or amount of secretion generated by histamine (Table 2).

## DISCUSSION

Although histamine and methacholine have different effects on the nasal mucosa, comparative studies of their effects in the same subjects are scarce. Doyle et al. (1990) provoked volunteers with and without allergy with several mediators. He demonstrated a nasal congestive response elicited by prostaglandin $D_2$>histamine>bradykinin>methacholine. Histamine induced larger amounts of secretion compared with other substances, and only histamine provoked sneezing.

In this study we demonstrated that histamine and methacholine responsiveness are only weakly associated. In fact, the statistically significant association in all subjects is caused by a good correlation in the healthy subject group, which can be distinguished from other groups by its low responsiveness to both agents.

The close association between histamine-induced nasal secretion and sneezes suggests that in contrast with the glandular stimulation by methacholine, nasal reflexes may play an important part in the secretory response to histamine.

The strong association between sneezes and secretion may confirm the results obtained by others (Konno et al., 1979, 1987; Raphael et al., 1989), who demonstrated the involvement of nasonasal reflexes as one-sided nasal challenge with histamine-induced contralateral secretion. This secretion could be suppressed by dissection of the vidian nerve (Konno et al., 1979, 1987). The contribution of transudation in histamine-induced secretion in this study could not be estimated as albumin and total protein were not measured. The absence of correlation between NAR and other symptoms may point at the different sites of action of histamine. On the other hand, correlations may be affected as histamine-induced NAR is a less reproducible response variable than reflex-mediated symptoms are (Gerth van Wijk et al., 1989).

In an earlier study we showed that nasal challenge with histamine may discriminate between healthy subjects and patients with allergic rhinitis, provided the secretory response and sneeze reaction are chosen as response variables (Gerth van Wijk et al., 1987). Methacholine was suitable to distinguish healthy subjects not only from atopic rhinitis patients, but also from non-allergic rhinitis patients characterized by symptoms of rhinorrhoea and sneezes (Gerth van Wijk et al., 1987, 1991).

The pathophysiology of nasal hyperreactivity, however, appears to be complex. The concept that increased epithelial permeability is a cause of nasal hyperreactivity (Mygind, 1978) has been questioned by Perssons et al. (1991), who showed that the influx of particles from the nasal cavity through the nasal mucosa is not increased in rhinitis patients. Instead, they put forward the hypothesis that plasma exudation may form a nasal barrier to noxious stimuli.

In this study we not only demonstrated a large variation in responsiveness to non-specific stimuli, we also observed individual differences in reaction pattern to various stimuli. Some subjects may have a marked nasal reaction to histamine without responsiveness to methacholine, suggesting that reflexes are more important than glandular responsiveness, while others show glandular secretion after methacholine stimulation without important involvement of reflexes (i.e. histamine responsiveness). If increased epithelial permeability is the major cause of nasal hyperreactivity, the association between histamine and methacholine sensitivity would be better than the correlation we observed.

In conclusion, nasal reactivity to non-specific stimuli is characterized by involvement of nasal glands and reflexes. However, the contribution of glandular responsiveness as measured by methacholine challenge and the involvement of irritant receptors or reflexes as measured by histamine provocation may vary between individuals.

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Dr. R. Gerth van Wijk
Department of Allergology
University Hospital Rotterdam
Dr. Molewaterplein 40
NL-3015 GD Rotterdam
The Netherlands