

Available online at www.sciencedirect.com

SCIENCE @ DIRECT®

BIOTECHNOLOGY
ADVANCES

Biotechnology Advances xx (2005) xxx–xxx

www.elsevier.com/locate/biotechadv

Food allergy and its relevance to industrial food proteins

E.N.C. Mills^{a,*}, H. Breiteneder^b^a*Institute of Food Research, Norwich Research Park, Colney, Norwich, NR4 7UA, UK*^b*Department of Pathophysiology, Medical University of Vienna, Vienna, Austria*

Received 17 January 2005; accepted 13 May 2005

Abstract

Food allergies can be defined as IgE-mediated hypersensitivity reactions and are quite distinct from food intolerances, such as Coeliac disease, with symptoms usually appearing within a matter of minutes of exposure. Around 1–2% of adults and up to 5–7% of children suffer from some type of food allergy with foods such as peanuts, tree nuts, wheat and soy, cow's milk, egg, fish and shellfish being responsible for the majority of reactions. The macromolecules recognised by IgE (generally proteinaceous in nature) are termed allergens. A brief description of the allergenic components present in the major allergenic foods is given followed by a short discussion regarding their importance in industrial proteins in the light of recent food labelling legislation for allergens.

© 2005 Published by Elsevier Inc.

Keywords: Allergenic foods; Labelling; Allergens

1. What is a food allergy and why is it a problem?

The terms food allergy and food intolerance are often used interchangeably and there is some confusion regarding as to how they differ. It is generally accepted that an allergy is a hypersensitivity reaction where symptoms appear rapidly following exposure to macromolecules (generally proteins) (Bruijnzeel-Koomen *et al.*, 1995). They are

* Corresponding author. Tel.: +44 1603 255295.

E-mail address: Clare.mills@bbsrc.ac.uk (E.N.C. Mills).

commonly mediated by a specific class of antibody, known as immunoglobulin E (IgE), which are normally generated as part of immune reactions to parasitic infections, but for reasons that are only partly understood can also be generated in following exposure to environmental agents, such as pollen, dusts, and foods. In contrast, food intolerances are reproducible non-immune-mediated reactions whose symptoms can sometimes take days to manifest themselves. They do not necessarily have an immunological basis although Coeliac disease, one of the best defined food intolerances triggered by gluten, is thought to be mediated by the cellular immune system.

IgE-mediated food allergies have two phases, the first involving sensitisation, where an IgE-response is generated towards a target macromolecule. The second phase occurs on re-exposure to an allergen when an allergic reaction takes place as pre-existing IgE binds the target macromolecules, triggering the release of histamine and other inflammatory mediators. It is these which cause the physiological changes that are manifested as allergic reactions. Symptoms can affect the skin (including rashes such as urticaria), gastrointestinal and respiratory systems and in rare instances some individuals experience life threatening anaphylactic reactions.

IgE binding per se is not indicative of an allergen being able to elicit an allergic response. Thus, peanut allergic patients have serum IgE which cross-reacts with soy proteins but generally suffer no allergic reaction when they eat soy containing foods. Multivalency is essential for an allergen to trigger release of histamine and other inflammatory mediators and it is thought that whilst carbohydrate determinants are widely found and can elicit IgE responses, they are largely monovalent and hence are generally unable to trigger histamine release.

It is generally assumed that sensitisation to the classical food allergens such as milk, egg, peanut and fish occurs via the gastrointestinal tract, although other types of food allergy, particularly to fresh fruits and vegetables, occur as a consequence of prior sensitisation to inhaled allergens such as pollen. Thus, individuals who become sensitised to birch pollen develop IgE to the major birch allergen Bet v 1, which also recognises homologous proteins present in fresh fruits and vegetables, giving rise to so-called cross-reactive allergy syndromes. Similarly individuals with latex allergy have IgE to the chitin-binding domain of the hevein polypeptides which make up the rubber latex network. An almost identical domain is found in the class I chitinases of a number of fruits including avocado, chestnut and banana, which the anti-latex IgE recognises, resulting in allergic reactions to these foods.

It has been estimated that around 1–2% of the population, and up to 8% of children suffer from some type of IgE-mediated food allergy (Helm and Burks, 2000). Only around 8 types of foods are responsible for causing the majority of food allergies, including a number of foods of plant origin such as peanuts, tree nuts, wheat and soy, together with allergens of animal origin including cow's milk, egg, fish and shellfish (Bush and Hefle, 1996). In general children outgrow their allergies, and it has been found that the annual incidence rate (new cases/year) of sensitisation to food allergens (egg, milk, soy, wheat) decreases from 10% at 1 year of age to 3% at 6 years of age. A brief summary of the allergens in these different foods is given below, with a brief introduction to plant food allergens which are described in more detail in the following chapter and in recent work (Mills et al., 2004a; Breiteneder and Radauer, 2004).

2. Allergenic foods of animal origin

2.1. Cow's milk

Allergens are found in both the whey (β -lactoglobulin, α -lactalbumin) and casein fractions, although other IgE-reactive proteins have been identified. β -Lactoglobulin is highly resistant to proteolysis, with IgE epitopes having been identified in four main regions located on the more mobile surface loops of the protein. The caseins also appear to contain thermostable epitopes, with IgE binding being located in around seven different regions of the protein (Wal, 2002).

2.2. Fish

The major allergen in fish is the muscle protein parvalbumin, which acts as a calcium buffer protein in fast muscle, binding the Ca^{2+} ions in a calcium binding motif known as an EF-hand. Parvalbumin is conserved across fish species, a factor responsible for the cross-reactive nature of allergens in cod, salmon, mackerel, herring and plaice, amongst many other fish species. The cod allergen, Gad c 1, possesses five IgE-binding regions evenly distributed along the length of the protein, one of which encompassed one of the Ca^{2+} binding sites. Like other calcium binding proteins Gad c 1 is heat-stable, with the holo-form being both more IgE-reactive and more heat-stable than the apo form (Bugajska-Schretter et al., 2000; Poulsen et al., 2001).

2.3. Egg

Major allergens originate primarily from egg white, and include ovomucoid (Gal d 1) and ovalbumin (Gal d 2), which constitute 10% and 50% of white proteins respectively. Both proteins are heavily glycosylated with 25% of the mass of ovomucoid comprising carbohydrate. IgE epitopes in ovomucoid are clustered in seven regions at the N- and C-terminal regions of the protein but do not encompass glycosylation sites. They are also resistant to enzymic digestion and denaturation. Two minor allergens, ovotransferrin (Gal d 3) and lysozyme (Gal d 4), have also been identified in egg white. In general cooking has been found to reduce allergenic activity of egg (Poulsen et al., 2001).

2.4. Shellfish and seafood

Tropomyosin, a heat-stable muscle protein, is the major allergen in shellfish and seafood, with highly homologous proteins being found in the commonly edible crustaceans. These homologies are responsible for the cross-reactive allergies observed between various types of seafood including shrimps, lobsters, crab, squid and abalone, and inhalant insect allergens, such as those from cockroaches. Two main linear IgE-binding sites have been identified in the shrimp allergen, Pen i 1, in the N- and C-terminal regions. The first two residues of the C-terminal epitope appear to be crucial for IgE binding and are not found in vertebrate tropomyosin. As a consequence of the lack of homology in the IgE epitopes there is no IgE cross-reactivity between crustacean and animal muscle

tropomyosins. In addition to being found in cooked meat, the allergen also leaches into cooking water (Lehrer et al., 2003).

3. Allergenic foods of plant origin

3.1. Legumes

The two major allergenic legumes are peanut and soy. Major allergens include the 7S (Ara h 1 for peanut, β -conglycinin for soy) and 11S seed storage globulins (Ara h 3 in peanut, glycinin in soy). In addition the 2S albumin of peanut (Ara h 2) is an important allergen, whilst in soybean a Bet v 1 homologue (Gly m 4) has been identified which appears to be resistant to processing, together with an allergenic inactivated form of a papain-related thiol protease, Gly m Bd 30K.

3.2. Tree nuts and seeds

The major allergens of seeds and nuts are the 2S albumins and the 7S and 11/12S globulins and include those from Brazil nut, walnut, hazelnut, cashew nut, sesame and mustard seeds. In addition to storage protein allergens, chestnut contains an endochitinase allergen Cas s 1 involved in the latex-fruit allergy syndrome.

3.3. Cereals

Wheat and the related cereals, barley and rye, contain a range of allergens including the prolamins (alcohol soluble storage proteins) which are responsible for food dependent exercise induced anaphylaxis and atopic dermatitis. Inhibitors of proteases and α -amylases of cereals have also been described as both inhalant (e.g. Baker's asthma) and food allergens.

3.4. Fresh fruits and vegetables

Fruit allergy is often associated with tree and grass pollen as well as latex allergy, and this form is generally associated with Bet v 1 sensitisation and induces oral allergy syndrome. Fruits involved include those of the *Rosaceae* with vegetables such as celery. Other types of fruit allergy occur, notable kiwi allergy, which involves the cysteine proteinase actinidin, and peach and related *Rosaceae* fruit allergies experienced in the south of Europe which are often more severe and are associated with allergy to the non-specific lipid transfer proteins.

4. Food allergies — the relevance for industrial proteins

Whilst there are many foods which are known to trigger food allergies we currently lack the epidemiological evidence as to the prevalence of allergies to these different

foods. There seems to be some consensus in the clinical community that the 8 types of foods originally identified by Bush and Hefle (1996) are responsible for the majority of reactions, many of which represent important sources of industrial proteins. For those involved in the manufacture and utilisation of industrial proteins, particularly in foods but also in other products such as cosmetics, an awareness of allergy issues is of increasing importance, particularly in the wake of recent legislation regarding labelling of allergens in foods (Mills et al., 2004b). Following on from the FAO–WHO Codex Alimentarius Commission amendment to the Codex General Standard for the Labelling of Prepackaged Foods, the European Union, the USA and other countries have been developing the necessary regulations to ensure that allergenic foods, or ingredients, are labelled on pre-packaged foods. Table 1 lists the allergenic foods (or derived ingredients) which will have to be labelled as allergens in accordance with the EU directive.

There are also associated concerns about so-called cross-contact allergens which may arise from use of common or adjacent processing lines to prepare foods that do and do not contain any allergenic ingredients. Given that a kiss from a person eating peanuts given to a severely peanut allergic child can be enough to trigger a severe reaction, this represents a considerable hazard for allergic consumers which is frequently “hidden”. Whilst manufacturers may protect themselves by placing “may contain” labels to deal with cross-contact allergens in foods, such a strategy runs the risk of devaluing labels and undermining consumers trust in food manufacturers. Our lack of knowledge on how much of an allergen causes a problem, and the development of associated analytical methodology with appropriate performance criteria and reference materials are also issues that will have to be met in the coming years. Awareness of the problems facing allergic consumers, good manufacturing practices to manage allergenic ingredients coupled with an effective dialogue with allergy sufferers, including good quality information on products, will undoubtedly help in managing the apparently rising tide of food allergies we are faced with.

Table 1

Major allergenic foods listed in annex IIIa of the EU directive on labelling of foods

<i>Cereals</i> containing gluten (i.e. wheat, rye, barley, oats, spelt or their hybridized strains), and products thereof
<i>Crustaceans</i> and products thereof
<i>Eggs</i> and products thereof
<i>Fish</i> and products thereof
<i>Peanuts</i> and products thereof
<i>Soybeans</i> and products thereof
<i>Milk</i> and products thereof (including lactose)
<i>Nuts</i> i.e. Almond, Hazelnut, Walnut, Cashew, Pecan nut, Brazil nut, Pistachio nut, Macadamia nut and Queensland nut and products thereof
<i>Celery</i> and products thereof
<i>Mustard</i> and products thereof
<i>Sesame</i> seeds and products thereof
<i>Sulphur dioxide</i> and sulphites at concentrations of more than 10 mg/kg or 10 mg/l expressed as SO ₂

Acknowledgements

Author HB wishes to acknowledge the support of the Austrian Science Fund Grant SFB F01802. ENCM acknowledges the support of BBSRC through the competitive strategic grant to IFR and the EU through InformAll (QLRT-2001-02284).

References

- Breiteneder H, Radauer C. A classification of plant food allergens. *J Allergy Clin Immunol* 2004;113:821–30.
- Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Moneret-Vautrin D, et al. Adverse reactions to food European academy of allergology and clinical immunology subcommittee. *Allergy* 1995;50:623–35.
- Bugajska-Schretter A, Grote M, Vangelista L, Valent P, Sperr WR, Rumpold H, et al. Purification, biochemical, and immunological characterisation of a major food allergen: different immunoglobulin E recognition of the apo- and calcium-bound forms of carp parvalbumin. *Gut* 2000;46:661–9.
- Bush RK, Hefle SL. Food allergens. *Crit Rev Food Sci Nutr* 1996;36(Suppl):S119–63.
- Helm RM, Burks AW. Mechanisms of food allergy. *Curr Opin Immunol* 2000;12:647–53.
- Lehrer SB, Ayuso R, Reese G. Seafood allergy and allergens: a review. *Mar Biotechnol* 2003;5:339–48 [NY].
- Mills ENC, Jenkins JA, Alcocer MJC, Shewry PR. Structural and biological relationships of plant food allergens. *Crit Rev Nutr Food Sci* 2004;44:379–407.
- Mills ENC, Valovirta E, Madsen C, Taylor SL, Vieths S, Anklam E, et al. Information provision for allergic consumers: where are we going with food allergen labelling? *Allergy* 2004;59:1262–8.
- Poulsen LK, Hansen TK, Norgaard A, Vestergaard H, Stahl Skov P, Bindslev-Jensen C. Allergens from fish and egg. *Allergy* 2001;56(Suppl 67):39–42.
- Wal JM. Cow's milk proteins/allergens. *Ann Allergy Asthma Immunol* 2002;89(Suppl 1):3–10.