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Breathing hot humid air induces airway irritation and cough in patients with allergic rhinitis

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ABSTRACT

We studied the respiratory responses to an increase in airway temperature in patients with allergic rhinitis (AR). Responses to isocapnic hyperventilation (40% of maximal voluntary ventilation) for 4 min of humidified hot air (HA; 49 °C) and room air (RA; 21 °C) were compared between AR patients ($n = 7$) and healthy subjects ($n = 6$). In AR patients, cough frequency increased pronouncedly from 0.10 ± 0.07 before to 2.37 ± 0.73 during, and 1.80 ± 0.79 coughs/min for the first 8 min after the HA challenge, but not during the RA challenge. In contrast, neither HA nor RA had any significant tussive effect in healthy subjects. The HA challenge also caused respiratory discomfort (mainly throat irritation) measured by the handgrip dynamometry in AR patients, but not in healthy subjects. Bronchoconstriction was not detected after the HA challenge in either group of subjects. In conclusion, hyperventilation of HA triggered vigorous cough response and throat irritation in AR patients, indicating the involvement of sensory nerves innervating upper airways.

1. Introduction

Allergic rhinitis (AR) is an inflammatory disease of upper airways characterized by nasal congestion and rhinorrhea, intermittent or persistent sneezing, pruritus in nose, eyes and throat, and coughing. The inflammatory reaction is characterized by early-phase and late-phase allergic responses similar to that in allergic asthma (Bousquet et al., 2012; Wallace et al., 2008). Repeated exposures to environmental allergens result in an IgE mediated type I allergic response that induces a type-2 helper T cell (TH2) inflammation. Cross-linking of IgE antibodies present on the surface of primed mast cells by an antigen activates them and results in degranulation and release of inflammatory mediators such as histamines, tryptase, and leukotrienes, which in turn leads to vasodilatation and increased vascular permeability. The recruitment of TH2 cells and secretion of IL-5 give rise to tissue eosinophilia that characterizes the late phase response (Middleton et al., 2009). Eosinophilic inflammation in turns can result in further tissue damage and sensitization of the afferent nerves innervating the nose, throat and upper airways due to release of additional inflammatory mediators.

Our laboratory has recently reported that an increase in airway temperature by hyperventilation of hot humid air for 4 min triggered an immediate and transient bronchoconstriction in patients with mild asthma, but not in healthy individuals (Hayes et al., 2012). The bronchoconstriction was accompanied by cough and prevented by pretreatment with ipratropium, a muscarinic receptor antagonist, suggesting an involvement of activation of airway sensory nerves and the cholinergic reflex pathway. Although direct evidence could not be established in that study, our results suggested activation of a temperature sensors expressed in the vagal bronchopulmonary sensory nerves is probably involved in eliciting these reflex responses. One possible candidate is the transient receptor potential vanilloid type 1 receptor (TRPV1). Indeed, chronic allergic inflammation is known to enhance both the sensitivity and the expression of TRPV1 in airway sensory nerves (Lee and Gu, 2009; Zhang et al., 2008).

TRPV1 is also abundantly expressed in the sensory nerve fibers innervating the pharynx, larynx and upper airways (Hamamoto et al., 2008, 2009; Sasaki et al., 2013; Yamamoto and Taniguchi, 2005). However, whether the sensitivity of these TRPV1-expressing sensory nerves is elevated resulting from the chronic inflammation

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of upper airways in AR patients is not yet known, and the reflex responses elicited by an increase in airway temperature in these patients have not been previously studied. This study was therefore carried out to answer these questions.

2. Methods

2.1. Subjects

Adult AR patients and healthy subjects were recruited by public advertisement. A screening interview and a spirometry test were performed in each subject after informed consent was obtained. The diagnosis of AR was confirmed according to the standard clinical guidelines in each patient and a documented positive allergy skin test (Wallace et al., 2008). The American Academy of Allergy, Asthma, and Immunology Joint Task Force on Practice Parameters questionnaire was used to assess and compare symptom severity and global impact of AR in all subjects (Spector et al., 2003). Due to the need to stop therapeutic medications for 2 weeks prior to beginning of the study, patients on steroids and/or have poor AR control were excluded. The study protocol was approved by the Institutional Review Board at the University of Kentucky.

2.2. Isocapnic hyperventilation challenge

A device designed to deliver air of desired temperature and humidity constructed by the University of Kentucky Center for Manufacturing was used as previously described (Hayes et al., 2012). Briefly, a humidified gas mixture of 4.5% CO_2 balanced with air at either hot (HA; 49 °C and 75–80% relative humidity measured by an Extech Hygro-Thermometer, model RH101; Nashua, NH) or room temperature (RA; 20–22 °C and 65–75% relative humidity) was delivered at 300 l/min through a large-bore (7.62 cm) stainless-steel conduit. During the hyperventilation challenge, the subject, while wearing a nose clip, breathed via a mouthpiece into this free stream of humidified gas mixture at ~40% of maximal voluntary ventilation (MVV), determined in each subject in a pre-test, for 4 min; CO_2 was added to maintain an isocapnic condition during hyperventilation. Humidity was generated from sterile isotonic saline by an ultrasonic atomizer (Sonaer Ultrasonics; Farmingdale, NY). The amounts of isotonic saline delivered in RA and HA were 12–14 and 56–60 μl/liter of air, respectively. Humidity and hyperventilation at 40% of MVV were used to facilitate the heat transfer from air to the airway tissue. Levels of end-tidal temperature (model IT-18, Physitemp, Clifton, NJ; time constant: 0.1 s) and CO_2 concentration (Novametrix 1260; Murrysville, PA) were measured before and after 2 min of hyperventilation when these changes reached steady state; and they were measured again at 8 and 16 min after the hyperventilation challenges.

2.3. Pulmonary function measurements

Airway resistance (R_{aw}) was measured continuously by a whole-body constant-volume plethysmography (SensorMedics, Yorba Linda, CA) for 6 min before and 16 min immediately after the hyperventilation challenge. During each measurement, the subject was asked to pant at a frequency of ~2 Hz for ~8 s; R_{aw} was determined by computer, using the center-fit method for the slope measurement within the flow range of ±0.5 l/s. Spirometry test was also performed along with the measurements of other physiological variables (body temperature, heart rate, arterial blood pressure, and oxygen saturation) before and after the challenge.

2.4. Measurement of cough frequency

The number of coughs was recorded manually by listening to and counting the number of explosive cough sounds before, during and after each hyperventilation challenge. A VitaloJAK cough monitor [developed by Vitalograph Ltd. (Lenexa, KS) and the Respiratory Research Group, University of Manchester, UK] was also used in the second half (61%) of the study for a more objective and quantitative measurement of the cough frequency (Smith et al., 2006). The device used a contact microphone placed on the chest wall, a second free field microphone and a custom-made digital recording device to record cough sounds. Cough signals recorded by the cough monitor were played back, and the cough numbers were counted by an individual not familiar with the protocol. Cough frequency measured as number of coughs per minute was then compared with those obtained from manual counting during the experiment; the difference between the data obtained from these two methods was generally less than 10%.

2.5. Measurement of respiratory sensation

Subjects were instructed to indicate the presence and express the degree of respiratory discomfort by squeezing an isometric handgrip dynamometer (model MLT003, ADInstruments; Colorado Springs, CO) with a magnitude of force proportional to the intensity of the sensation felt (Burki et al., 2005; Muza and Zechman, 1984) at intervals of ~2 min following both HA and RA hyperventilation challenges. The resultant voltage generated from the dynamometer transducer was recorded continuously in conjunction with the measurements of R_{aw} and cough responses. To compare the response between subjects, the level of discomfort in each subject was quantified by calculating each response signal as a percentage of the maximum handgrip signal (as 100%) that was determined in each subject before each experiment. After the experiment, the subject was asked to describe verbally if there was any type of respiratory discomfort, and if so, the location of the evoked sensation.

2.6. Study design

HA and RA hyperventilation challenges were given at a random sequence in each subject, usually on two different days. When both challenges were given in the same day, at least 2 h elapsed for recovery. The responses to HA and RA hyperventilation challenges were compared in both AR patients and healthy subjects.

2.7. Statistical analysis

A two-way analysis of variance (ANOVA) was used for the statistical evaluation of the results. When the ANOVA showed a significant interaction, pair-wise comparisons were made with a post hoc analysis (Fisher's least significant difference). Comparisons between the two groups (AR patients vs. healthy subjects) were made using the one-way ANOVA. Data are reported as means ± SEM. P values of <0.05 were considered significant.

3. Results

Seven AR patients between 21 and 43 (35 ± 3) year of age and six healthy subjects between 25 and 48 (32 ± 3) year of age were enrolled in the study; the subject characteristics are shown in Table 1. The AR symptom severity assessment data (Table 1) show that several symptoms with mean scores exceeding 3.5 (out of a total score of 7.0), including sneezing (3.57 ± 0.53; $n = 7$), nasal congestion (5.0 ± 0.58), itchy nose (3.93 ± 0.74), postnasal drip (4.0 ± 0.68), chronic cough (3.57 ± 0.65), eye (3.57 ± 0.53) and ear symptoms (3.57 ± 0.43), were found in AR patients, but none in