

The effect of gastric digestion on food allergy

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Purpose of review

The role of the stomach as the primary location of protein digestion is very well recognized, leading to classification of proteins as digestion-resistant or digestion-labile. This review analyses the role of gastric digestion in food allergy.

Recent findings

Hindrance of gastric digestion by elevation of the gastric pH, the therapeutic goal of anti-ulcer medication, was recently shown to trigger food allergy via oral sensitization in a murine food allergy model. The relevance in humans was assessed in an observational study of 152 gastroenterological patients who were medicated with anti-ulcer drugs due to dyspeptic disorders. Twenty-five percent of all patients developed a boost or de-novo IgE formation towards regular constituents of the daily diet. The clinical relevance of the induced antibodies was confirmed by positive skin and oral-provocation tests. Moreover, the importance of gastric digestion was also proven for food-allergic patients, as the allergenicity of allergens were reduced up to a 10 000-fold by gastric digestion.

Summary

These recent studies indicate for the first time the important gate-keeping function of gastric digestion, both in the sensitization and the effector phases of food allergy.

Keywords

allergens, digestion, food allergy, food safety, sensitization

Introduction

Since the very beginning of food-allergy research, special focus has been attributed to the question of ingestion and distribution of food allergens in the body. Due to the well-accepted physiological role of the stomach as the primary location of dietary protein degradation, at the beginning of the twentieth century scientists focused their attention on the role of undigested allergens as the causes for allergic symptoms. However, it was not until the mid-1990s that the first classification of food allergens into digestion-resistant and degradation-labile proteins was published [1]. Based on the proposed categorization only digestion-resistant food allergens were believed to harbour sensitizing capacity [2]. Consecutively, in-vitro digestion tests using simulated gastric fluid (SGF) were developed and their results became decisive for recommendations on the allergenicity potential of food proteins. These developments thus had broad implications for regulatory institutions and the food industry, because 'novel proteins' introduced onto the market have to undergo this test, besides others, before issue [3].

This review aims to give an overview on the pathophysiological background and on recent research in the field of mechanisms of food allergy with a special focus on the stomach as the gate-keeper for food proteins.

Food ingestion and the physiology of protein digestion

The journey of proteins in the alimentary bolus through the gastrointestinal tract starts in the mouth. Three major and several minor salivary glands produce and secrete an alkaline fluid consisting mainly of water, electrolytes, mucus and enzymes, which functions as a lubricant and binder of masticated food into a macerated bolus enabling easy transport through the esophagus. Dry food is solubilized, a prerequisite for tasting, and saliva constantly flushes the oral cavity, which is an important factor for oral hygiene. Salivary IgAs, peroxidase, anti-bacterial peptides like proline-rich proteins, defensins and lysozyme are protectors against pathogens and prevent overgrowth of oral microbial flora [4–6]. Furthermore, food proteins come into contact with the oral mucosa, which in some cases is the first site of antigen uptake. This is not surprising as the quick and sufficient uptake of pharmaceuticals via the oral mucosa is well established and has been exploited for numerous indications [7]. Recently, the effective absorption of intact peanut proteins via the oral mucosa with implications for anaphylaxis has been

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Abbreviations

LOAEL lowest observed adverse effect level
NOAEL no observed adverse effect level
SGF simulated gastric fluid

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reported [8^{••}]. In contrast, the sublingual route is today routinely used for the treatment of type I allergy [9[•]].

After a very quick esophageal passage the macerated food reaches the acidic milieu of the gastric lumen. The 2–3 l of gastric juices produced every day consist mainly of mucus, hydrochloric acid and proteases. The bicarbonate-rich mucus being produced by the mucous cells covers the gastric mucosa as a protective factor [10]. Hydrochloric acid is the secretory product of the highly specialized parietal cells in the corpus of the stomach. The acidic milieu *per se* acts as an important bactericidal and parasitic barrier [11^{••}], as it ensures the denaturation of proteins. However, there is another important function of hydrochloric acid, as low pH is a prerequisite for activation of the major gastric protease, pepsin. This enzyme was discovered by the German physiologist, histologist and cytologist Theodor Schwann in 1836. Its precursor pepsinogen is produced by the gastric mucosal chief cells and is converted into its active form pepsin under acidic conditions by disruption of the electrostatic interactions between the prosegment and the active enzyme, leading to conformational changes of the prosegment, which initiates the activation reaction [12]. The 44 amino acids blocking the large active-site groove are clipped off by proteolytic cleavage carried out by the enzyme itself, which leads to a conformational change of the active enzyme moieties and allows access to the active groove and activation of its protease function (Fig. 1) [13,14]. For the enzymatic activity of pepsin the optimal acidic conditions range from pH 1.8 to 3.2 [15[•]].

Gastric transit takes an average of 2 h. Subsequently, remaining peptides are exposed to a variety of proteases and peptidases in the originally neutral pH of the intestinal environment. However, due to an acquired reflex, pancreatic juices are excreted, which leads to a dramatic pH shift and the addition of proteases that work optimally

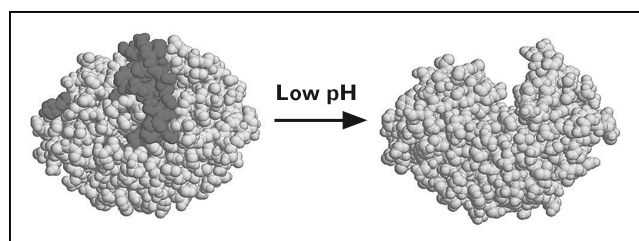
at alkaline pH. The most prominent among them are the pancreatic proteases trypsin, chymotrypsin and carboxypeptidase, leading to a break-up of the peptides into single amino acids or very small peptides of no longer than three amino acids. These are absorbed easily by active transport across the epithelium. Peptides of less than eight amino acids in length do not react with structures involved in antigen recognition or presentation and are therefore ignored in immunological terms.

Characteristics of food allergens and routes of sensitization

It has been observed that food allergens, as with all allergens, are mostly proteins or glycoproteins with a molecular weight ranging between 3 and 90 kDa, thereby enabling immune recognition. However, this characteristic does not discriminate between an allergen, an immunogen and a tolerogen. In spite of the large variety of the human diet and the thousands of proteins contained in food, most allergic reactions are elicited by only few dietary compounds. Milk, egg and peanut proteins are responsible for most reactions in childhood [16[•],17], whereas peanuts, tree nuts, fish and shellfish gain importance as allergens in adults [18^{••}]. Therefore, the likelihood of becoming sensitized correlates with exposure and consumption habits, so fish allergy is more frequently found in coastal areas, where fish is an important source of food [19[•]]. Moreover, researchers agree that the abundance of certain proteins in food might correlate with their importance as food allergens. Approximately 20% of the total shrimp-tail protein content is formed by the major shrimp allergen Pen a 1. However, this feature is not generally transferable as parvalbumin, the major fish allergen, is not the predominant muscle protein in fish. Another quality attributed to food allergens is their resistance to the harsh conditions of food preparation and pH extremes during gastrointestinal transit, as conformation has been revealed to be important for IgE binding to food allergens [20[•]]. Thus, on the one hand, resistance to denaturation during food processing, such as freezing or heating, seems to be important [21]. On the other hand, the stability of food proteins in the face of gastric digestion has been investigated intensively, and results suggests that only proteins that are resistant to gastric digestion might lead to sensitization [1]. This lead to the postulate that food allergens can be divided into sensitizing (true, complete) food proteins and non-sensitizing elicitors (incomplete allergens) [2].

Using the in-vitro digestion test as a criterion, several major food allergens could indeed be classified as true, digestion-stable food allergens, such as the major allergen 2 S albumin from Brazil nuts or white sesame seeds [21,22]. They are able to sensitize directly upon ingestion via the oral route without primary respiratory exposure. To detect those food proteins with strong sensitizing

Figure 1 Transformation of pepsinogen into the mature enzyme pepsin



In the acidic gastric milieu the 44 N-terminal amino acids, which block the enzyme's active site in specific interaction with the substrate-binding groove (dark grey), are clipped off. Thus the enzyme pepsin is activated for binding and cleavage of protein chains. This figure was created with the program Protein Explorer 2.411 Beta using the structural information given under RCSB Protein Data Bank accession numbers 3PSG and 5PEP [13,14].

potential gastric digestion tests have been used in safety evaluations for novel dietary compounds, such as exotic fruits, new food additives and genetically modified foods [23^{••}].

Following the above-mentioned classification non-sensitizing food allergens are capable of eliciting reactions only after primary respiratory sensitization with cross-reactive allergens [24[•]]. Among the different pollen-associated food allergies, the ones associated with birch pollen allergy are undoubtedly the most studied, as it was recognized very early on that 50–93% of birch pollen-allergic patients suffer from IgE-mediated reactions to related foods. Here the explanation is molecular mimicry between allergen molecules from different sources. Birch allergens exhibit extensive cross-reactivity, for example with proteins found in hazelnut, apple, cherry, nectarine, plum, kiwi, apricot, pear, potato, celery, carrot, soy bean and even exotic fruits such as jackfruit [25,26[•]].

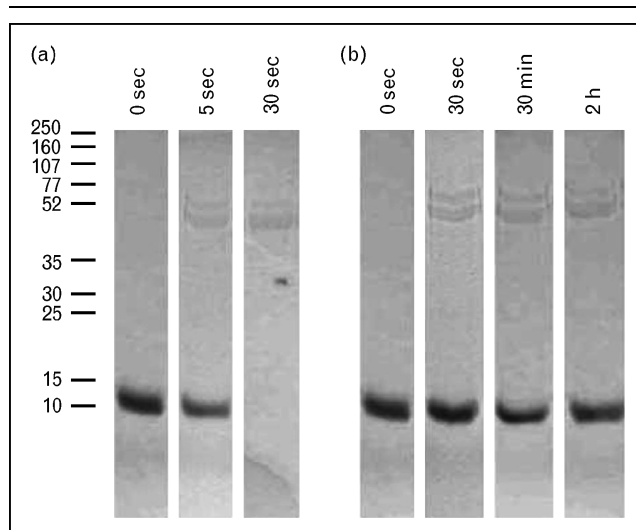
Despite this association between pollen and food allergies and despite the fact that most hazelnut proteins are easily digestible, severe reactions to hazelnut and other allergens have been observed without any association to airborne allergy [27]. Furthermore, the role of hazelnut as a potent elicitor of food allergic reactions has been confirmed by double-blind placebo-controlled food challenges in a multi-centre study [28]. Moreover, recent studies have reported the digestibility of major food allergens in general [29], which thus do not show the features believed to be typical of true food allergens. The question that remains is how these proteins may sensitize via the oral route in any way, if peptically degraded.

Peptic digestion depends on gastric pH

SGF experiments are convenient tools to characterize food proteins of interest. In these assays the sample proteins are incubated with pepsin at low pH for various time intervals [1]. Interestingly, some of the most common food allergens responsible for severe reactions in allergic patients, such as the major fish allergen parvalbumin (Fig. 2a), were degraded within a few seconds, even though described as a resistant protein in the literature. Considering the described pH dependency of pepsin activation, parvalbumin remained stable up to 2 h of digestion when we elevated the pH of the SGF solution to 5.0 (Fig. 2b). Surprisingly, only a slight pH elevation—to pH 2.75 in the case of codfish and to pH 3.0 for milk-induced complete inhibition of protein digestion [30^{••},31^{••}].

This is a clinically important observation as low gastric acid output or complete loss of digestive function are regular consequences of gastrectomy or atrophic gastritis. Hypoacidity is also a physiological feature in newborns and is induced iatrogenically by acid-suppression medi-

Figure 2 Time kinetics of in-vitro gastric digestion of parvalbumin from codfish



(a) The effects of pepsin at pH 2 on protein digestion after 5 and 30 s treatment were analysed by Coomassie-stained SDS/PAGE. Lane 1 shows untreated parvalbumin. (b) Pepsin at pH 5.0 shows no effects on parvalbumin in Coomassie-stained SDS/PAGE even after 2 h treatment.

cation for dyspepsia or anti-ulcer treatment. In these settings protein digestion is severely hindered and potential allergens may pass through the stomach.

Epidemiology of dyspeptic disorders and characteristics of anti-ulcer medication

Dyspeptic disorders such as gastroesophageal reflux disease, gastritis, erosions or ulcers are among the most frequent complaints seen by primary care physicians, and affect all age groups [32[•],33[•]]. Nevertheless, in most cases the symptoms are medicated by the patients without seeking medical advice [34] using antacids or anti-ulcer drugs such as H₂ receptor blockers and proton-pump inhibitors. Antacids act via neutralization of intraluminal acid, while Sucralfate shows also an additional cytoprotective effect on the gastric mucosa. Anti-ulcer drugs are potent antagonists of acid secretion by gastric parietal cells. H₂ receptor blockers inhibit histamine-stimulated acid secretion, whereas proton-pump inhibitors act via irreversible binding to the proton pump responsible for gastric acid secretion, the H⁺/K⁺-ATPase. Despite these different mechanisms of action, both types of drug effectively elevate the gastric pH to an average of 5 within a few days of treatment [35^{••},36].

Taking into consideration the frequency of dyspeptic disorders it is not surprising that these anti-ulcer drugs are among the top sellers for the pharmaceutical industry, especially as potent proton-pump inhibitors have been approved for over-the-counter sales in several countries. In a Taiwanese cohort the prevalence of anti-ulcer drug use rose from 9.6 to 15.9% between 1997 and 2001.

Regarding the age distribution the highest medication intake was in the elderly (60 years and above), with a prevalence of 25.9% in 2001 [37]. English surveys on prescription habits have revealed that in 1996 14% of the total district prescription costs and 2% of the health authority budget was spent on anti-ulcer drugs. Interestingly, 80% of the costs were generated by repeated prescriptions for longer time periods without further medical consultation [38–40]. Additionally, other recent studies confirmed the prolonged intake of these drugs, frequently in the absence of a clear diagnosis or clinical investigation [41^{••},42[•]]. It is tempting to speculate that these prescription habits are due to the fact that the stomach's function as a protective barrier has been underestimated for a long time.

The role of anti-ulcer drugs in the development of food allergy

The first correlation between food and drug allergy and dyspeptic disorders was reported in 1984, even though drug-allergic reactions had been ascribed to multi-pharmaceutical treatment, and the food allergy to hereditary and alimentary factors [43]. Furthermore, high IgE levels and food-specific IgE in the gastrointestinal mucosa have been observed in peptic ulcer patients [44–46]. Even antacid drugs themselves have been found to trigger IgE-mediated anaphylaxis [47]. Interestingly, none of these studies has addressed the question of whether the functional effects of acid-inhibiting drugs might directly influence the development of food allergy.

While following up a patient who had reported severe anaphylactic symptoms after the consumption of Russian Beluga caviar [48], we characterized this novel food allergen using the SGF test. Unexpectedly, all caviar proteins were degraded within a few seconds. The only noticeable item in the case history was that the patient had been using acid-suppression treatment due to a gastric ulcer since first consuming caviar. This prompted us to address the question of whether anti-ulcer drugs really play a role in the development a food-allergic phenotype. Indeed, a mouse model of true food allergy was developed with the help of anti-ulcer drugs [49,50^{••}]. Obviously in these animals eosinophils also participated in the allergic inflammation [51], similarly to that observed previously in human allergic esophagitis.

Consequent clinical studies indicated the relevance of our findings for human patients. After 3 months of anti-ulcer therapy 25% of anti-ulcer-treated patients revealed a boost in IgE formation towards a regular constituent of the daily diet, and 15% even showed de-novo IgE formation [30^{••}]. Fifty percent of all tested food antigens were digestible *in vitro*, which would had been misinterpreted as non-sensitizing elicitors according to the old classification [2].

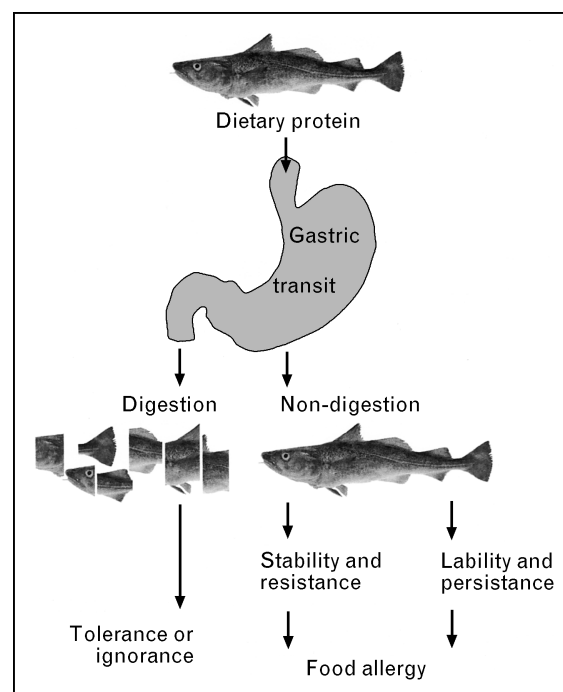
In situations of impaired gastric digestion, such as hypoacidity, digestion-labile food antigens acquire sensitizing capacity as they survive the gastric transit conformationally intact. This is a precondition for B-cell recognition and antibody production (Fig. 3).

Accordingly, these findings question the accuracy of the protein-digestion test in the safety evaluations of novel proteins. Of course, SGF assays identify digestion-stable dietary compounds as possible allergens. However, these tests do not allow conclusions on consumer safety regarding degradation-labile food antigens, because they are not representative in situations of insufficient gastric digestion [52^{••},53].

Threshold levels: how much is too much in situations of impaired gastric digestion?

Consumers and therefore legislative authorities are not only interested in avoiding novel sensitizations, but also in the safety of patients with manifest food allergies. One effort is the strict labelling of food ingredients that are the most frequent elicitors of severe adverse reactions (Table 1) [54]. Despite these strict labelling regulations, problems of accidental allergen contamination or

Figure 3 Mechanisms of food-allergy induction



Conformational epitopes are preconditions for IgE induction. Resistance of these epitopes can be ascribed to a stabilized protein structure; for example via disulfide bonds. On the other hand, persistence of normally degradable epitopes can be due to a reduced digestion capacity of the stomach. Consequently, labile food proteins losing their conformation by gastric degradation lead to tolerance or immune ignorance. However, when food proteins survive gastric transit in an intact form, sensitization and food allergy can be triggered.

Table 1 Food ingredients and products thereof that have compulsory labelling in the European community

Food ingredients and products thereof

Cereal containing gluten
Crustaceans
Eggs
Fish
Peanuts
Soy beans
Milk (including lactose)
Nuts
Celery
Mustard
Sesame seed
Sulphur dioxide and sulphites

production errors threaten allergic consumers. The imposition of absolutely no allergen content in food products creates enormous problems for the food industry, as different goods are manufactured within the same facilities, leading to possible contamination with traces of allergens [55]. Therefore, major endeavours are made to define threshold doses, also called LOAELs (lowest observed adverse effect levels) or NOAELs (no observed adverse effect levels) for the different allergens [56**]. As outlined by a consensus protocol in 2004, low-dose trials of double-blind placebo-controlled food challenges in highly sensitized patients should allow estimation of the LOAELs or NOAELs for different allergenic food compounds [57].

We have assessed very recently the allergenic potential of digested and undigested codfish allergens in several in-vitro experiments. Radioallergosorbent test (RAST) inhibition experiments revealed an activity reduction by gastric protein degradation of up to 10 000-fold. In histamine-release assays with passively sensitized basophils the digested allergens were able to trigger a release only at rather high concentrations, whereas the undigested codfish proteins were also biologically active at very low concentrations [31**]. These data clearly indicated that in the effector phase of food allergy, when the triggering cells are already armed with specific IgEs, gastric digestion markedly alters the reactivity pattern towards allergens. It can be expected that allergic patients might react at relatively lower allergen concentrations in situations of gastric indigestion. Therefore, threshold levels are relative values in situations of hindered gastric digestion.

Conclusion

Gastric digestion has an important gate-keeping function in the sensitization and effector phases of food allergy. Consequently, situations of reduced digestive capacity represent a threat to consumers of becoming sensitized to food proteins. Similarly, acid-suppressed food-allergic individuals may experience severe reactions upon accidental allergen ingestion or low-dose protein intake.

The connection between acid-suppression drugs and allergy to ingested proteins should be acknowledged by physicians, and gastroenterological patients instructed accordingly. In contrast to today's liberal distribution and consumption of these drugs, in future their use should be restricted to clear indications and possibly include allergy monitoring in patients who are undergoing long-term treatment. Similarly, safety assessments of novel dietary compounds have to be reconsidered, as digestion-labile proteins might acquire allergenic potential in situations of impaired digestion capacity.

Acknowledgements

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 246).

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