

Seafood allergy

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Purpose of review

Given the importance and prevalence of seafood in our economy and diet, interest in the adverse effects of seafood-induced allergic reactions has increased both in the lay population and the scientific arena. The purpose for this review article is to provide an overview and discussion of current seafood-allergy research.

Recent findings

Current research has produced the discovery of new seafood allergens as well as a better understanding of the interactions of allergens with the host, and the relationships of IgE antibodies with specific allergens. Crossreactivity of similar molecules from seafood and nonseafood sources provides a better understanding of an allergen's role in seafood allergy and a basis to improve patient identification and treatment.

Summary

Findings in recent literature show potential for more precise diagnosis and safer, more effective treatment of seafood allergies.

Keywords

allergen crossreactivity, food allergy, seafood allergy, shrimp

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Introduction

Food allergy is defined as a hypersensitivity reaction to food and can produce a range of symptoms affecting the skin, respiratory tract, and the gastrointestinal tract through IgE-mediated and nonIgE-mediated reactions [1•]. The prevalence of a particular food allergy is largely determined by geographic location and the cultural diet of a population. For instance, the Scandinavian countries have one of the highest consumption rates of cod fish, and in the United States peanut is widely consumed not only in its natural form, but also in processed forms such as peanut butter and peanut oil. Consequently, a higher prevalence of cod fish allergy is seen in Norway, and a relatively high prevalence of peanut allergy is found in the United States. However, such generalizations of food consumption are starting to blur due to changing dietary habits influenced by improvements in transportation of food, and globalization of society and commerce, which facilitate exchanges of diverse ethnic foods. It has been estimated that 6% of children in the United States have food allergies, primarily to milk, egg, peanut, wheat, and soybeans, and that 2% of adults are allergic mainly to seafood, peanut, and tree nuts [2,3].

Concerns regarding food allergy

Lay interest in food allergy, and specifically seafood allergy, has been increasing. Although high morbidity and mortality rates are associated with allergic reactions to food, there is a lack of safe and effective treatment options for food allergies besides avoidance. Due to these limitations, the topic of food substitutions and fillers is of growing concern because they may contain hidden allergens that can pose potentially life-threatening allergic reactions in unsuspecting consumers. For instance, imitation crabmeat is usually composed of Alaskan pollack or monkfish. Also, although its allergenicity is unknown, it is not common knowledge that the chitin of shrimp is used as a filler in pills and other medications. There are various routes through which individuals can be exposed to food allergens. Food allergens are not only ingested, but they can also be inhaled via respiratory droplets, contacted directly on to skin, and inadvertently transferred through cooking water. For instance, there was a recent report of a shellfish-allergic patient who experienced anaphylaxis after kissing her boyfriend who had recently consumed shrimp [4••]. In addition, occupational allergic reactions have been documented in snow crab workers who were exposed to allergens through handling of crab products as well as inhalation of water droplets containing crab

allergens, generated during cooking of crab. Asthma, rhinitis, conjunctivitis, urticaria, contact dermatitis, and even systemic anaphylaxis have been reported in this population [5,6]. Another point for concern is allergen crossreactivity. There is data to suggest that IgE antibody reactivity to one allergen can lead to reactions to similar molecules in other substances through allergen crossreactivity. It has been estimated that 50% of persons who are allergic to a particular species of fish will be allergic to a second species of fish, and that 75% of those allergic to a crustacean will also be allergic to another type of crustacean [7•].

Manifestations of food-induced allergic reactions

It is important to note that reactions to allergens can manifest in various ways, depending on the route of exposure. Generally, exposure to an allergen by inhalation produces respiratory symptoms such as rhinitis and bronchospasm while ingestion of the same allergen can lead to diarrhea, hives, and/or anaphylaxis. Also, much lower doses of inhaled allergens may cause respiratory reactions since these are deposited in a relatively benign environment compared with those causing ingestion-related allergies. Ingested allergens generally require higher doses to elicit a reaction because they are deposited in the harsher environments of the gastrointestinal tract [8]. Untersmayr and colleagues [9•] showed that administration of antacids may favor the development of food-induced allergic reactions in mice by protecting allergenic proteins from degradation. Caviar proteins were introduced to both the study group, which received either sucralfate, ranitidine, or omeprazole, and the control group (no antacids) through the feedings. Compared with the control mice, the group that received antacids showed significant levels of IgE antibody against caviar, T-cell reactivity, and eosinophil and mast cell counts in the gastrointestinal tract [9•]. Beyer [10] proposes that the linear nature of food allergens, compared with the conformational structure of aeroallergens, may help them to survive the digestive process of the gastrointestinal tract.

Importance of seafood

Seafood is important to the worldwide economy and diet. Using the United States as an example, according to the National Marine Fisheries Service, the US fishing industry grossed approximately US\$20.5 billion with about 57 billion pounds of seafood landed during 1997–2002. In 2002 alone it was estimated that 7.2 billion pounds of finfish were caught, with notable leaders in this category being walleye pollack, atlantic menhaden, pacific cod, and salmon. In the same year, 1.3 billion pounds of shellfish were landed; the leading contributors were shrimp, crab, squid, and clam in descending order [11].

Established allergens

Given the tremendous impact that seafood has on our society, past research has focused investigations on seafood allergies and their allergens. Parvalbumin protein is a major allergen found in the muscles of fish and amphibians. One of the first and most extensively characterized parvalbumins is Gad c 1, a major allergen in Baltic cod that regulates calcium flow in muscle sarcoplasm [12–14]. In invertebrates such as crustaceans, molluscs, insects, and arachnids, one of the best-known allergenic proteins is tropomyosin, which is also found in the muscle. Pen a 1 is a shrimp tropomyosin that has been identified as a major allergen to which approximately 85% of shrimp-allergic human subjects show reactivity [15,16]. Other commonly known nonseafood tropomyosin aeroallergens are Der p 10/Der f 10 in house dust mites [17,18] and Per a 7 in the American cockroach [19,20].

New seafood allergens

Over the past few months, research has yielded the identification and characterization of several new seafood allergens. The first was reported by Yu and coworkers [21•], who proposed a new allergen, Pen m 2, in black tiger shrimp. In this study, sera from shrimp-allergic subjects showed IgE binding to *Penaeus monodon* crude extract. One of the IgE-binding proteins was Pen m 2, a 40-kDa structure with arginine kinase activity, which shows approximately 90% similarity with arginine kinases from another species of shrimp (*Marsupenaeus japonicus*), lobster (*Homarus gammarus*), and crawfish (*Procambarus clarkii*). Some 27% of sera from shrimp-allergic subjects showed IgE antibody reactivity with Pen m 2, whereas 72% showed IgE reactivity with tropomyosin [21•]. Another recently identified seafood allergen is Gad m 1 in Atlantic cod fish, which was introduced by Das Dorez *et al.* [22•]. A 24-kDa protein was identified that bound serum IgE and was also recognized by monoclonal antiparvalbumin antibody. The allergen was cloned using PCR primers and was found to be a dimer consisting of 11.5-kDa structures with properties characteristic of β -parvalbumin. Interestingly, Gad m 1 shares greater homology of amino acid sequence with Sal s 1 from salmon (75%) than with Gad c 1 from Baltic cod (62.3%). However, the percentage of patient sera reacting to Gad m 1 was not specified [22•]. Finally, Hamada and colleagues [23•] have reported Sco j 1, Sco a 1, and Sco s 1 from mackerel (*Scomber japonis*, *S. australasicus*, and *S. scombrus*, respectively) as β -parvalbumin proteins, and these are suggested to be major allergens in mackerel. Sco j 1, Sco a 1, and Sco s 1 have very similar IgE-binding epitopes and show a high degree of crossreactivity. Amino acid sequencing of Sco j 1 by cDNA cloning techniques demonstrated a 58% homology with Gad c 1 from cod, 65–75% with parvalbumins (β 1 and β 2) from Atlantic salmon, and

75% with the parvalbumins Cyp c 1.01 and Cyp 1.02 from carp [23••]. Gad m 1, Pen m 2, and the Sco allergens are promising findings, but the degree of their clinical significance as important allergens in humans requires further evaluation.

Allergen crossreactivity

In addition to these recent discoveries, much of current literature is dedicated to studies involving crossreactions of tropomyosin allergens in seafood. This is due in part because the tropomyosins are a family of highly conserved proteins which show a great degree of amino acid sequence homology. The crosssensitizing panallergenic nature of tropomyosin leads to IgE antibody reactivity to different types of organisms such as crustaceans, insects, and arachnids [24]. This has been supported by the work of Fernandes *et al.* [25••] in which nine shellfish-naïve, dust-mite-allergic Orthodox Jews who showed positive prick-skin-test reactivity to shrimp (*Penaeus setiferus*) were selected. All nine subjects showed prick-skin-test positivity to house dust mite, and two out of seven showed prick-skin-test positivity to cockroach mix. A serum pool from three subjects who were dust-mite-allergic and prick-skin-test positive to shrimp showed that reactivity to house-dust-mite tropomyosin by immunoblot could be reduced with a shrimp extract or Pen a 1 in an inhibition assay [25••]. This supports the idea that the highly preserved homologous nature of tropomyosin in shrimp, cockroach, and house dust mites is conducive to crossreactivity among various invertebrates, leading to indirect IgE sensitization to allergens in previously unexposed subjects.

Ramifications of crossreactivity can potentially complicate attempts to diagnose and treat food allergies. The concept of crossreactions between allergens has led to the analysis of IgE antibody binding to epitopes at the level of amino acid sequences and its physical structure. In an article by Ayuso and coworkers, eight major Pen a 1 IgE-antibody-binding epitopes were identified. Then the binding of IgE antibody to Pen a 1-homologous epitopes in Per a 7 (cockroach) and Der p 10/Der f 10 (house dust mite), which differ by specific amino acid substitutions, was studied. Interestingly, shrimp-allergic sera recognized six out of eight Pen a 1-homologous peptides in Per a 7, seven out of eight in Der p 10/Der f 10, and seven out of eight in Hom a 1 (lobster) [26]. Several questions arise: what is the clinical significance of IgE antibody crossreactivity between similar molecules? Can treatment of seafood allergy with immunotherapy be complicated by crossreactions of antigens by possibly sensitizing individuals to other allergenic substances and inducing allergic manifestations? It has been reported that immunotherapy with dust-mite antigen may sensitize some patients to certain foods such as shrimp, limpet, snail, and squid [27–30]. So,

crossreactivity of allergens occurs, but are these clinically significant allergic reactions? Can treatment directed to one specific allergy induce the development of other allergies?

Trend in seafood allergy research

The trend in seafood allergy research is leaning toward furthering our knowledge of IgE antibody reactivity to allergens at the molecular level and applying this information to developing more precise methods of diagnosis and safer treatment modalities. Although crossreactivity with homologous epitopes on various allergens has been shown, IgE reactivity may not necessarily result in the development of clinically significant allergic reactions to all the allergens with which they interact. This potential for diagnostic confusion can be averted by more precise investigations into allergen reactivity to aid in distinguishing between epitope reactivity versus clinical disease. Are there specific IgE-antibody-binding combinations of these epitopes that lead to clinically significant allergic responses to a particular allergen? If so, perhaps clinical allergies can be diagnosed more precisely.

Treatment

In addition to diagnosis of allergies, another focus in research is the development of safer, more effective treatments for seafood allergies. Several potential therapeutic options have been proposed, such as the antiIgE antibody Chinese herbal medicine, food allergy herbal formula-1 (FAHF-1) [31], and interleukin-12 treatment [32], both of which may reduce peanut-induced anaphylaxis, and alteration of epitopes to produce hypoallergenic foods and/or safer vaccines for immunotherapy [33]. On the latter, epitopes can be genetically altered, either by modifying their physical structure or their amino acid sequence, in order to suppress the allergenicity of a particular substance. This technology can be applied to food as well by genetically engineering key epitopes such that hypoallergenic foods can be produced. Indeed, a report by Lehrer and Bannon [34••] describes the effects of substitution of critical amino acids in Pen a 1 epitopes that resulted in significant reduction of IgE antibody binding. Presently, immunotherapy to desensitize patients to food allergies is not practiced due to risk of severe systemic reactions such as bronchospasm, angioedema, and anaphylactic shock [35–37]. However, immunotherapy may be offered in the future if antigens with suppressed allergenic activity can be safely administered and show effectiveness in human subjects.

Conclusion

Seafood has held an important standing in the diet and economy of humankind for thousands of years. However, adverse reactions to seafood consumption are commonly

seen, many of which are allergic in etiology. We have recently come to understand and identify the mechanism of seafood allergy and its allergens. With continued efforts in understanding the nature of allergens, their relationship to similar molecules and other allergenic substances, and their interactions with the host, the future of seafood allergy research holds many exciting possibilities for the development of precise diagnosis and safer, more effective treatment of food allergies.

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