

temperature difference could be perceived either directly by elevated blood temperature affecting cells in the hypothalamic preoptic area, or indirectly by blood temperature first affecting peripheral neuronal receptors, which in turn stimulate the preoptic area. It would have been tempting to assume that direct heating of the blood could bypass peripheral neuronal receptors. However, because sequential skin temperatures were not recorded along with oral temperatures, this assumption cannot be established. Nevertheless, this case is a unique example of the temperature difference needed to be perceived by the central temperature regulation system in order to provoke the common efferent reflex leading to hives in CU.

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Royal jelly-induced asthma and anaphylaxis: Clinical characteristics and immunologic correlations

Roland Leung, MD, FRACP,^a Francis C. K. Thien, MD, FRACP,^a
Brian Baldo, PhD,^b and Daniel Czarny, FRACP, FRCP^a
Victoria and St Leonards, Australia

Royal jelly is a secretion of the hypopharyngeal glands of young worker honeybees (*Apis mellifera*) and is widely used in the community as a health tonic. About half of its dry weight consists of protein; other components are free amino acids, fatty acids, sugars, vitamins, and some miner-

als.^{1,2} Despite its widespread use, its claimed benefits remain unproven.

Our group recently reported five cases of royal jelly-induced asthma and anaphylaxis.³ We now provide further clinical details, with preliminary immunologic investigations of these five and two additional cases, which confirm that they were true IgE-mediated reactions.

CLINICAL DETAILS

The clinical details of the seven patients investigated are summarized in Table I. All had a history of mild to moderate asthma and gave a clear history of reactions temporally related to intake of royal jelly.

From ^aAsthma & Allergy Unit, Department of Respiratory Medicine, Alfred Hospital, Victoria; and ^bKolling Institute of Medical Research, Royal North Shore Hospital, St Leonards. Reprint requests: Associate Professor Daniel Czarny, Asthma and Allergy Unit, Department of Respiratory Medicine, Alfred Hospital, Commercial Rd., Prahran, Vic 3181, Australia.

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TABLE 1. Clinical details and skin test reactions of subjects sensitive to royal jelly

Patient No.	Age (yr)	Sex	First time to take royal jelly?	If not first ingestion of royal jelly, duration since first ingestion	Type of royal jelly	Time from ingestion to onset of reaction (min)	Type of reaction	Treatment required	Skin prick test to royal jelly
1	26	F	No	2 days	Capsules	90	Acute life-threatening asthma attack	Nebulized bronchodilators and intravenous steroids	Positive 10 × 10 mm
2	19	F	Yes	N/A	Liquid in vials	20	Asthma, rhinitis, and upper airway obstruction	Inhaled epinephrine and antihistamines	Positive 6 × 6 mm
3	23	F	Yes	N/A	Capsules	60	Acute wheezing	Spontaneous resolution	Positive 9 × 4 mm
4	33	F	No	Taken royal jelly once 2 years ago	Fresh royal jelly, half teaspoon	20	Acute asthma, rhinoconjunctivitis, and angioedema	Intramuscular epinephrine and systemic steroids	Positive 8 × 8 mm
5	66	M	No	Not known	Liquid in vials	30	Asthma, anaphylaxis, and respiratory arrest	Intramuscular epinephrine nebulized bronchodilators, and systemic steroids	Positive 6 × 4 mm
6	30	F	No, second	2 days earlier	Capsules	20	Acute asthma	Nebulized bronchodilators	Positive 10 × 7 mm
7	43	F	Yes	N/A	Liquid in ampule	5	Dyspnea, wheezing, and angioedema with hypotension	Nebulized bronchodilators, antihistamines	Positive 15 × 5 mm

N/A, Not applicable.

All had positive skin prick test responses to royal jelly. Two patients had confirmatory oral royal jelly challenges, and the clinical details of patient 1 are given below.

Case 1

Patient 1 is a 26-year-old woman who has had mild asthma since the age of 2 years, which had been controlled with sodium cromoglycate and salbutamol. For symptoms of an upper respiratory tract infection, she had taken 2 naturopathic royal jelly/ginseng capsules. Within 1½ hours, she had a rapidly progressive attack of asthma with her peak expiratory flow rate dropping from 400 to 80 L/min. Emergency admission to hospital was necessary, and she required treatment with nebulized bronchodilators and intravenous steroids. She had a complete recovery over the next 24 hours. Subsequent investigation showed a positive skin prick test reaction (10 mm wheal) to fresh royal jelly taken from a hive on the day of the test. Results of testing with bee venom

were negative. Single-blind oral challenge with royal jelly capsules provoked acute asthma within 90 minutes (Fig. 1). Results of similar challenges with ginseng alone or placebo were negative.

METHODS

Immunologic investigations

Water-soluble extracts of Fresh Royal Jelly (Natural High, Foster, NSW Australia) were obtained by mixing the royal jelly with distilled water, ultracentrifugation, and membrane dialysis of the supernatant at 4° C. The dialysate was freeze-dried, and protein content was determined before storage at 4° C.

Sera from the seven patients were obtained, as well as stored sera from 63 subjects with known allergy to bee venom and 75 subjects with clinical allergic rhinitis, eczema, or allergic asthma. Other sera were obtained from nonallergic laboratory staff members to be used as controls.

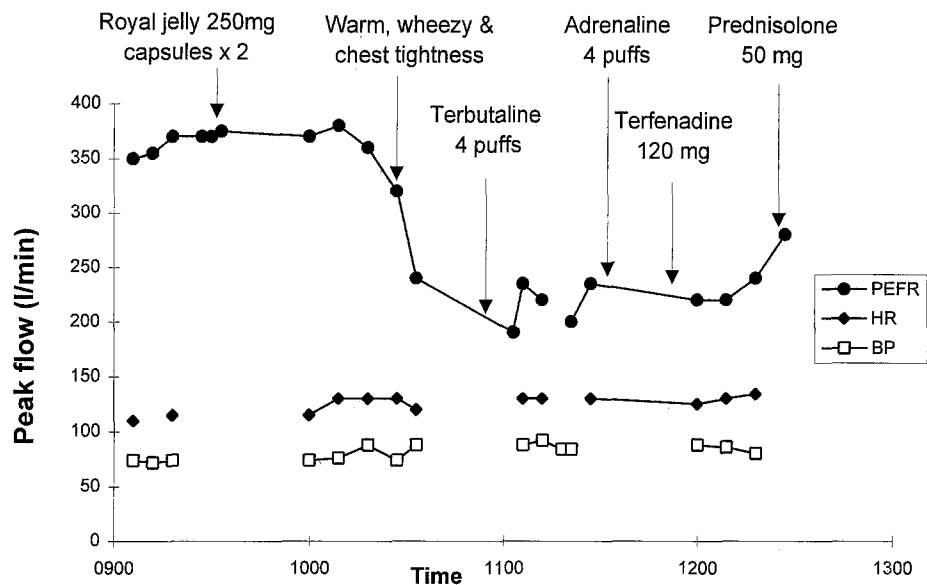


FIG. 1. Royal jelly challenge in a sensitive subject (patient 1). *PEFR*, Peak expiratory flow rate; *HR*, heart rate; *BP*, blood pressure.

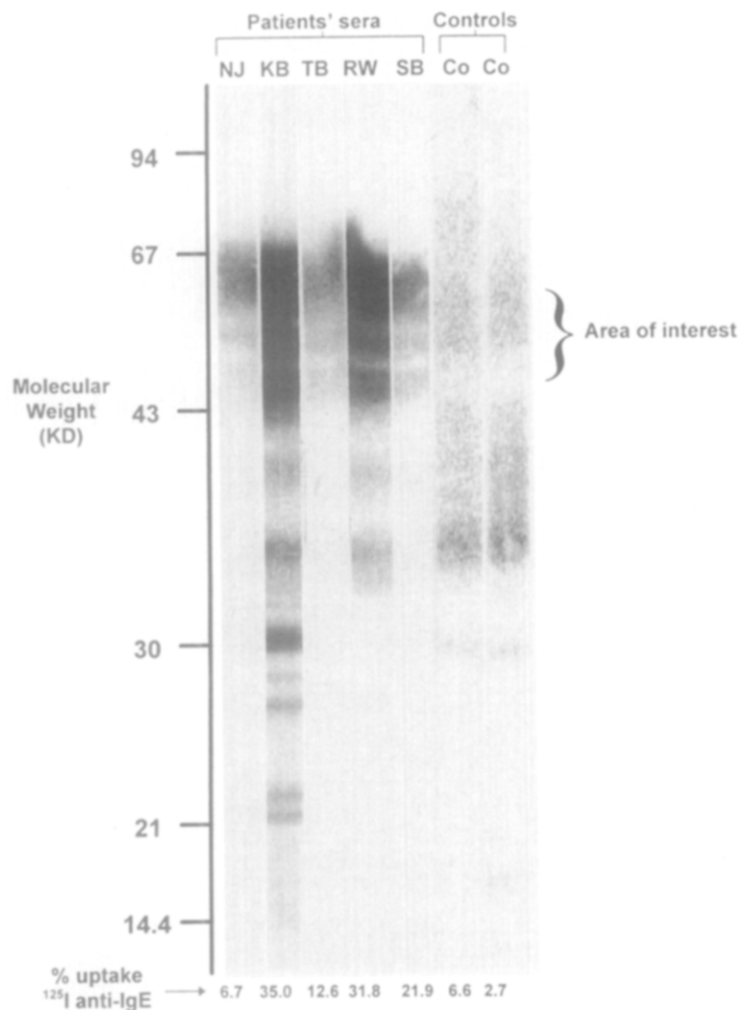


FIG. 2. Immunoblot of royal jelly with sera from five patients and two control subjects.

Sera were tested for royal jelly-reactive IgE antibodies with 6 mm nitrocellulose disks as previously described.⁴ Results were expressed as percentage uptake of iodine 125-anti-IgE. Sodium dodecylsulfate-polyacrylamide gel electrophoresis was carried out on royal jelly solution, and separated proteins were transferred to nitrocellulose (Fig. 2). IgE-binding proteins were identified as previously described, and detection was achieved by addition of ¹²⁵I-anti-human IgE.⁵

RESULTS

Compared with sera from nonallergic control subjects, all sera from patients with royal jelly sensitivity showed elevated levels of uptake of anti-IgE antibodies by nitrocellulose disks with adsorbed royal jelly proteins. Two sera had uptake of 1.3%, but the other five had levels at least 10 times higher than that of nonallergic control subjects who had an uptake of 0.3% to 0.6%. Among sera from those with known allergy to bee venom and other allergic subjects, 38% and 52% showed uptake of anti-IgE at least twice that of nonallergic control subjects, respectively.

Protein staining after sodium dodecylsulfate-polyacrylamide gel electrophoresis of reduced royal jelly proteins revealed 18 to 20 bands with a heavy cluster in the molecular weight region of 25 to 75 kd. Immunoblotting studies showed that sera from all royal jelly-sensitive subjects reacted with the ~55 and 47 kd components and three sera also reacted with the ~40 and 39 kd bands. All sera from subjects allergic to bee venom also detected the ~55 kd band, but none reacted with the ~47 kd proteins. In addition, these sera also reacted with the higher molecular weight (~94, 67, and 60 kd) bands. A similar binding profile was seen in positive sera from subjects with clinical allergy, whereas no detectable binding of anti-IgE was evident in sera from nonallergic control subjects.

DISCUSSION

We have shown that subjects with clinical sensitivity to royal jelly possess serum IgE antibodies to a number of royal jelly components. Although the antibody-binding patterns were heterogenous, two proteins of molecular weight ~55 and 47 kd were recognized by sera from all subjects, suggesting

that these two components may be the major allergenic proteins of royal jelly. Of interest is the recognition of these proteins by sera from a number of patients with bee venom sensitivity and other common allergic disorders. This finding could imply that there are many "sensitized" individuals at risk for adverse reactions when exposed to royal jelly. Alternatively, it could indicate mere cross-reactivity between royal jelly antigen with commonly occurring environmental allergens. In support of the hypothesis that some individuals could be "pre-sensitized" by previous exposure to cross-reacting allergens other than royal jelly, three of the seven patients reported here had no previous history of royal jelly ingestion. Two of the patients (nos. 1 and 6) had taken a dose for the first time once 2 days earlier, which was followed by mild wheezing, and one patient (no. 4) had taken royal jelly once 2 years before the acute reaction. There did not appear to be any identifiable risk factors, but six of the seven patients were female and all patients were atopic, with positive grass pollen reactions. Three of the seven patients were also skin tested with bee venom and showed negative reactions.

Considering the amount of royal jelly used in the community, there are surprisingly few reports of anaphylaxis. This is a preliminary report of the possible immunologic basis of life-threatening reactions to royal jelly, and further investigations are underway.

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