Hot, Humid Air Partially Inhibits the Nasal Response to Allergen Provocation

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Background: We have previously reported that preconditioning allergic subjects with hot, humid air (HHA) (temperature, 37°C; relative humidity >95%) in an environmental chamber resulted in partial inhibition of the early response to nasal allergen challenge.

Objective: To investigate whether this inhibitory effect could be achieved by inhalation of HHA via a face mask.

Design: Randomized, 4-way crossover study.

Subjects: Eighteen subjects with seasonal allergic rhinitis participated in the study outside of their allergy season.

Interventions: Subjects underwent preconditioning with room air (RA) (temperature, 25°C; relative humidity <20%) or HHA either in a chamber or delivered via a face mask for 1 hour prior to and during nasal challenge with diluent for the allergen extract followed by 2 increasing doses of allergen.

Results: Net changes from diluent challenge for all parameters were compared between HHA and RA in each delivery method. Hot, humid air delivered by mask significantly inhibited the mean±SEM number of allergen-induced sneezes (HHA, 2.7±0.6; RA, 6.6±2.1; P=.03), congestion score (HHA, 2.3±0.5; RA, 3.4±0.5; P=.01), and secretion weights (HHA, 26.9±4.4 mg; RA, 38.6±5.0 mg; P=.048). However, HHA inhaled in a chamber significantly inhibited only the mean±SEM allergen-induced congestion (HHA, 1.2±0.4; RA, 3.6±0.6; P=.002) and pruritus (HHA, 0.7±0.3; RA, 2.3±0.5; P=.002) scores.

Conclusions: Preconditioning the nasal mucosa with HHA partially decreases the early response to nasal challenge with antigen irrespective of the administration technique. The secretory response, however, is only inhibited by localized delivery of HHA to the nose. The inhibitory effects of HHA are therefore probably related to local changes in the nasal mucosa and are not dependent on total body exposure to HHA.

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Several investigators have studied the effect of hot, humid air (HHA) (temperature, 37°C; relative humidity >90%) on the nasal mucosa. Previous studies have demonstrated the beneficial effect of HHA on nasal symptoms in patients with the common cold and allergic rhinitis, although other studies have failed to show a beneficial effect of HHA inhalation on these conditions. Objective evidence of increased nasal patency after HHA exposure compared with room air (RA) exposure in both allergic and healthy subjects has also been reported.

Johnston et al found that local nasal hyperthermia reduced allergen-induced nasal blockage and vascular leakage, but had no effect on sneezing, rhinorrhea, or tryptase levels. In a similar study using allergen provocation, Jankowski et al demonstrated that preconditioning allergic subjects with HHA in an environmental chamber led to significant reductions in antigen-induced vascular permeability as measured by levels of N-alpha-tosyl-l-arginine methyl esterase and albumin when compared with preconditioning in normal (temperature, 22°C; relative humidity, 50%) or cold, dry (temperature, 4°C; relative humidity, 30%) environments.

Desrosiers et al found that exposure to HHA minimally affected the response to nasal challenge with histamine. Thus, the previously reported decrease in the early nasal response to antigen challenge after HHA preconditioning did not result from decreased end-organ sensitivity to histamine but probably resulted from reduction in mast cell activation or from a direct effect on the nasal vasculature.
SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Eighteen volunteers with a history of seasonal allergic rhinitis were recruited (10 men and 8 women aged 19-38 years; mean age, 24 years). Their allergic status was confirmed by history and positive skin puncture test results for either ragweed or timothy grass. All subjects had previously reacted to nasal challenge with allergen by sneezing 2 or more times and by a 2-fold or more increase in the weight of generated nasal secretions compared with the weight of those obtained after diluent challenge (4% phenol-buffered saline; Bayer Corp, Spokane, Wash). All subjects were studied out of their allergy season. The study was approved by the institutional review board of the University of Chicago, Chicago, Ill, and written informed consent was obtained from each subject prior to study entry.

EXPERIMENTAL PROTOCOL

We performed a randomized 4-way crossover study of the early response to nasal antigen provocation comparing the effects of exposure to HHA (temperature, 37°C; relative humidity, 90%) with those of exposure to RA (temperature, 20°C; relative humidity, 30%) delivered by mask (with the airflow reaching 10 L/min) or in a chamber. On the day of challenge, the subjects presented to the laboratory and were allowed to rest for 15 minutes so that equilibration of the nasal mucosa with the environmental conditions of the laboratory was achieved. They breathed either HHA or RA for 1 hour prior to and during localized allergen challenge. At least 2 weeks separated the challenges to avoid any priming effect one challenge might have on the other.

ALLERGEN CHALLENGE

Each challenge was begun with a series of baseline measurements (Figure 1). Preweighed filter paper disks (Shandon Inc, Pittsburgh, Pa) were placed on the anterior portion of the nasal septum just posterior to the mucocutaneous junction for 30 seconds under direct visualization using a headlight, a nasal speculum, and a d Buckfill forceps to collect nasal secretions. Symptoms of nasal congestion, itching, and rhinorrhea were recorded by the subjects. Five nasal lavages were then performed with 5 mL of lactated Ringer solution (Baxter Healthcare Corp, Deerfield, Ill) in each nostril to bring mediator levels to a stable baseline. Ten minutes after the first baseline measurements, a second series of baseline measurements was obtained. Subjects were then instructed to breathe air at one of the 4 different settings for a 1-hour conditioning period by inhaling and exhaling through the nose. At the end of the conditioning phase, the baseline measurements were repeated. Five minutes after the third series of baseline measurements was obtained, nasal challenge with diluent was performed to control for nonspecific reactivity of the nasal mucosa. Fifty microliters of the diluent for the allergen extracts (4% phenol-buffered saline) was placed on a filter paper disk and applied to the anterior nasal septum for 60 seconds. Thirty seconds after removal of the challenge disk, a dry, preweighed disk was applied to the anterior nasal septum at the site of challenge and kept in place to collect nasal secretions for 30 seconds (30-second time point). Similarly, secretions were also collected at the 2-minute time point. After 8 minutes, symptoms were recorded by the subject, and the number of sneezes during the past 10 minutes was recorded by the investigator. The subjects were then asked to blow their noses to clear any accumulated secretions before starting the next challenge. Next, 2 consecutive allergen challenges were performed by applying 50 µL of either ragweed or timothy grass extracts (Bayer Corp, Elkhart, Ind) at 2 concentrations (1:2000 and 1:200 wt/vol). Secretions, sneezes, and symptoms were measured using the same technique that was used after diluent challenge.

COLLECTION OF NASAL SECRETIONS

Collection disks were kept in Eppendorf tubes (Fisher Scientific, Pittsburgh, Pa), and the disk-tube combinations were weighed before collection of secretions. After collection of nasal secretions, the disks were replaced in the Eppendorf tubes and weighed with a Mettler AE 240 analytical balance (Mettler Instruments, Hightstown, NJ). The precollection weight was subtracted from the postcollection weight to determine the weight of secretions collected in 30 seconds.

SNEEZES AND SYMPTOM SCORES

The number of sneezes after each challenge was counted and recorded by the investigator performing the challenges. Symptoms of runny and stuffy nose for each nostril and a combined sensation of itchy nose and throat were graded on a scale as follows: 0, no symptoms; 1, very mild symptoms; 2, mild symptoms; 3, moderate symptoms; 4, severe symptoms; and 5, very severe symptoms.

MEDIATOR ASSAY

Levels of human serum albumin were assayed in recovered secretions to allow evaluation of plasma leakage. After collection of nasal secretions, all disks were eluted in 300 µL of 0.9% saline (Baxter Healthcare Corp, Deerfield, Ill) at room temperature for 30 minutes. The disks were then squeezed to the bottom of the tubes, and the eluate was removed, frozen, and stored at −20°C until assayed. Samples obtained from the same subject during exposure to the different environmental conditions were always measured in the same assay to eliminate interassay variability. Human serum albumin was measured by an enzyme-linked immunosorbent assay (ELISA) sensitive to albumin at 1 × 10−12 g/L.17

STATISTICAL ANALYSIS

For both diluent and allergen challenges, secretion weights and albumin levels were expressed as the average of the values at the 2 collection time points. Changes in each parameter after allergen challenge under the 4 different conditions were calculated by subtracting values obtained after diluent challenge from those after allergen challenge (net change over diluent). Because the data were not normally distributed, nonparametric statistics were used. Net changes for each parameter after exposure to the 4 different conditions were analyzed by Friedman analysis of variance. If a significant difference was found, post hoc analysis between RA and HHA exposures was performed using Wilcoxon signed rank test. P = .05 (2-tailed) was considered significant.
In another study, using localized antigen provocation, we found that preconditioning with HHA compared with RA could partially reduce the early response to allergen. There were significant inhibitory effects on histamine release as well as the vascular and neural responses, with no effect on the glandular response.16 We hypothesized that this partial inhibitory effect on the early response to nasal allergen challenge was caused by an increase in mucosal temperature. To address this hypothesis, we investigated whether this inhibitory effect on allergen provocation could also be achieved by inhalation of HHA via a face mask.

**RESULTS**

For HHA and RA in each type of setting (face mask and chamber), we compared values for 5 parameters: secretion weight, stuffy nose symptom scores, albumin levels, number of sneezes, and itchy nose and throat symptom scores. Baseline values for all measured parameters were compared for the 4 visits and remained unaffected by nasal lavage. All parameters were unaffected by the preconditioning period. There were no significant changes from baseline after diluent challenge.

Challenge with increasing doses of antigen caused significant increases in all parameters compared with diluent challenge. Values for each time point after diluent and allergen challenges are shown in **Figures 2, 3, 4, 5, and 6**. The net change from diluent challenge for all parameters was used for comparisons of the responses obtained after preconditioning with RA and HHA in each setting. Hot, humid air delivered by mask had no significant effect on the mean±SEM allergen-induced pruritus score (HHA, 1.6±0.5; RA, 2.3±0.5; *P* = .25) or albumin level (HHA, 0.208±0.029 g/L; RA, 0.270±0.043 g/L; *P* = .17), but it led to a significant reduction in the mean±SEM secretion weight (HHA, 32.4±12.5 mg; RA, 42.6±14.8 mg; *P* = .048).

**Figure 1.** Protocol. The different interventions, including nasal secretion collection, symptom scoring, nasal lavages, and diluent and antigen challenges, are depicted by arrows. The time intervals between the sets of arrows are indicated in the spaces separating them. The solid box represents challenges performed and time spent either in the environmental chamber or with the face mask. The temperature and relative humidity for hot, humid air were 37°C and >95%, respectively; for room air, 20°C and 30%.

**Figure 2.** Secretory response. A. The mean secretion weights for 18 subjects at each time point after exposure to hot, humid air (HHA) or room air (RA) delivered by mask or inhaled in a chamber. B and C, Individual mask and chamber data for the net change from diluent challenge for secretion weights after exposure to each of the environmental conditions. B1 indicates first baseline measurement; B2, second baseline measurement; B3, third baseline measurement; DIL, challenge with diluent for allergen extract; AG1, allergen challenge with 1:2000 wt/vol; and AG2, allergen challenge with 1:200 wt/vol.
to significant reductions in the mean±SEM number of allergen-induced sneezes (HHA, 2.7±0.6; RA, 6.6±2.1; 
*P* = .03), congestion score (HHA, 2.3±0.5; RA, 3.4±0.5; 
*P* = .01), and secretion weight (HHA, 26.9±4.4 mg; RA, 38.6±5.0 mg; 
*P* = .048) (Table).

Hot, humid air in an environmental chamber had 
no effect on the mean±SEM number of allergen-
induced sneezes (HHA, 3.3±0.9; RA, 5.3±1.3; 
*P* = .15), secretion weight (HHA, 37.6±5.2 mg; RA, 35.9±4.5; 
*P* = .65), or albumin level (HHA, 0.177±0.037 g/L; RA: 
0.222±0.037 g/L; *P* = .10), but it led to significant reduc-
tions in the mean±SEM allergen-induced congestion 
(HHA, 1.2±0.4; RA, 3.6±0.6; *P* = .002) and pruritus (HHA, 0.7±0.3; RA, 2.3±0.5; *P* = .002) scores (Table).

**COMMENT**

In this study, we compared the effect of HHA and RA on 
the nasal response to allergen challenge using 2 different 
delivery methods (mask or environmental chamber). Our 
results demonstrated that HHA inhaled in a chamber sig-
ificantly inhibited nasal and throat pruritus and nasal con-
gestion after allergen challenge. These results are similar 
to our previously published results.16 There was also a ten-
dency toward a decreased number of sneezes and lower 
albumin levels after HHA exposure in the chamber, but 
these differences did not attain statistical significance. We 
found that HHA delivered by mask significantly inhib-
ited secretion weights, number of sneezes, and nasal con-
gestion scores after allergen challenge. There was also a 
tendency toward decreased nasal and throat pruritus scores 
and albumin levels after exposure to HHA by mask.

Johnston and colleagues13 compared the effects of pre-
treatment with air at either 44°C or 31°C and 100% rela-
tive humidity delivered by face mask for a 30-minute pe-
riod before allergen challenge in allergic subjects out of their 
allergy season. They found that air at 44°C reduced the 
allergen-induced increase in nasal airway resistance and 
vascular leakage but had no effect on sneezing and rhinor-
rhoea. This study differs from ours in that a higher tempera-
ture and increased water exposure were used as well as a 
different timing of exposure in relation to challenge. Their 
results differ from ours in that there was no inhibition of 
sneezing or rhinorhoea as measured by secretion weights, 
which could be related to differences in study design. We 
performed the challenges with the patients continuously 
breathing HHA, whereas Johnston et al challenged their 
subjects 30 minutes after exposure. The effects of condi-
tioning may be transient; thus, discontinuing exposure 
after 30 minutes may reduce its potency.15

Our data showed that there were beneficial inhibi-
tory effects of HHA delivered by both methods on the na-
sal response to allergen challenge, which agrees with other

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**Figure 3.** Neural response. A, The mean number of sneezes for 18 subjects at each time point after different exposures. B and C, Individual mask and chamber data for the net change from diluent challenge for the number of sneezes after exposure to each of the environmental conditions. Bars indicate median values (see Figure 2 legend for expansion of abbreviations).

**Figure 4.** Neural response. A, The mean itchy nose/throat symptom scores for 18 subjects at each time point after different exposures. B and C, Individual mask and chamber data for the net change from diluent challenge for itchy nose/throat symptom scores after exposure to each of the environmental conditions. Bars indicate median values (see Figure 2 legend for expansion of abbreviations).
Preconditioning the nasal mucosa with HHA by either of the 2 techniques partially decreases the early response to nasal challenge with antigen. The significant changes included the reduction in nasal congestion by both delivery methods. The secretory response and sneezing were only inhibited by localized delivery of HHA to the nose. It seems that delivery of HHA by mask might be more effective in inhibiting the early allergic response than delivery via a chamber. This could be related to more heat and water delivery to the nasal mucosa via the mask compared with passive inspiration in the chamber.

The most likely mechanisms underlying the beneficial effects of HHA in reduction of the early allergic response are modification of nasal mucosal temperature or reduction in nasal secretion osmolality. One of the primary functions of the nose is to condition inspired air. To achieve this, the nasal mucosa has to deliver heat and water to cooler, dry inhaled air. This can cause an increase in the osmolality of nasal secretions as a result of evaporation of water from the nasal mucosal surface. There is evidence that mast cells and basophilic leukocytes release histamine both in vitro and in vivo upon ex-
posure to hyperosmolar solutions and that hyperosmolar secretions can activate nerves, blood vessels, and mast cells.\textsuperscript{14} On the other hand, Rouadi and colleagues\textsuperscript{25} recently demonstrated that inhaling heated, humidified air leads to water deposition on the nasal mucosa in a flow-dependent manner. This would cause dilution of nasal secretions and subsequent reduction of the osmolality of nasal secretions. Mann and colleagues\textsuperscript{26} also found that breathing warm, humid air could lower the osmolality of tracheal secretions in dogs. Thus, the inhibitory effect of HHA on the acute allergic response might be related to the normalization of nasal secretion osmolality and a reduced stimulation of the nasal end organs.

The optimal functioning temperature of mast cells in the nasal mucosa is probably in the range of normal nasal mucosal temperature (30°C–32°C).\textsuperscript{27} Temperature above or below this optimum may alter the function of mast cells. Fully saturated air at 37°C could increase nasal mucosal temperature and may lead to a reduced early allergic response. In support of this theory are in vitro findings that mast cell and basophil histamine release is reduced at the temperature of 40°C.\textsuperscript{28,29} In further support of the concept that HHA may reduce the early allergic response by increasing nasal mucosal temperature is the recent study by Assanasen and colleagues\textsuperscript{30} demonstrating that increasing nasal mucosal temperature by the immersion of the feet in warm water led to partial inhibition of the early response to allergen challenge. In these experiments, raising the nasal mucosal temperature by an average of approximately 2°C from baseline led to significant reductions in allergen-induced sneezing, secretion weights, and levels of albumin in recovered nasal lavages.

More heat and water delivery to the nasal mucosa via the mask compared with passive inspiration in the chamber may cause a greater increase in nasal mucosal temperature and more dilution and reduction in the osmolality of nasal secretions, resulting in a larger inhibitory effect on the allergic response. Our data suggest that the inhibitory effects of HHA are probably related to local changes in the nasal mucosa and are not dependent on total body exposure. Furthermore, the demonstration of inhibition of the allergic response after mask conditioning with HHA will enable us to perform future experiments more easily and conveniently.

\textbf{CONCLUSIONS}

We have shown that conditioning the nasal mucosa with HHA prior to antigen challenge partially inhibits the neural and vascular responses to allergen irrespective of the technique used to administer the HHA; however, delivery by mask might be more effective in inhibiting the early allergic response than delivery via a chamber. These inhibitory effects are probably caused by local changes in the nasal mucosa.

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