

Higher Histamine Sensitivity in Non-atopic Subjects by Skin Prick Test May Result in Misdiagnosis of Eggplant Allergy

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Eggplant (aubergine; *Solanum melongena* L.), a member of the nightshade family, is widely consumed as a vegetable. A high incidence of allergic reactions to eggplant appears to be commonly experienced among Indians, presumably due to its high histamine content. Therefore, it appeared interesting to investigate the histamine content of different varieties of eggplant (green and purple round; green and purple slender long) using raw, cooked, and dialyzed extracts. A significant varietal difference in the histamine content of eggplant varieties was observed. Highest amount was present in the green round variety (2.41 mg/100 g fresh weight in raw and 2.07 mg/100 g in cooked extracts). The histamine content of other varieties (in mg/100 g raw) is: green slender long (1.80), purple slender long (1.35), and purple round (0.89). Histamine is stable to heat-processing, since only 11–14% loss was observed upon cooking. Skin prick test (SPT) on non-atopic subjects (without any history of eggplant allergy) using four varieties of raw and cooked eggplant extracts revealed that only subjects with a lower threshold for histamine produce positive results equivalent to that seen between 10–100 µg/mL histamine dihydrochloride. It can be concluded that the amount of histamine present in eggplant does not produce a positive SPT response in a majority of non-atopic subjects, and that a positive response in a few subjects are likely to be misdiagnosed as eggplant allergy.

Keywords Adverse reaction, Eggplant, Histamine, Skin prick test, *Solanum melongena*, Varietal difference.

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INTRODUCTION

The 'Solanaceae' family includes mainly four important vegetables, namely potato, tomato, eggplant, and bell pepper of which, the cultivated eggplant or aubergine (*Solanum melongena* L.) ranks 12th among the vegetable crops (Ensminger et al., 1995); Asia alone accounts for 93% of world production (FAO, 2001). Commonly known as brinjal in India, eggplant is an important vegetable in the Indian diet (Lawande and Chavan, 1998). Adverse reactions to eggplant appear to be commonly experienced by a considerable number in the Indian population (Pramod and Venkatesh, 2004; 2008; Apollo Hospitals Group, 2008; Harish Babu et al., 2008); a rare case of anaphylaxis to eggplant has been reported (Lee et al., 2004).

Based on positive case histories and skin prick tests (SPT) with eggplant extracts, it has been found that the incidence of eggplant allergy ranges from 6.4 to 10% among adults. Further, it has been analyzed that this high incidence does not reflect true eggplant allergy (Harish Babu et al., 2008); some factors responsible for this high incidence may include the contribution of biogenic amines (histamine: 2.9–3.8 mg; tyramine: 0.3 mg; tryptamine: 0.05–0.3 mg; all per 100 g fresh weight) (Udenfriend et al., 1959; Feldman, 1983), secondary metabolites such as pigments, alkaloids, phytoestrogens, etc. (Duke's Phytochemical and Ethnobotanical databases, 2008). Generally, it is assumed that the significant presence of histamine in eggplant seems to contribute to the high incidence of adverse reactions to eggplant.

Histamine is the potent mediator released in all allergic reactions. However, ingestion of histamine-rich foods causes adverse reactions such as headache, nausea, hot flushes, skin rashes, sweating, and respiratory distress, cardiac and intestinal problems (Wantke et al., 1993; Santos, 1996). Therefore, histamine has been implicated as the causative substance in numerous adverse reactions related to foods. Foods containing high amounts of histamine are fish, cheese, meat, vegetables (sauerkraut, spinach, eggplant, and tomato), and alcoholic beverages (Maintz and Novak, 2007). The concentration of histamine varies extensively not only between different food groups, but also within the varieties (Santos, 1996; Bodmer et al., 1999).

In contrast to IgE-mediated food allergy wherein ingestion of even a small amount of the food elicits allergic symptoms, the cumulative amount of histamine is crucial in the case of histamine intolerance. Histamine in food extracts (1/1000 w/v) did not interfere in intradermal skin tests (May, 1976). A high incidence of 'false positive' reactions in non-allergic persons to extracts of strawberry, spinach, cheese and fermented foods may be due to unwarranted use of high concentrations for the skin tests (Fontana et al., 1963; Doeglass and Nater, 1968).

Very little information is available on the histamine content of different varieties of eggplant used in India; moreover, information about the clinical symptoms caused by different varieties is lacking. Considering the potential

adverse effects that histamine can have and the relatively few data available from the literature on the interference of histamine present in allergen extracts on SPT response, it appeared very important to study the effect of histamine on the skin test response in non-atopic subjects. The major objectives of this study are to quantitate the amount of histamine in four varieties of raw, cooked, and dialyzed eggplant extracts, and to examine the concentration-dependent skin test response of histamine in non-atopic individuals to find out if histamine present in eggplant is a contributory factor in producing false positive results.

MATERIALS AND METHODS

Analytical grade histamine dihydrochloride (histamine.2HCl) and *o*-phthalaldehyde were procured from Sigma-Aldrich Chemical Co., St. Louis, MO.

Analytical grade *n*-butanol and fluorometric grade *n*-heptane were procured from Qualigens Fine Chemicals, Mumbai, India.

Four varieties of fresh eggplant [green round type (*S. melongena* var. *esculentum*, GE), green slender long type (*S. melongena* var. *serpentinum*, GS), purple round type (*S. melongena* var. *esculentum*, PE), and purple slender long type (*S. melongena* var. *serpentinum*, PS)], (Kashyap et al., 2003), tomato-round variety (*Lycopersicon esculentum*), and soybean (*Glycine max*) flour samples were obtained from local supermarkets. Tomato (1.5–2.2 mg histamine/100 g), and soybean (0–0.22 mg histamine/100 g) were used as reference controls in histamine quantitation assay (Feldman, 1983; Williams et al., 1992).

Skin Prick Test

This was carried out after obtaining clearance from the Institutional Human Ethics Committee; informed consent was obtained from all the non-atopic subjects. Since it is known from our work that the highest incidence of eggplant allergy is seen in the 16–30 years age group, we selected subjects from this age group (Harish Babu et al., 2008). SPT was performed on non-atopic subjects, aged 20–25 years (without any history of allergic diseases such as allergic rhinitis, asthma, food and drug allergies including eggplant allergy) as per the standard procedure (Sanico et al., 2002) using sterile prick lancetter (Bayer Pharmaceutical Division, Spokane, WA, USA).

Eggplant extracts (raw, cooked, and dialyzed) along with positive control (1.66 mg/mL histamine.2HCl equivalent to 1 mg/mL histamine base) and negative control [50% glycerinated phosphate-buffered saline (PBS)] were used for SPT. Each sample was pricked with a separate sterile lancet to avoid sample carryover. The wheal and flare diameters were measured after 20 min.

A wheal diameter of 3 mm greater than that of the negative control was considered positive.

As the protein content of eggplant is low (~1% by fresh weight) (Lawande and Chavan, 1998), and a significantly lower SPT response with 10% w/v extracts in our experience, there is a good probability of missing potential eggplant-allergic subjects leading to an underestimation of the incidence of eggplant allergy. Hence, we have used 50% w/v extracts for SPT in all our studies.

Preparation of Eggplant Extracts

Raw Extract. Fresh eggplant extract (50% w/v) was prepared by blending eggplant in a rotating blade homogenizer for approximately 5 min in PBS, pH 7.4. The extract was filtered through cheesecloth and centrifuged at $12,000 \times g$ at 4°C for 15 min. In order to remove the fine particulates, the supernatant was filtered through Whatman No.1 filter paper, and this is designated as 50% w/v raw extract. Tomato and defatted soybean extracts were prepared in an identical way as that of eggplant extract, but at 10% (w/v) concentration.

Cooked Extract. Cooked eggplant extract (50% w/v) was prepared by keeping eggplant cut-pieces in PBS at 100°C for 10 min, and then allowed to cool. The cooked eggplant along with the buffer used for cooking was subjected to the procedure described above for the preparation of raw eggplant extract.

Dialyzed Extract. Both raw and cooked eggplant extracts were separately dialyzed using 3.5 kD cut-off dialysis membrane in distilled water at 4°C for 2 d, to remove the histamine present in the extracts.

Quantitation of Histamine in Eggplant Extracts

Histamine was quantitated by the fluorometric method (Siegel et al., 1990). One milliliter of eggplant extracts was pipetted into several polystyrene tubes containing 300 mg NaCl and 1.25 ml *n*-butanol. To these, 0.1 mL of 3 N NaOH was added quickly, and the tubes were vortexed and centrifuged at $600 \times g$ at 4°C for 5 min. The top butanol layer (1 mL) was transferred to a fresh tube containing 0.6 mL of 0.12 N HCl followed by the addition of 1.9 mL *n*-heptane. The tubes were shook for 1 min by rapid inversion, allowed to settle for 5 min for clear phase separation. The bottom acid layer (0.5 mL) was carefully transferred to fresh tubes containing 0.5 mL of 0.12 N HCl. To each tube, 0.1 mL of 1 N NaOH was added followed immediately by the addition of 25 μ L of 0.2% *o*-phthalaldehyde, and vortexed. The reaction was carried out on an ice bath for 40 min, and then stopped by adding 0.05 mL 2 M phosphoric acid. After vortexing, the samples were brought to ambient temperature in the dark for 15 min. The fluorescence intensity of the samples were read in a spectrofluorometer (λ_{EX} =360 nm; λ_{EM} =450 nm). Based on the calibration

curve for histamine.2HCl (1 to 200 ng/mL), results were calculated in ng/mL of histamine.2HCl, and then expressed as ng/mL of histamine (note: 1.66 mg histamine.2HCl = 1 mg histamine).

Statistical Analysis

To test the statistical difference of the histamine content between the eggplant varieties, one-way analysis of variance (ANOVA) was used. A p-value of < 0.05 was considered to be statistically significant. The statistical analysis was performed using SPSS Software Package 10.0 version (SPSS Inc., Chicago, IL, USA).

RESULTS

Histamine Content of Eggplant Varieties

Quantitation of histamine in 4 varieties of eggplant was determined by fluorometry. Table 1 shows the histamine contents of four varieties of eggplant as analyzed in raw, cooked, and dialyzed extracts. The histamine contents of eggplant varieties ranged from 0.89–2.41 mg/100 g (fresh weight);

Table 1: Histamine content and SPT of extracts of eggplant varieties.

Samples	Histamine, mg/100 g fresh wt. (Mean $\pm$ s.e.m.)	Wheal diameter, mm ^a (Mean $\pm$ s.e.m.)
Negative control ^b	n.a.	1.0 $\pm$ 0.0
Positive control ^b	n.a.	5.0 $\pm$ 0.2
<i>Raw extract</i>		
Soybean ^c	0.14 $\pm$ 0.03	n.a.
Tomato ^c	1.33 $\pm$ 0.21	n.a.
<i>Eggplant extracts^d</i>		
GE	2.41 $\pm$ 0.13	3.6 $\pm$ 0.3
GS	1.80 $\pm$ 0.28	3.0 $\pm$ 0.3
PS	1.35 $\pm$ 0.16	2.2 $\pm$ 0.1
PE	0.89 $\pm$ 0.12	2.3 $\pm$ 0.2
<i>Cooked extract</i>		
Soybean	0.12 $\pm$ 0.03	n.a.
Tomato	1.19 $\pm$ 0.14	n.a.
<i>Eggplant extracts</i>		
GE	2.07 $\pm$ 0.43	3.7 $\pm$ 0.2
GS	1.58 $\pm$ 0.22	3.2 $\pm$ 0.1
PS	1.16 $\pm$ 0.24	2.5 $\pm$ 0.2
PE	0.79 $\pm$ 0.10	2.3 $\pm$ 0.1

n.a.=not applicable ^aSPT considered positive if the wheal diameter is 3 mm greater than negative control; since flare was observed in only 2 out of 13 subjects, only wheal diameter is given ^bnegative control, 50% glycerinated PBS; positive control, 1.66 mg/mL histamine.2HCl ($\approx$ 1 mg/mL histamine base) ^cSoybean and tomato were used as reference controls ^dEggplant extracts: GE, green round; GS, green slender long; PS, purple slender long; PE, purple round. Statistical analysis of histamine content: GE vs. PS (p < 0.05); GE vs. PE (p < 0.01).

the highest value was seen in the case of the green round variety (GE). Purple round variety (PE) has the lowest histamine content (0.89 mg/100 g fresh weight). Among the four varieties of eggplant used here, the green round (GE) and slender long (GS) varieties have higher histamine content than the purple round (PE) and slender long (PS) varieties.

It was observed that the histamine content of the green round (GE) variety is significantly different from the purple slender long (PS) ($p < 0.05$) and the purple round (PE) ($p < 0.01$) varieties, but not significantly different from the green slender long (GS) variety. Therefore, the histamine content between the green and purple eggplant varieties shows varietal difference.

The histamine content of cooked eggplant extracts (Table 1) ranged from 85.8–89.1% of the values obtained for the corresponding raw eggplant extracts, with a mean value of 87.3%. This indicates that there is a loss of approximately 11–14% in histamine content upon cooking. The histamine contents of dialyzed samples of raw extracts of the eggplant varieties ranged from 0.07–0.12 mg/100 g (data not shown). Similar values were found for the dialyzed samples of corresponding cooked extracts (data not shown).

Effect of Eggplant Extracts on SPT in Non-atopic Subjects

To study the effect of different concentrations of histamine in eggplant extracts, SPT was carried out on non-atopic individuals using raw, cooked, and dialyzed extracts of 4 varieties. One milliliter of raw eggplant extracts (non-glycerinated) contains the following amounts of histamine in various varieties: 40.3 μg (green round), 27.1 μg (green slender long), 20.5 μg (purple slender long), and 12.6 μg (purple round) (Fig. 1).

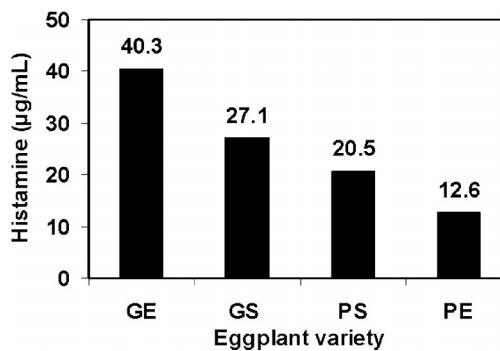


Figure 1: Histamine content ($\mu\text{g/mL}$) of raw eggplant extracts used for SPT (note: 100 $\mu\text{g/mL}$ of histamine.2HCl $\equiv$ 60.2 $\mu\text{g/mL}$ of histamine). GE, green round; GS, green slender long; PS, purple slender long; PE, purple round.

The results of the SPT in terms of the mean wheal/flare response are shown in Table 1. The SPT results were negative in all the subjects tested with the exception of 2 subjects who showed positive SPT to all the varieties of eggplant in both raw and cooked forms.

Among the four varieties of eggplant, these two subjects reacted more positively to the green varieties (wheal/flare diameters of 4/12 to 5/20 mm) than the purple varieties (3/0 to 4/16 mm). Typical wheal/flare associated with histamine positive control was absent in all the subjects excepting subject # 1 and 2. The dialyzed extracts were negative (wheal/flare response of 1/0 mm) in all the subjects (data not shown).

Assessment of Histamine Sensitivity in Non-atopic Subjects by SPT

Five subjects were selected from the 13 non-atopic subjects who gave a positive SPT response with at least one of the eggplant extracts. The SPT response as a function of histamine. 2HCl concentration ranging from 0.1–1000 µg/mL is shown in Table 2. It is seen that the minimum concentration of histamine.2HCl required for a positive SPT response is 100 µg/mL (equivalent to 0.06 µg/mL histamine base). Only in the case of subject # 1, a positive SPT response is seen at 10 mg/mL histamine.2HCl. Thus, only one non-atopic subject reacted to histamine at one-tenth concentration compared to the rest of the non-atopic subjects. Hence, it may be noted that only one subject behaved differently from the rest of the subjects indicating that the threshold of histamine sensitivity is lower for this subject. Generally, 1 mg/mL histamine.2HCl produces wheals having 4.5 mm diameter (Dreborg et al., 1987).

Table 2: SPT results of histamine sensitivity for assessing threshold in non-atopic subjects^a

Histamine.2HCl concentration (µg/mL)	Wheal/flare diameter, mm ^b				
	Subject number				
	1	2	3	4	5
Negative control ^c	1/0	1/0	1/0	1/0	1/0
0.1	2/0	2/0	1/0	2/0	1/0
1.0	2/0	3/0	2/0	2/0	2/0
10.0	4/16	4/0	3/0	3/0	2/0
100.0	4/20	4/16	3/16	4/16	3/0
1000.0	5/25	5/20	4/20	5/16	4/16

^aSubjects # 1 and 2 (from the 13 non-atopics in Table 1) who tested positive for eggplant extracts.

^bSPT considered positive if the wheal diameter is 3 mm greater than negative control.

^cnegative control. 50% glycerinated phosphate-buffered saline.

DISCUSSION

Histamine occurs naturally in certain foods as elaborated earlier. Among the vegetables, histamine is present to a moderate extent in spinach (2.0–6.0 mg/100 g), tomato (0.7–3.0 mg/100 g), and eggplant (2.6–3.8 mg/100 g) (Feldman, 1983; Williams et al., 1992; Moret et al., 2005; ECARF, 2005). It has been shown that fresh and baked eggplant contains 2.9–3.8 and 2.5–2.6 mg histamine, respectively, per 100 g (Feldman, 1983). We have observed varietal difference in the histamine content of eggplant varieties. Compared to the eggplant variety having the lowest histamine content (PE), the other 3 varieties have approximately 1.5- to 3-fold higher histamine content. With respect to the color of the eggplant, the green varieties appear to contain more histamine than the purple varieties. Our data on histamine in cooked extracts shows that a uniform loss of 11–14% is seen in different varieties of eggplant upon cooking. This is in agreement with the report that boiling eggplant in PBS at 100°C for 10 min does not destroy histamine or cause any increase in histamine due to histidine decarboxylation (Feldman, 1983).

It has been reported that ingestion of histamine-containing foods such as cheese, certain vegetables, meats, and red wines can cause ‘dry’ flushes and produce histaminuria (Feldman, 1983; Spencer and Wilkin, 1994). Histamine-releasing foods (chocolate, papaya, strawberry, pineapple, banana, and certain nuts) can also cause urticaria and angioedema through direct mast cell degranulation, i.e., non-immunologically without the participation of IgE (Muller, 2004). It has been suggested that foods containing high but non-toxic levels of biogenic amines or the ‘histamine-releasing foods’ may exacerbate symptoms in mastocytosis (Vlieg-Boerstra et al., 2005).

Histamine found in pollen, mold, and food extracts could, on rare occasions, produce false positive results in allergy diagnosis such as SPT and basophil histamine release assays, and therefore could affect the results (Williams et al., 1992). Oral administration of 75 mg histamine—a dose found in normal meals—can provoke immediate as well as delayed symptoms in 50% of healthy females without a history of food intolerance (Wöhrle et al., 2004). Hence, in cases of non-confirmation of food allergy by allergy diagnosis or internal disorders (mastocytosis), histamine content in foods should strongly be considered for evaluation.

The incidence of adverse reactions to eggplant was rather high compared to any of the reported food allergies to vegetables and fruits in the Indian population (Pramod and Venkatesh, 2004; Harish Babu et al., 2008). Initially, it was surmised that the high incidence of food allergy to eggplant (6.4–10%) based on case histories and positive SPT was due to the high content of histamine in eggplant. However, from the present study it appears that the amount of histamine in different varieties of eggplant (12.6–40.3 µg/mL) used for SPT does not elicit false positive results as this histamine concentration lies

between 10 and 100 $\mu\text{g/mL}$ of histamine.2HCl, which produces positive responses in only a few non-atopic subjects.

These subjects can be classified as highly sensitive subjects with respect to histamine reactivity in SPT., i.e., they have a lower threshold. In such subjects, histamine intolerance can easily be mistaken for eggplant allergy.

In conclusion, the differences in the amount of histamine content among the extracts of various eggplant varieties used for SPT do not have an influence on the SPT results. However, histamine sensitivity in some individuals should be considered as an important factor in diagnosing eggplant allergy based on only skin prick test diagnosis.

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