Ⅱ．研究成果の刊行に関する一覧

研究成果の刊行に関する一覧表

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Ⅲ．研究成果の刊行物・別冊

Nutraceutical Proteins and Peptides in Health and Disease

Edited by

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Preface

Recent advancement of science has demonstrated myriad biological activity associated with food proteins and peptides. Reports of the beneficial health effects of some peptides, short-chain and otherwise, have been appearing in the literature. A variety of such peptides may be prepared upon hydrolysis of proteins, using either chemical or enzymatic processes, from a number of source materials, including milk, soy protein, and other plant as well as animal sources. These peptides may have a positive influence on calcium absorption, regulation of serum cholesterol, and the action of proteins as immunomodulators. Furthermore, a number of peptides may possess antimicrobial properties and, hence, may enhance the body's defense mechanisms or be used for rendering microbial stability to foods. Hydrolysis of proteins may also lead to the production of hypoallergenic products, and some may have, in part, inhibitory effects for angiotensin-I-converting enzymes (ACE). Thus, they may have applications in the treatments for blood pressure, heart failure, and myocardinal infarction, as well as diabetic conditions. Bioactive peptides may also be influential in stress reduction through an opiate-like effect.

Quantitative structure–activity relationships have been developed for evaluating the biological role of peptides. Some of the effects are arising from the specific amino acid sequence of individual peptides. Meanwhile, the antioxidant activity of such products has been demonstrated, and this activity may be responsible, at least in part, for some of the biological properties of peptides. Finally, recent developments in proteomics may help in providing novel means for further clarifications regarding the activity and role of biopeptides.

We are grateful to all the authors for their state-of-the-art contributions that made the publication of this book possible. This is the first book covering discussions on bioactive proteins and peptides in the area of nutraceutical and functional foods and can serve as a compendium of information for biochemists, nutritionists, food scientists, and health professionals in universities as well as in government and industry research laboratories. The book could also be used as a reference by senior undergraduate and graduate students. We extend our appreciation to Jennifer Kovacs-Nolan for her help in editing the manuscript.

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Fereidoon Shahidi

24 Meat Allergy

Soichi Tanabe and
Toshihide Nishimura

CONTENTS

24.1 INTRODUCTION

Meat and its products are important foods because of their high nutritional value and palatability. Especially in western diets, meat is a main source of protein, for example, Americans eat about 30 kg of beef per person per year. Generally, meat is less allergenic than common allergy-inducing foods such as cow's milk, hen's egg, wheat, peanuts, and so on. Thus, a quarter century ago, children with food allergies were advised to be placed on an elimination diet that included beef (1). However, there is increasing evidence that even meat can provoke allergic reactions in sensitizing patients. The prevalence of beef, pork, and chicken allergy was reported to be 73%, 58%, and 41%, respectively, among 57 subjects with suspected meat allergies in USA (2). In Japanese children with food allergies, the prevalence of chicken allergy was reported to be the highest (4.5%) with allergies to other meats following (3%), based on a questionnaire study (3). Although IgE binding to cooked meat is weaker than to raw meat, some patients are sensitive to well-cooked meat.

This brief chapter presents general information on meat allergy and its allergens, with the main focus on beef allergy. We will also discuss the stability of meat allergens, which may help readers in the design of hypoallergenic meat products.

24.2 BEEF ALLERGY AND ITS ALLERGENS

Beef allergy is reported to occur with an incidence between 3.3 and 6.5% among children with atopic dermatitis (1–4). This can increase to about 20% in children with cow's milk allergy (4). The major beef allergens are bovine serum albumin (BSA, *Bos d* 6, 66 to 67 kDa) (4–9) and bovine gamma globulin (BGG, *Bos d* 7, 160 kDa) (8–10). In addition, actin, myoglobin, and tropomyosin sometimes cause allergic reactions, while myosin is rarely allergenic (4,8). BSA and BGG are also present in milk, thus some children with cow's milk allergy are sensitive to beef as well. In this respect, as suggested by Ayuso et al. (10), sensitization to beef may be secondary to milk allergy (since milk is introduced first in the diet).

Serum albumin is one of the most widely studied and applied proteins in biochemistry. It is also the most abundant protein in the circulatory system, accounting for 60% of total serum protein, with a concentration of approximately 40 mg mL^{-1} (11–13). Serum albumins comprise about 580 amino acid residues and are characterized by a low content of tryptophan and a high content of cysteine and charged amino acids such as aspartic and glutamic acids, lysine, and arginine. The tertiary structure comprises three domains, I, II, and III (aa 1–190, 191–382, 383–581) that assemble to form a heart-shaped molecule. The fact that a major component of serum acts as an allergen is very surprising for the following reason: it is remarkable that albumins from animals, which are very similar in sequence, structure, and function to human serum albumin (HSA), are recognized by the human immune system as allergens instead of inducing tolerance.

Trials to identify the immunoglobulin E (IgE)-binding epitopes of BSA have been performed by several groups (5,6). For example, Beretta et al. (6) reported that the C-terminal region (aa 500–574) of BSA may be an epitopic area for patients based on analyses of tryptic hydrolyzates of BSA. In the meantime, we carried out a break-through study, in which the precise regions of IgE-binding as well as T-cell epitopes were identified (5).

Prior to our experiments, we hypothesized that BSA-specific antibodies and T cells react primarily with sequential epitopes in which the amino acid sequences differ greatly between BSA and HSA. To clarify this hypothesis, 16 peptides (Nos. 1–16) corresponding to such regions were synthesized as candidate epitopes (Table 24.1). Among them, at least two regions, aa 336–345 (No. 7) and aa 451–459 (No. 15), were found to be the major IgE-binding epitopes (Figure 24.1A). In inhibition ELISA (enzyme-linked immunosorbent assay), EYAV (aa 338–341) and LILNR (aa 453–457) bound to patient IgE antibodies and were found to be the cores of the IgE-binding epitopes.

Among eight IgE-binding epitopes, three were found to contain an EXXV motif (HPEYAVSVLL (No. 7), PVESKVT (No. 12), and VMENFVAF (No. 15)). The corresponding sequences in HSA are HPDYSVVLLL, PVSDRVT, and VMDDFAAF, respectively. Comparing two epitopic sequences (Nos. 7 and 15) in BSA with the corresponding sequences in HSA, it is likely that E residues (E338 and E547) are important for recognition by IgE antibodies, since the corresponding residues in HSA are D in both peptide Nos. 7 and 15. Therefore, two analogue

TABLE 24.1
Amino Acid Sequences Syntherized Peptides and Comparsion with the Corresponding Sequences in HSA

Peptide	Sequence Synthesized		Corresponding Sequences in HSA
No. 1	ESHAGCEKS	(57–65)	ESAENCDKS
No. 2	DDSPDLPKLKPDPNTLC	(107–123)	DDNPNLPRLVRPEVDVMC
No. 3	CDEFKADEKKFWGKY	(123–137)	CTAFHDNEETFLKKY
No. 4	LLYANKYNGVFQEC	(153–166)	LLFFAKRYKAAFTEC
No. 5	PKIETMREKVLTSS	(178–191)	PKLDELRDEGKASS
No. 6	EKDAIPEDLPPLTADFAEDK	(292–311)	ENDEMPADLPSLAADFVESK
No. 7	HPEYAVSVLL	(336–345)	HPDYSVVLLL
No. 8	PHACYTSVFDKLKHLVDEP	(364–382)	PHECYAKVFDEFKPLMEEP
No. 9	NCDQFEKLG	(389–400)	NCELFEQLG
No. 10	VGTRCCTKPESERM	(431–444)	VGSKCCHPEAKRM
No. 11	LSLILNRLC	(451–459)	LSVVLNQLC
No. 12	PVESKVT	(466–472)	PVSDRVT
No. 13	PKAFDEKLFT	(497–506)	PKEFNAETFT
No. 14	TLPDTEKQI	(513–521)	TLSEKERQI
No. 15	VMENFVAF	(545–552)	VMDDFAAF
No. 16	LVVSTQTAL	(573–581)	LVAASQAAL
	EYAV	(338–341)	
	LILNR	(453–457)	
E338D	HPDYAVSVLL	(336–345)	
E547D	VMDNFVAF	(545–552)	

Underlined residues represent amino acid differences between BSA and HSA. (Tanabe et al., 2002)

peptides, E338D (HPDYAVSVLL) and E547D (VMDNFVAF), with amino-acid substitutions from E to D were synthesized (see Table 24.1), and their IgE-binding abilities were characterized (14). As a result, the substitution of the glutamic acid in the EXXV sequence with aspartic acid led to a remarkable reduction in IgE-binding ability (Figure 24.1B). Thus, ^{338}E and ^{547}E in BSA were thought to be important for recognition by patient IgE antibodies. In other words, the difference between D (human type) and E (bovine type) at positions 338 and 547 seems to be a major cause of the allergenicity of BSA. According to the three-dimensional structure of HSA, these two D residues are located at the surface of the molecule (Figure 24.2). Although the three-dimensional structure of BSA is not available, the corresponding E residues at positions 338 and 547 in BSA are assumed to be located similarly to the D residues in HSA, since the tertiary structures of BSA and HSA are very similar to one another (12). Therefore, it is possible that IgE-antibodies in allergic patients easily recognize E residues at positions 338 and 547 on the surface of BSA, with the allergic reaction taking place subsequently.

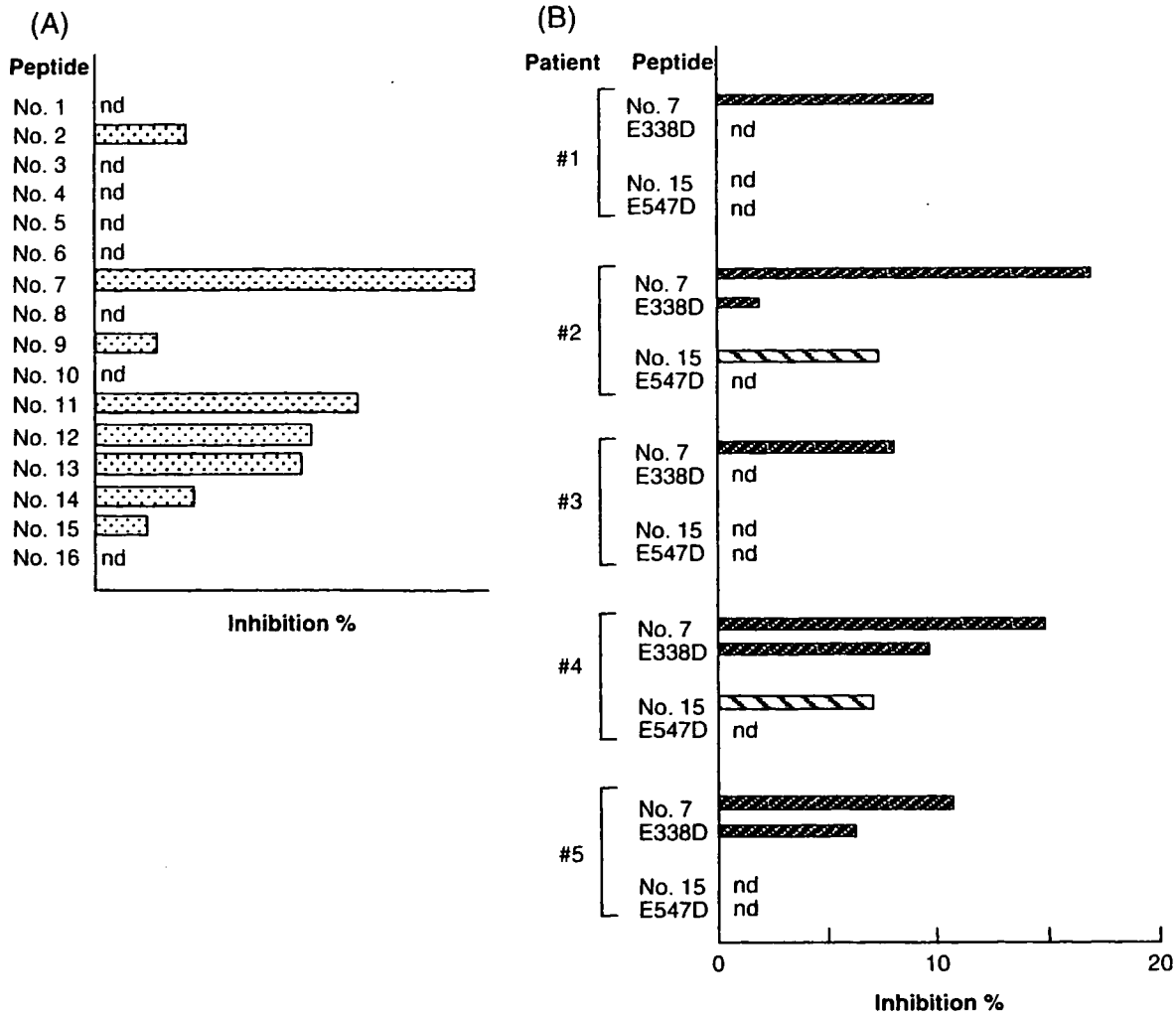

FIGURE 24.1 Inhibition ELISA of the synthetic peptides listed in Table 24.1. (A) Inhibition ELISA of 16 BSA peptides using pooled serum. From S. Tanabe, Y. Kobayashi, Y. Takahata, F. Morimatsu, R. Shibata, T. Nishimura. Some human B and T cell epitopes of bovine serum albumin, the major beef allergen. *Biochem. Biophys. Res. Commn.*, 293: 1348–1353, 2002, with modifications. With permission. (B) Inhibition ELISA of aa336–345 (No. 7), aa451–459 (No. 15), E338D and E547D using serum from 5 individual patients (#1–#5). From S. Tanabe, R. Shibata, T. Nishimura. Hypoallergenic and T cell reactive analogue peptides of bovine serum albumin, the major beef allergen. *Mol. Immunol.*, 41: 885–890, 2004. With permission.

As for the epitopes of bovine gamma globulin (BGG), Ayuso et al. (10) predicted conformational epitopes, since they found that IgE reactivity to BGG completely disappeared when beef extracts were treated under reducing conditions. In addition, they stressed BGG as the only major clinically relevant beef allergen (10).

24.3 PORK ALLERGY AND ITS ALLERGENS

Although pork allergy is relatively rare, it may manifest as atopic dermatitis and oral allergy syndrome (OAS), among other possibilities. The frequency of sensitization in the skin prick test (SPT) to pork was reported to be 2% in Germany (15).

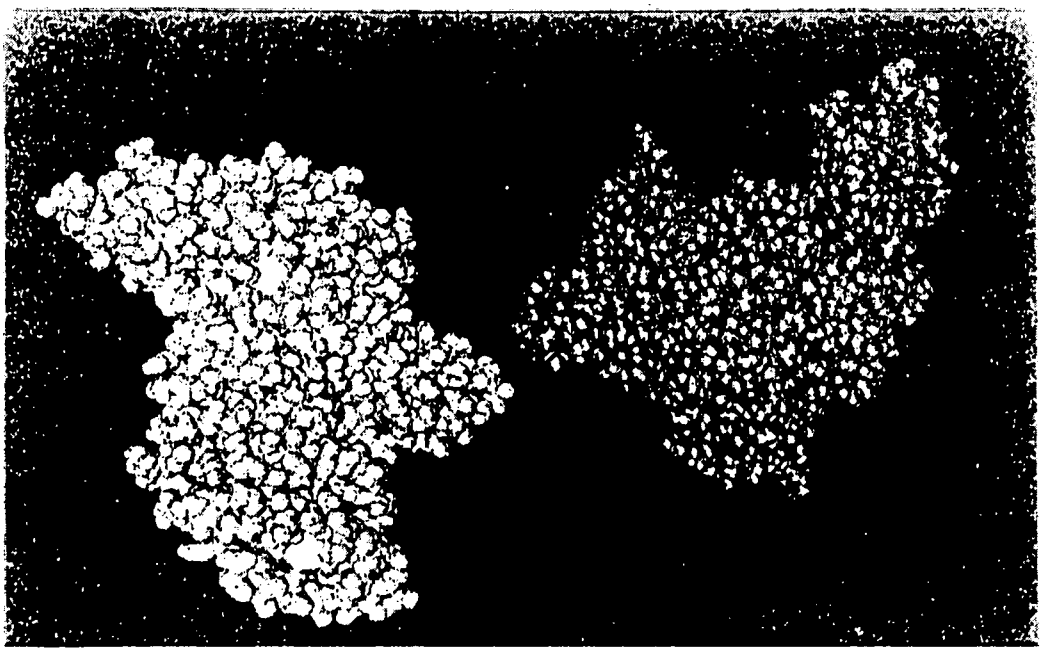

FIGURE 24.2 The molecular structure of HSA is shown in gray, and the two aspartic acid residues (upper, D338; lower, D547) are highlighted in white. The drawing was generated with software Cn 3 D version 4.1 (www.ncbi.nlm.nih.gov). From S. Tanabe, R. Shibata, T. Nishimura. Hypoallergenic and T cell reactive analogue peptides of bovine serum albumin, the major beef allergen. *Mol. Immunol.*, 41: 885–890, 2004. With permission.

The cross-reactivity of porcine meat and cat epithelia/dander has been reported and called "pork-cat syndrome" (16–18). Nearly all patients with IgE antibodies to pork also have IgE antibodies to cat epithelia/dander. However, among patients with IgE antibodies to cat epithelia/dander, only some (~20%) have IgE antibodies to pork (16).

Hilger et al. (18) performed immunoblotting and cross-inhibition assays and found that porcine serum albumin (PSA) and cat serum albumin (*Fel d* 2) are jointly recognized molecules. Inhibition assays have shown that the spectrum of IgE reactivity to cat serum albumin completely contains IgE reactivity to PSA, suggesting that sensitization to cats is the primary event (18).

The phenomenon of cross-sensitization between inhalants and food allergens is of increasing importance clinically. Allergic cross-reactions between pollen allergens and food allergens of plant origin are well known (e.g., birch pollen–hazelnut–apple and mugwort–celery allergic clusters).

Besides serum albumin, several other IgE-binding proteins (51-, 40-, and 28- to 30-kDa) have been detected in pork (19). It should be noted that even pork kidney and gut sometimes cause allergic reactions (19).

24.4 CHICKEN ALLERGY AND ITS ALLERGENS

Similar to the cross-reactivity between porcine meat and cat epithelia/dander (pork-cat syndrome) described earlier, there is cross-reactivity between chicken and hen's egg yolk, which is known as "bird-egg syndrome" (20–22). Egg yolk contains significant quantities of serum proteins. In bird-egg syndrome, the cross

reacting allergen has been reported to be α-livetin in egg yolk (20), which is identical to chicken serum albumin (*Gal d* 5) (23). Chicken serum albumin can act as both an inhalant and a food allergen in patients with bird-egg syndrome (21). In this regard, sensitization to meat may be secondary to hair and dander sensitization (especially in veterinarians) as well as secondary to milk allergy, as described above.

Other than chicken serum albumin, several allergens have been reported by Ayuso et al. (2). Their immunoblotting data showed the existence of eight bands (150-, 66-, 45-, 31-, 28-, 24-, 20-, and 17-kDa) in raw chicken meat that react with patients' sera.

For the convenience of the reader, the major meat allergens are summarized in Table 24.2. The importance of serum albumin as a cross-reacting meat allergen needs to be reemphasized.

24.5 SERUM ALBUMIN AS A CROSS-REACTING MEAT ALLERGEN

Restani et al. (24) reported the cross-reactivity between serum albumins from different animal species. SPT and immunoblotting were performed for each of seven serum albumins (beef, sheep, pig, horse, rabbit, turkey, and chicken) (24). As a result, a clear relationship was found between the sequence homology of different serum albumins with BSA and the percentage of positive SPT and immunoblotting in the serum of beef-allergic children (Table 24.3). Therefore, the use of alternative meats in meat-allergic patients must be carefully evaluated on an individual basis (4).

As described earlier, cat serum albumin is one of the cat allergens. Also, dog serum albumin is known as a cross-reacting allergen (25); all patients allergic to cat serum albumin also showed high IgE titers to dog serum albumin, even when they had no contact with dogs. Thus, it can be said that serum albumin is an important inhalant allergen as well as food allergen.

TABLE 24.2
Major Meat Allergens (Summary)

Meat	Allergen	Cross-reactive allergen
Beef	Serum albumin (*Bos d* 6)	Other serum albumins - overlap with cow's milk allergy-
	Gamma globumin (*Bos d* 7)	Especially lamb and vension (but weakly to pork and chicken) - overlap with cow's milk allergy-
Pork	Serum albumin	Cat serum albumin (*Fel d* 2) - pork-cat syndrome-
Chicken	Serum albumin (*Gal d* 5)	Identical to α-livetin in egg yolk - bird-egg syndrome-

TABLE 24.3
Relationship Between Sequence Homology of Different Serum Albumins and Positive Responses Obtained in SPT and Immunoblitting in the Sera of Beef-Allergic Children (With Permission from the American College of Nutrition)

Species	% Homology with BSA	% of positive responses (n=6)	
		SPT	Immunoblotting
Beef	100.00	100	100
Sheep	92.26	100	66.7
Pig	78.84	50	50
Horse	74.14	50	0
Rabbit	-	33.3	0
Turkey	-	33.3	0
Chicken	44.98	0	0
Human	76.28	-	0

(Restani et al., 1997)

24.6 METHODS OF REDUCING THE ALLERGENICITY OF MEAT ALLERGENS

There are at least two treatments available that can reduce or abolish the allergenicity of meat allergens, heat and enzymatic treatment.

24.6.1 HEAT TREATMENT

Fiocchi et al. (7) reported the effect of heating on the allergenicity of beef and BSA. In their study, 10 children with beef allergy and positive SPT to BSA were evaluated by SPT and DBPCFC (double-blind, placebo-controlled food challenge). Among them, 7 children were found to be sensitive to heated BSA (100°C for 5 minutes) by SPT, and 4 children were positive by DBPCFC. According to these results, heating appeared to partially reduce the allergenicity of BSA and beef but did not completely abolish allergenicity. On the other hand, Werfel et al. (26) reported that BSA and BGG were heat labile in the beef sample.

Pork allergens are also resistant to heat treatment, at least to some extent. Atanaskovic-Markovic et al. (27) reported that six pork allergens were detected even in cooked/roasted pork and concluded that cooked/roasted pork retains allergenic epitopes capable of inducing IgE-mediated food allergy.

A recent study by Quirce et al. (21) showed that heating reduced, but did not abolish, the allergenicity of chicken serum albumin (α-livetins). It should be noted that in some cases of chicken allergy, heating (140°C for 20 minutes in a conventional oven) may result in the formation of new allergenic moieties, as suggested by Ayuso et al. (2).

Of course, as shown using milk whey proteins, the thermal stability of proteins can be influenced by the pH (28), divalent cations (29,30), sugar content (30), and lipid concentration of the solution in which the proteins are dissolved. Thus, further detailed studies are needed to clarify the effectiveness of heat treatment.

Taken together, meat allergens are "partially" heat labile, and this fact can explain why some sensitized patients may tolerate well-cooked meat, but not raw meat. Patients reacting only to meat cooked to rare may not need to maintain a complete meat elimination diet. However, it should be noted that heating cannot "completely" abolish the allergenicity of meat allergens.

24.6.2 Enzymatic Treatment

Several protein hydrolyzate-based products such as whey-based formulas (31), hypoallergenic rice (32), and hypoallergenic flour (33), have been produced and considered suitable for use in the management of allergic patients. The merit of these products is that they possess the same nutritional value as the intact proteins. Therefore, if a hydrolytic reaction could decompose the structures of meat allergens, then the product (hypoallergenic meat) would be of great benefit for patients.

Fiocchi et al. (34) investigated the effect of peptic digestion on the allergenicity of BSA as well as ovine serum albumin (OSA) as measured by SPT, RAST (radioallergosorbent test) and SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) analysis using 12 children with beef and lamb allergies (The reason OSA was included is that lamb is often suggested as a substitute for beef and milk in atopic children). All were SPT positive for intact BSA and OSA. The authors reported that peptic digestion decreased the allergic potential even after only 5 minutes of hydrolysis; 67% of the children became SPT negative for hydrolyzed BSA, and 75% became SPT negative for hydrolyzed OSA. After 2 hours of hydrolysis, only 17% reacted to hydrolyzed BSA and none to hydrolyzed OSA. However, 4-hour-hydrolyzed BSA still induced an SPT response in the same 7 17% of children who were positive to 2-hour-hydrolyzed BSA. From this data, it was concluded that peptic digestion can influence the allergenicity of serum albumins but not completely abolish allergenicity in severely allergic patients. The more rapid disappearance of SPT reactivity for OSA than for BSA during peptic digestion was also confirmed. This appears to support the clinical observation that ovine meat is generally less allergenic than bovine meat.

Although pepsin alone is incapable of abolishing the allergenicity of BSA completely, it remains possible that BSA allergenicity can be eliminated by using a combination of several enzymes. However, it should be noted that extensive hydrolysis of meat proteins usually leads to the loss of such physicochemical properties as gel-/network-forming activity.

24.6.3 Other Treatments

High-pressure treatment has recently been considered a useful technique for food processing, and the efficiency of this treatment in modifying meat properties has

been reported (35). Changes in the allergenicity of BGG by high pressure treatment were investigated (36). However, high pressure treatment at 200 to 600 MPa failed to decrease the allergenicity of BGG.

It is of interest that industrially heat-treated (steaming) and sterilized (at 122°C for 40 minutes) homogenized beef evoked no clinical reaction in DBPCFC subjects (7,34). This treatment seems to be most effective for eliminating allergenicity.

24.7 SUMMARY

The major beef allergens are bovine serum albumin (*Bos d* 6) and bovine gamma globulin (*Bos d* 7). In addition, actin, myoglobin, and tropomyosin sometimes cause allergic reactions, while myosin rarely does.

Porcine serum albumin and cat serum albumin (*Fel d* 2) are jointly recognized as molecules in pork-cat syndrome, the cross-reactivity between pork meat and cat epithelia/dander. Besides serum albumin, several other IgE-binding proteins are detected in pork.

Chicken serum albumin (*Gal d* 5), which is identical to α-livetin in egg yolk, is responsible for bird-egg syndrome, the cross-reactivity between chicken and hen's egg yolk. In addition to serum albumin, several other IgE-binding proteins are detected in chicken meat.

Since serum albumin is a known dog and cat allergen, it is an important inhalant allergen as well as a food allergen.

Meat allergens are relatively heat labile and easily hydrolyzed by digestive enzymes; however, it should be noted that heating and digestive processes cannot "completely" eliminate the allergenicity in severe allergic patients.

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ORIGINAL ARTICLE

IgE Cross-reactivity between Fish Roe (Salmon, Herring and Pollock) and Chicken Egg in Patients Anaphylactic to Salmon Roe

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ABSTRACT

Background: Salmon roe (SR) anaphylaxis has often been reported and SR-containing foods are designated as 'recommended for allergic labeling' ; however, there have been no reports about its allergenicity, including its cross-reactivity. Because its cross-reactivity is controversial, clinicians are often confused concerning education regarding its dietary elimination. The purpose of this study was to examine the cross-reactivity between SR and other kinds of fish roe, salmon, or chicken egg (CE).

Methods: We measured the specific-IgE to SR, herring roe (HR), pollock roe (PR), salmon and CE using RAST in 27 patients with a fish allergy and 26 control subjects. Then, using the sera of 2 patients with SR anaphylaxis, an ELISA inhibition study was performed to examine the cross-reactivity between SR and HR, PR, salmon or CE. We then compared the IgE binding patterns to SR between the anaphylaxis patients and fish allergy patients with immunoblotting.

Results: There were positive correlations between SR and HR or PR, but none between SR and salmon or CE. In the ELISA study using sera from two patients with SR anaphylaxis, IgE-binding to SR was inhibited more than 50% only when the sera were pre-incubated with HR, inhibited almost 50% by PR in a dose-dependent manner, but not inhibited by CE or anisakis. Salmon inhibited the IgE binding to SR more than 50% in a SR-anaphylaxis patient. The IgE binding patterns to SR from anaphylaxis patients were almost identical and unlike those of patients with fish allergy.

Conclusions: There was a cross-reactivity between SR and HR, but no relationship between SR and CE.

KEY WORDS

anaphylaxis, chicken egg, cross-reactivity, food allergy, salmon roe

INTRODUCTION

There have been very few reports about allergy to fish roe. In western countries, there have been a few case reports, one reporting an anaphylaxis to caviar[1] and the other a severe IgE-mediated reaction to the roe of 2 species.[2] In Japan, even though salmon roe (SR) is listed as a 'recommended for allergic labeling' food because of some patient reports of anaphylaxis to SR, there have been no scientific reports on its allergenicity. Generally, fish roe consists of yolk and vitelline, while there is no protein corresponding to the white of chicken eggs (CE). In fish, the yolk proteins originating from vitellogenin are classified as lipovitellin, phosvitin and a beta'-component. In a report using sera from several SR allergic patients, the beta'-component was identified as the main allergen.[3]

We were burdened with devising a diet for patients allergic to CE or fish if they asked to eat SR. We also have no answer as to whether SR anaphylactic pa-

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