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The influence of gastric digestion on the development of food allergy

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Summary

Food allergy represents an increasing health concern worldwide. To identify mechanisms and risk factors associated with food allergy development major research efforts are ongoing.

For a long time only food allergens that are resistant to gastric enzymes were accepted to harbor sensitizing capacity via the oral route. However, over the past years several studies reported that even important food allergens can be readily degraded by digestive enzymes. Interestingly, a number of *in vitro* experiments confirmed that impairment of physiological gastric digestion by elevating gastric pH levels was associated with protein resistance. Additionally, pharmacological gastric acid suppression was found to be a risk factor for food allergy induction. In contrast, protein modifications resulting in increased susceptibility to digestive enzymes were reported to decrease the sensitization capacity via the oral route. The here reviewed data highlight the important gate keeping function of physiological gastric digestion in food allergy.

Keywords

food allergy; sensitization; gastric digestion; allergenicity

Introduction

From a psychological point of view food intake should be associated with pleasure and well-being. However, an increasing number of patients especially in the Western population experience unpleasant, in some cases even life threatening reactions upon ingestion of specific dietary compounds. Over the past decades food allergy, i.e. the immunological reaction against harmless dietary protein compounds,1 has steadily increased. To date it is generally accepted that more than 2 % and less than 10 % of the general population are affected by this disease1 corresponding to approximately 220-250 million patients world-wide. Additionally, several studies demonstrate that the number of food allergic patients has considerably increased over the past decades.2 Furthermore, a substantial economic burden

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Declaration of interest
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comprising of health care as well as personal expenses has been identified directly related to the diagnosis of food allergy. While in the US the overall cost associated with childhood food allergy was defined to be as high as 25 billion $ per year, a large European study reported a doubling of patients' based health care costs associated with food allergy irrespective of the different countries included in the study.3, 4 Thus, it is not surprising that this disease has also gained awareness of regulatory authorities with the aim to enhance the safety of allergic consumers. In the European Union, an adopted regulation has become affective in December 2014 requiring labeling of the 14 main food allergens not only on manufactured, pre-packed food products, but also food directly sold e.g. in restaurants.5

To enhance patients' safety and to develop prevention and treatment strategies it is essential to identify mechanisms and risk factors for the development of food adverse reactions.

In affected patients the development of food allergy is associated with the lack of induction or the loss of oral tolerance towards dietary compounds.6 Together with immunological events such as immune exclusion and cellular interactions associated with regulatory mechanisms, also physical properties of the intestinal epithelium, an intact mucosal barrier consisting of tight epithelial cells as well as mucus and bacterial layers are of paramount importance for the development and maintenance of oral tolerance.7 Also specific characteristics of dietary proteins acting as allergens i.e. small size, solubility, and stability to food processing and food digestion during the transit trough the gastrointestinal tract contribute to food allergy induction.8 Especially stability to digestive enzymes and food processing is well accepted to represent an important characteristic of allergenic food compounds and are considered in test procedures defining the allergenicity of novel dietary proteins, which enter the food market.9

Assessment of protein digestibility *in vitro*

In laboratory settings, food protein digestibility is evaluated simulating the physiological degradation along the gastrointestinal tract upon protein ingestion. After a rapid passage through the esophagus food proteins enter the gastric lumen together with all other food components in a macerated chyme. Here, substances are exposed to low gastric pH resulting in protein denaturation. Additionally, major gastric proteases, pepsins, being secreted into the gastric lumen by chief cells of the gastric glands get activated by intraluminal acidity. These enzymes have their optimal activity at pH levels below 3.2 and cleave protein amino acid (AA) chains preferentially at phenylalanine, tyrosine, and leucine residues.10 After initiating protein cleavage in the stomach, resulting peptide fragments are peristaltically transported into the duodenum where low pH levels of the chyme trigger secretin secretion. 11 This hormone stimulates a subsequent release of pancreatic proteases and peptides into the intestinal lumen, and peptide fragments are further degraded to short AA chains or single AAs serving as nutrition of the human body.11 However, they are too small to interact with the human immune system.10 Based on this knowledge sequential exposure of specific proteins to gastric and/or intestinal proteases in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) experiments is performed to assess digestibility of food proteins.12 Results generated in these assays have led to the assumption that only digestion-stabile, so-called class I food proteins to harbor the capacity to induce food allergy via the oral route.8

However, there is growing evidence that a number of major allergen, which are responsible for severe allergic reactions, are degraded in SGF experiments (Fig. 1) and, thus, may not be able to trigger allergic sensitization via the oral route.10 We have demonstrated that physiological gastric digestion extensively reduces IgE binding and histamine releasing capacity of cod fish allergens.13 Taking into consideration these data, it remains questionable whether *in vitro* digestion assays might at all provide reliable results regarding protein allergenicity as important food allergens would not prove digestion stability in these assays.14

Hindered gastric digestion and induction of food allergy

When gastric digestion was impaired due to hypoacidity in SGF assays, digestion-labile food proteins remained stable for the average gastric transit time of 2 hours.13, 15 As reviewed previously,10 there are numerous situations which may be associated with elevated pH levels in the gastric lumen: the first two years of live, atrophic gastritis, and intake of gastric acid suppression drugs. Of interest, several experimental studies in mouse models repeatedly revealed a direct link between gastric acid suppression by all different forms of available pharmacological acid reducing medication (Sucralfate, H2 receptor blockers, proton pump inhibitors, antacids and base powder) and the development of food allergy. We were able to demonstrate the induction of elevated allergen-specific IgE levels, positive skin tests and anaphylactic reactions upon oral provocations measuring the anaphylaxis marker mouse mast cell tryptase 1 (mMCP1) and core body temperature.16–23 Microscopic analysis of the gastrointestinal mucosa revealed influx of eosinophilic granulocytes and mast cells into the gastrointestinal mucosa.17, 23 Furthermore, repeated immunizations with fish allergens under gastric acid suppression resulting in fish allergy induction and caused elongation of intestinal villi and elevated numbers of mucus producing goblet cells.24 In addition to murine experiments, the association between pharmacological gastric hypoacidity and sensitization towards food proteins was verified in human studies. In an observational study including 153 previously non-allergic patients with dyspeptic disorders being treated with either H2 receptor blockers or proton pump inhibitors for three month an increase or *de novo* formation of IgE towards regular constituents of the daily diet could be observed. Sensitization was confirmed by positive skin tests.15 In a sub-group of patients, positive oral provocation tests resulted in diagnosis of food allergy towards hazelnut.20 However, not only gastric acid suppression might impede peptic protein digestion. Recently, surgical elimination of gastric digestion due to bariatric gastric bypass operations was demonstrated to be associated with increasing number of sensitizations towards food proteins diagnosed by specific IgE and positive skin tests after surgical intervention.25 The influence of gastric digestion on allergy development might not only be of relevance for adult patients but also for other age groups. In a mouse model during pregnancy, food allergy induction after gastric acid suppression was not only observed in mothers, but also influenced the offsprings' immune response by favoring a Th2 milieu.19 These results were underlined by a population based health register study reporting a correlation between maternal anti-ulcer drug intake and the development of childhood asthma.26 Furthermore, two studies confirmed the relevance of this mechanism also for childhood food allergy: A questionnaire study revealed a correlation between increasing numbers of food allergy in

children and anti-ulcer drug intake,27 and analysis of an insurance data base reported an association between gastric acid suppression and increased risk for food allergy development.28 Also in aged individuals an association between impaired gastric digestion by hypoacidity and food allergy was demonstrated. In mouse experiments as well as in human studies incomplete food allergen digestion by elevation of gastric pH levels was a risk factor for food allergy development also in immunosenescence.21, 29 Based on this knowledge we have developed a standardized immunization protocol in Balb/c mice of oral immunizations under gastric acid suppression resulting in food allergy induction towards the model allergen of interest.16 This protocol has been applied in several mechanistic studies highlighting the importance of gastric digestion in the sensitization phase of food allergy. In one of our studies tyrosine nitration, a chemical protein modification observed in situations of environmental pollution due to smog and ozone exposure but also endogenously during inflammatory processes and ageing in the human body, was evaluated. This modification was previously found to be associated with enhanced allergenicity when injected systemically.30 However, when nitrated proteins were administered via the oral route a reduced *de novo* sensitization capacity was determined.22 These results were partially explained by enhanced digestibility of the nitrated Ovalbumin (OVA), a major hens' egg allergen used as a model allergen in these study, highlighting the important gate-keeping function of gastric digestion in food allergy.

Conclusions

Based on the here reviewed data it is evident that functional gastric digestion is important for food allergy prevention. Impairment of physiological peptic digestion has repeatedly been reported to be associated with food allergy induction. On the other hand, allergen modifications being related with enhanced susceptibility to gastric enzymes showed decreased sensitization capacity. For patients' safety it is therefore essential to limit situations of hypoacidity to the treatment of medically diagnosed dyspeptic disorders. By raising common knowledge and awareness the aim should be avoidance of long-term medication and patients' overuse due to over-the-counter availability of these drugs associated with self-medication.

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References

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010; 126:S1–58. [PubMed: 21134576]
2. Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics. 2009; 124:1549–55. [PubMed: 19917585]
3. Fox M, Mugford M, Voordouw J, Cornelisse-Vermaat J, Antonides G, de la Hoz Caballer B, et al. Health sector costs of self-reported food allergy in Europe: a patient-based cost of illness study. Eur J Public Health. 2013; 23:757–62. [PubMed: 23402805]

4. Gupta R, Holdford D, Bilaver L, Dyer A, Holl JL, Meltzer D. The economic impact of childhood food allergy in the United States. JAMA Pediatr. 2013; 167:1026–31. [PubMed: 24042236]
5. Regulation: (EU) No 1169/2011 of the European Parliament and of the council. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:304:0018:0063:EN:PDF
6. Brandtzaeg PE. Current understanding of gastrointestinal immunoregulation and its relation to food allergy. Ann N Y Acad Sci. 2002; 964:13–45. [PubMed: 12023193]
7. Brandtzaeg P. Gate-keeper function of the intestinal epithelium. Benef Microbes. 2013; 4:67–82. [PubMed: 23257015]
8. Lorenz AR, Scheurer S, Vieths S. Food allergens: molecular and immunological aspects, allergen databases and cross-reactivity. Chem Immunol Allergy. 2015; 101:18–29. [PubMed: 26022861]
9. Evaluation of Allergenicity of Genetically Modified Foods. http://www.who.int/foodsafety/publications/biotech/en/ec_jan2001.pdf
10. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. J Allergy Clin Immunol. 2008; 121:1301–8. quiz 9-10. [PubMed: 18539189]
11. Pali-Schöll I, Jensen-Jarolim E. Anti-acid medication as a risk factor for food allergy. Allergy. 2011; 66:469–77. [PubMed: 21121928]
12. Astwood JD, Leach JN, Fuchs RL. Stability of food allergens to digestion in vitro. Nat Biotechnol. 1996; 14:1269–73. [PubMed: 9631091]
13. Untersmayr E, Poulsen LK, Platzer MH, Pedersen MH, Boltz-Nitulescu G, Skov PS, et al. The effects of gastric digestion on codfish allergenicity. J Allergy Clin Immunol. 2005; 115:377–82. [PubMed: 15696099]
14. Jensen-Jarolim E, Untersmayr E. Food safety: in vitro digestion tests are non-predictive for allergenic potential of food in stomach insufficiency. Immunol Lett. 2006; 102:118–9. [PubMed: 16139368]
15. Untersmayr E, Bakos N, Schöll I, Kundi M, Roth-Walter F, Szalai K, et al. Antiulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J. 2005; 19:656–8. [PubMed: 15671152]
16. Diesner SC, Knittelfelder R, Krishnamurthy D, Pali-Scholl I, Gajdzik L, Jensen-Jarolim E, et al. Dose-dependent food allergy induction against ovalbumin under acid-suppression: a murine food allergy model. Immunol Lett. 2008; 121:45–51. [PubMed: 18824031]
17. Diesner SC, Olivera A, Dillahunt S, Schultz C, Watzlawek T, Forster-Waldl E, et al. Sphingosine-kinase 1 and 2 contribute to oral sensitization and effector phase in a mouse model of food allergy. Immunol Lett. 2012; 141:210–9. [PubMed: 22020265]
18. Pali-Schöll I, Herzog R, Wallmann J, Szalai K, Brunner R, Lukschal A, et al. Antacids and dietary supplements with an influence on the gastric pH increase the risk for food sensitization. Clin Exp Allergy. 2010; 40:1091–8. [PubMed: 20214670]
19. Schöll I, Ackermann U, Ozdemir C, Blumer N, Dicke T, Sel S, et al. Anti-ulcer treatment during pregnancy induces food allergy in mouse mothers and a Th2-bias in their offspring. FASEB J. 2007; 21:1264–70. [PubMed: 17227952]
20. Schöll I, Untersmayr E, Bakos N, Roth-Walter F, Gleiss A, Boltz-Nitulescu G, et al. Antiulcer drugs promote oral sensitization and hypersensitivity to hazelnut allergens in BALB/c mice and humans. Am J Clin Nutr. 2005; 81:154–60. [PubMed: 15640475]
21. Untersmayr E, Diesner SC, Bramswig KH, Knittelfelder R, Bakos N, Gundacker C, et al. Characterization of intrinsic and extrinsic risk factors for celery allergy in immunosenescence. Mech Ageing Dev. 2008; 129:120–8. [PubMed: 18083215]
22. Untersmayr E, Diesner SC, Oostingh GJ, Selzle K, Pfaller T, Schultz C, et al. Nitration of the egg-allergen ovalbumin enhances protein allergenicity but reduces the risk for oral sensitization in a murine model of food allergy. PLoS One. 2010; 5:e14210. [PubMed: 21151984]
23. Untersmayr E, Schöll I, Swoboda I, Beil WJ, Förster-Waldl E, Walter F, et al. Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. J Allergy Clin Immunol. 2003; 112:616–23. [PubMed: 13679824]
24. Pali-Schöll I, Yildirim AO, Ackermann U, Knauer T, Becker C, Garn H, et al. Anti-acids lead to immunological and morphological changes in the intestine of BALB/c mice similar to human food allergy. Exp Toxicol Pathol. 2008; 60:337–45. [PubMed: 18524557]

25. Shakeri-Leidenmühler S, Lukschal A, Schultz C, Bohdjalian A, Langer F, Birsan T, et al. Surgical elimination of the gastric digestion by Roux-en-Y gastric bypass impacts on food sensitization – a pilot study. Obesity Surgery. 2015

26. Dehlink E, Yen E, Leichtner AM, Hait EJ, Fiebiger E. First evidence of a possible association between gastric acid suppression during pregnancy and childhood asthma: a population-based register study. Clin Exp Allergy. 2009; 39:246–53. [PubMed: 19134022]

27. DeMuth K, Stecenko A, Sullivan K, Fitzpatrick A. Relationship between treatment with antacid medication and the prevalence of food allergy in children. Allergy Asthma Proc. 2013; 34:227–32. [PubMed: 23676571]

28. Trikha A, Baillargeon JG, Kuo YF, Tan A, Pierson K, Sharma G, et al. Development of food allergies in patients with gastroesophageal reflux disease treated with gastric acid suppressive medications. Pediatr Allergy Immunol. 2013; 24:582–8. [PubMed: 23905907]

29. Bakos N, Scholl I, Szalai K, Kundi M, Untersmayr E, Jensen-Jarolim E. Risk assessment in elderly for sensitization to food and respiratory allergens. Immunol Lett. 2006; 107:15–21. [PubMed: 16876879]

30. Gruijthuijsen YK, Grieshuber I, Stocklinger A, Tischler U, Fehrenbach T, Weller MG, et al. Nitration enhances the allergenic potential of proteins. Int Arch Allergy Immunol. 2006; 141:265–75. [PubMed: 16931888]

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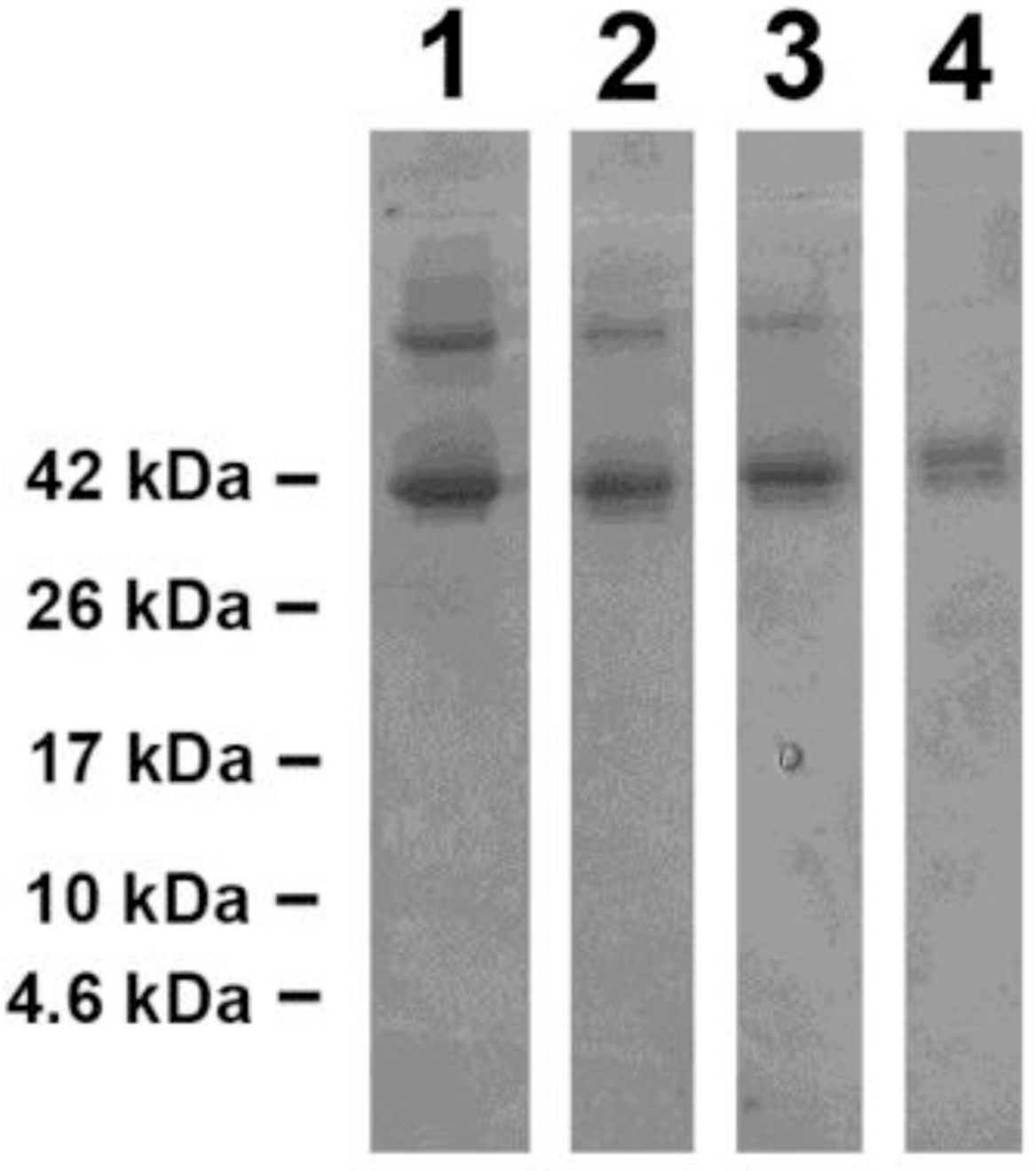

Figure 1. Digestion of OVA proteins by SGF experiments.

The major hens' egg allergen OVA (undigested, lane 1) was incubated with SGF made of NaCl and pepsin containing drug Enzynorm *f*® (Nordmark, Germany) at pH 1.5 for 1 min (lane 2), 30 min (lane 3) and 2 hours (lane 4). Proteins were separated by SDS-PAGE.