Nasal provocation of patients with allergic rhinitis and the hypothalamic-pituitary-adrenal axis

Demetrios Kalogeromitros, MD, PhD*; E. Katerini I. Syrigou, MD*; Michael Makris, MD*; Duraisamy Kempuraj, PhD†; Nikolaos G. Stavrianeas, MD, PhD*; Magdalini Vasiadi, BS†; and Theoharis C. Theoharides, MS, MPhil, PhD, MD**†‡

Background: Allergic rhinitis is a common problem involving activation of nasal mast cells and irritability. The hypothalamic-pituitary-adrenal (HPA) axis is stimulated in cases of emotional or environmental stress, and mast cells have been implicated in stress-induced immune responses.

Objective: To investigate whether intranasal challenge of patients allergic to a single antigen would stimulate the HPA axis.

Methods: Plasma corticotropin and cortisol levels were measured 20, 40, 60, 80, 100, and 120 minutes after intranasal antigen administration in healthy volunteers (n = 3) and in patients with rhinitis who are allergic to Parietaria (n = 10).

Results: Mean ± SD corticotropin levels were 24.43 ± 14.38 pg/mL in patients compared with 8.83 ± 5.02 pg/mL in controls, and this increase was statistically significant (P = .049). Patient cortisol levels also increased to a mean ± SD of 8.87 ± 4.90 pg/mL (at 40 minutes) compared with 4.36 ± 1.72 pg/mL in controls (P = .11 due to 1 outlier). Compared with individual patient prechallenge levels, corticotropin levels increased in 7 patients and cortisol levels increased in 5 at 40 minutes.

Conclusion: These results suggest that allergic rhinitis may activate the HPA axis. A larger study with additional controls is required for definitive conclusions.

INTRODUCTION

Allergic rhinitis is a chronic condition that affects 10% to 25% of the population,1 with a significant impact on patients’ lives, especially the quality of sleep.2 The allergic patient is characterized by emotional instability, sometimes called the “allergic irritability syndrome,”3 and increased anxiety.4,5 Stress has also been shown to increase morbidity in children with asthma.6 Allergic rhinitis involves the activation of nasal mast cells,7 which are now considered important in immunity,8 especially on mucosal surfaces.9 Mast cells are also implicated in nervous-immune interactions10 and in the pathogenesis of inflammatory conditions worsened by stress.11 We hypothesized that nasal mast cell stimulation by allergens may release molecules that could activate the hypothalamic-pituitary-adrenal (HPA) axis. These molecules could include corticotropin-releasing hormone (CRH),12 histamine,13 interleukin 1 (IL-1),14 IL-6,15 and prostaglandins.16,17 The HPA axis may then become overactive, leading to unwanted behavioral and physical consequences.

PATIENTS AND METHODS

Individuals with a history of rhinitis to Parietaria officinalis pollen were enrolled on the basis of the following inclusion criteria: (1) aged 18 to 60 years and (2) a positive history of allergic rhinitis during the latest pollen season confirmed by either a positive skin prick test reaction (wheal diameter >3 mm) or a positive radioallergosorbent test result for specific serum IgE (>0.70 kU/L) for Parietaria pollen (UniCAP; Pharmacia Diagnostics, Uppsala, Sweden). Exclusion criteria were (1) uncompensated asthma (peak expiratory flow rate <80% of the reference value); (2) symptoms of allergic, viral, or infectious rhinitis within 2 weeks of the nasal provocation test (NPT); (3) symptoms of allergic rhinitis during the study; (4) major nasal septum deviation or polypsis; (5) use of medications that might affect the test variables during the week before study onset (oral or topical antihistamines, corticosteroids or antidepressants with antiallergic properties, and antihypertensive agents); (6) pregnancy or the absence of adequate contraception; and (7) a nonspecific nasal reaction on nasal challenge test (NPT). Three nonatopic individuals who fulfilled the criteria were (1) uncompensated asthma (peak expiratory flow rate <80% of the reference value); (2) symptoms of allergic, viral, or infectious rhinitis within 2 weeks of the nasal provocation test (NPT); (3) symptoms of allergic rhinitis during the study; (4) major nasal septum deviation or polypsis; (5) use of medications that might affect the test variables during the week before study onset (oral or topical antihistamines, corticosteroids or antidepressants with antiallergic properties, and antihypertensive agents); (6) pregnancy or the absence of adequate contraception; and (7) a nonspecific nasal reaction on nasal challenge test (NPT). Three nonatopic individuals who fulfilled the criteria were included in this study as controls. The NPTs were performed outside the Parietaria pollen season to exclude concomitant natural exposure to the allergen. The Attikon Hospital Human Subject Review Board approved the re-
search protocol, and written informed consent was obtained from each volunteer.

The NPT started with the determination of nonspecific reactivity.18 Two actuations (mean ± SD, 0.12 ± 0.01 mL) from nasal spray bottles containing challenge material were nebulized into each nostril of all the participants at end inspiration. Five and 10 minutes after the challenge, the number of sneezes was recorded, and the subjective symptoms of nasal itchiness and nasal congestion were evaluated by means of a visual analog scale (0 = absent and 10 = severe). Peak nasal inspiratory flow (PNIF) was also determined at 5 and 10 minutes. This sequence was repeated at each allergen concentration every 20 minutes. The same batch of standardized allergen (ALK-Abello, Copenhagen, Denmark) was used throughout the study, and serial dilutions (2, 4, and 8 BU/mL) were prepared in phosphate-buffered saline solution immediately before NPT.

The nasal reaction threshold (combined threshold) was reached when a decrease in PNIF of 40% or greater of baseline values was recorded 5 or 10 minutes after the challenge and at least 1 of the 2 following clinical criteria were fulfilled: (1) 5 or more sneezes and (2) total score greater than 10 on the visual analog scale of nasal itchiness and nasal congestion at 5 or 10 minutes.18 Peak nasal inspiratory flow was measured using a flow meter (Jaeger, Wurzburg, Germany). The best of 3 consecutive measurements of PNIF was registered.

Before the protocol onset and 0, 20, 40, 60, 80, 100, and 120 minutes after reaching the nasal reaction threshold (a positive NPT reaction) or an equivalent time in control subjects, blood samples were collected via an intravenous catheter and were centrifuged, and the plasma was stored at −20°C until assay. These time points were chosen because they are typically used during the HPA challenge test. Patients were not followed up past 120 minutes to determine when cortisol levels recovered to prechallenge levels. Plasma corticotropin (100B Dyno Test; Brahms, Berlin, Germany) and cortisol (EU; Diasorin, Stillwater, MN) concentrations were determined by means of radioimmunoassay for each time point. Six patients were excluded because of recent medication use and 3 more owing to a nonspecific nasal reaction at the inclusion NPT. Ten patients (5 men and 5 women) finally completed the whole study and were included in the analysis; their mean ± SD age was 49.7 ± 8.5 years (range, 35–59 years). Three controls (1 man and 2 women) with a mean ± SD age of 32.3 ± 7.5 years (range, 28–41 years) made up the control group. All the participants were excluded by means of a visual analog scale (0 = absent and 10 = severe).

The mean ± SD corticotropin and cortisol levels were compared with those of controls at different time points after challenge, and individual values at different time points were also compared with time 0 for each participant using the nonparametric Mann-Whitney U test. Significance was set at P < .05.

RESULTS

Results are presented as scattergrams to show the individual participant variability (Fig 1A and C) and with the actual values connected in line drawings to show the pattern of change for each individual patient (Fig 1B and D). There was considerable variability among patients that may be due to their degree of sensitivity to the allergen or other inherent factors.

The corticotropin levels increased in most patients (7 of 10) compared with prechallenge levels. The mean ± SD corticotropin levels after challenge were 24.43 ± 14.38 pg/mL at 40 minutes and 21.75 ± 8.21 pg/mL at 60 minutes; these were significantly higher compared with those of control subjects at 40 minutes (8.83 ± 5.02 pg/mL; P = .049) and 60 minutes (10.23 ± 3.56 pg/mL; P = .04) (Fig 1A and B).

Mean ± SD plasma cortisol levels also increased in patients (8.87 ± 4.90 and 8.57 ± 3.38 pg/mL at 40 and 60 minutes, respectively) compared with controls (4.36 ± 1.72 and 4.66 ± 1.85 pg/mL at 40 and 60 minutes, respectively) (Fig 1C and D), but this difference was not significant owing to 1 outlier value (P = .01). However, compared with the individual patient prechallenge levels at 40 minutes, cortisol levels were increased in 5 patients, remained the same in 1, and decreased in 4. The corticotropin and cortisol levels of controls were unaffected (Fig 1).

DISCUSSION

These results suggest that intranasal challenge of patients allergic to a single antigen may stimulate the HPA axis. However, no definitive conclusion can be made because the effect recorded was weak and variable; furthermore, the effect of priming with repeated antigen exposure on the HPA axis is not known. Other possibilities must also be excluded: (1) actual values must be recorded for the effect of the pollen extract diluent, although preliminary results showed no effect; (2) this study should be repeated in the evening when endogenous cortisol levels are low because challenge studies performed in the morning, when cortisol levels are higher do not occur as readily; and (3) a possible effect on the HPA axis of the stress of the nasal occlusion should be excluded, but this is difficult to control for. Nasal occlusion could be excluded by means of intranasal histamine challenge in controls and patients, but histamine has also been shown to stimulate the HPA axis.13

The effect we observed could be due to molecules released in the nose that reach the median eminence and the pituitary through the cribriform plexus.20 For example, histamine13 and prostaglandin21 are synthesized by mast cells and can activate the HPA axis; IL-6 is also synthesized by mast cells and is an independent activator of the HPA axis.15 Furthermore, human mast cells also release IL-6 in response to IL-1, and IL-1 can independently stimulate the HPA axis.14
Human mast cells also release CRH on allergic stimulation. Once inflammation develops, CRH could also be synthesized by infiltrating lymphocytes, although this is likely to be a delayed response. This late phase may also involve cytokines/chemokines released from basophils and eosinophils, both important in allergic inflammation. Brain and nasal mast cells could then be further activated by CRH or somatostatin released from the hypothalamus. Measurement of IL-6 or CRH in nasal fluid after antigen challenge would confirm mast cell mediator involvement.

We had first proposed that brain mast cells may act as an “immune gate to the brain.” We later showed that mast cells could be activated by acute stress and increase the permeability of the blood-brain barrier through activation of specific CRH receptors. Intracerebral administration of the mast cell secretagogue compound 48/80 increased HPA axis.

Figure 1. Plasma corticotropin (A and B) and cortisol (C and D) levels of controls (C) (n = 3) and patients with allergic rhinitis Parietaria (P) (n = 10) challenged with this specific antigen. Results are presented as scattergrams (A and C), where the means of the control and patient groups are shown as short horizontal bars, and with the time points connected (B and D) to appreciate the pattern of change for each individual patient. The values for the controls were arbitrarily increased by 3 points on the x-axis to separate them from the patient values for easier readability. Blood samples were collected before any challenge (time 0) and after positive specific nasal provocation tests with increasing amounts of Parietaria (2, 4, and 8 BU/mL) every 20 minutes (up to 120 minutes). Plasma corticotropin and cortisol levels were measured blindly.
activity in rats, with accompanying corticosterone secretion. Intracerebral activation of brain mast cells in dogs sensitized to ovalbumin also led to HPA axis activation. However, in both these cases, the trigger had to be given intraventricularly, clearly not a physiologic state. In a study of rats immunized to hemocyanin, intraventricular challenge with large amounts of antigen induced a small increase in the corticosterone level. However, anaphylactic reactions may release sufficient systemic amounts of histamine and cytokines to either reach the pituitary or cross the blood-brain barrier and activate the HPA axis, possibly in an effort to minimize this response through the secretion of adrenal corticosteroids.

The ability of nasal mast cells to activate the HPA axis may help explain the increased association of allergic rhinitis and anxiety. It will be interesting to investigate whether nonallergic triggers, such as cigarette smoke, could also activate the HPA axis in nonallergic individuals. Mast cells may act as "sensors" of environmental stress, possibly providing an explanation for the "irritable allergic patient" concept and the popular saying "we smell danger." In general, these results support the diverse roles of mast cells.

ACKNOWLEDGMENTS

We thank Biocheck Int SA, Medical Diagnostic Center, Athens, Greece, for the corticotropin and cortisol measurements and Jessica Christian for her patience and word processing skills.

REFERENCES


Requests for reprints should be addressed to:
Theoharis C. Theoharides, MD, PhD, MS, MPhil
Department of Pharmacology and Experimental Therapeutics
Tufts University School of Medicine
136 Harrison Ave
Boston, MA 02111
E-mail: theoharis.theoharides@tufts.edu