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The Maillard reaction and food allergy: Impacts on sensitisation and on elicitation

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Key points

- The Maillard reaction (glycation) influences both allergic sensitization and elicitation
- The specific conditions of how glycation has been performed are important for eventual findings, probably explaining contradictory observations
- Glycated allergens interact with antigen presenting cells via specific receptors
- In general, when isolated allergens are studied, glycation seems to decrease IgE-binding; physiological relevance of using isolated allergens is limited, however
- Matrix components are very relevant for the immunological effects as caused by whole foods, as they also interact with allergens upon heating
- Aggregation of allergens is an important factor in either stage of the allergic reaction cascade
- Simple IgE-binding tests are insufficient to estimate the effect of glycation on elicitation; more advanced testing, such as crosslinking assays, are minimally required

Abstract

The Maillard reaction, alias glycation, is a non-enzymatic reaction between free amino groups of proteins and reducing sugars in foods upon heating. Glycated proteins interactions with specific receptors on antigen presenting cells, which leads to

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a modified immunological response. Aggregation of glycated proteins also changes their immunological properties. Literature is sometimes conflicting, emphasizing the need for rigorous standardization of experimentation.

Generally, glycation of isolated allergens leads to a reduction in their ability to bind to IgE. Surprisingly, glycated allergens as present in whole foods are likely the primary sensitizer. As proteins are seldomly consumed in their isolated form, the relevance of these studies is in mechanistic aspects but much less in physiological relevance. Simple IgE-binding tests are insufficient to estimate the effect of glycation on IgE-binding, as they ignore e.g. glycation-induced aggregation. More advanced testing, such as cross-linking tests, are minimally required for this purpose.

Introduction

The Maillard reaction (MR, glycation) is one of most common, non-enzymatic, reactions occurring between proteins and sugars and was first described by the French chemist Louis-Camille Maillard in 1912 (Maillard, 1912). MR leads to condensation of sugars with proteins by a covalent bond between free amino groups of amino acids (mostly lysine and arginine) and the carbonyl groups of a reducing sugar, and also leads to protein aggregation. The MR occurs naturally during regular food processing as well as meal preparation at home (cooking, frying, baking) and proceeds faster at higher temperatures.

Hence the MR leads to structural alterations in food proteins, thereby influencing both their immunogenicity and allergenicity. This chapter addresses the impact of the MR on both allergic sensitization as well as on allergic elicitation.

Allergic sensitization and the Maillard reaction

Maillard reaction

Maillard reaction products (MRPs) are widely present in thermally processed foods like coffee, cereal, bakery products or roasted meat and are responsible for the brown color of these products, but also give an attractive flavor making the products tasty (Hellwig and Henle, 2014; Teodorowicz et al., 2017; Starowicz and Zieliński, 2019).

The MR is typically divided in the early, intermediate and final stage, each one characterized by different types of formed Maillard Reaction Products (MRPs). A few excellent reviews have been published describing the formation of the MRPs in food systems as well as *in vivo* in the tissues (Van Boekel, 2001; Thorpe and Baynes, 2003; Hellwig and Henle, 2014, Twarda-Clapa et al., 2022), therefore the chemism of the MR will be explained in short. The reaction starts typically when a free amino group of protein reacts with a reducing sugar (a saccharide with an aldehyde or ketone group). This early stage of MR leads to the formation of a Schiff base, the first but unstable product of the reaction. Subsequently, the Schiff base undergoes Amadori rearrangement resulting in the formation of a more stable 1-amino-1-deoxy-2-ketose, called Amadori rearrangement products (**Fig. 1**B). The type of formed products depends on whether the type of sugar used in reaction contains an aldose or ketose. These intermediate Amadori products undergo further subsequent chemical rearrangements: condensation with additional amines, dehydration and oxidative fragmentations to finally form a number of heterogeneous Advanced Glycation End Products (AGEs) (**Fig. 1**C) (Van Boekel, 2001).

MRPs play a crucial role in imparting functional properties, such as texture, taste, smell, and appearance, to food proteins. This makes the Maillard reaction significant to consumers and the food industry (Starowicz and Zieliński, 2019). In addition to functional alterations, recent studies have also revealed that the MR-induced conformational and biochemical modifications of proteins impact its biological properties such as digestibility (Zenker et al., 2020b; Pischetsrieder and Henle, 2012), immunogenicity and allergenicity (Vissers et al., 2011; Moghaddam et al., 2014; Stojadinovic et al., 2014; Liu et al., 2016a,b; Perusko et al., 2018; Zenker et al., 2019; Teodorowicz et al., 2021; Briceno et al., 2023). Here, we define immunogenicity as the ability of a material to elicit an immune response, and allergenicity as its ability to interact with IgE-type antibodies (Verhoeckx et al., 2015).

Formation of MRPs and structural changes in proteins

As explained above, MRPs are formed during heat treatment of foods. However heating or extended cooking times of (reducing) sugar-containing foods lead not only to formation of MRPs/AGEs but also to a number of a heat-induced structural changes of the MR-modified proteins. It is important to keep in mind that glycation and structural modification of proteins occur simultaneously, and hence proper controls are required to discriminate the effect of heating and respectively MR, on physico-chemical features, e.g. size (aggregation) and consequently on biological properties, e.g. immunogenicity resp. allergenicity, of proteins (Teodorowicz et al., 2017).

The initial, partly reversible, step in the MR is a protein to start denaturing and unfolding upon heating. Upon increasing heat load, proteins aggregate irreversibly. The extent of these structural changes is dependent on temperature, applied heat load, water activity, protein concentration, presence of other proteins, and inherent stability of the protein under study (Davis and Williams, 1998; Wijayanti et al., 2014). Protein unfolding may lead to exposure of, in the native state hidden in the interior, structural elements such as β-sheets, and hence change hydrophobicity (Kim et al., 2005). These neo-β-sheet structures may also lead to amyloid fibril formation. Additionally, protein aggregation can be promoted and the MR can influence the type of aggregates that are formed (**Fig. 1**A). In conclusion, heat treatment of proteins results in an effect on the protein 3-dimensional structure itself and the interaction of specific amino acids with reducing sugars due to the MR, as illustrated in **Fig. 1**.

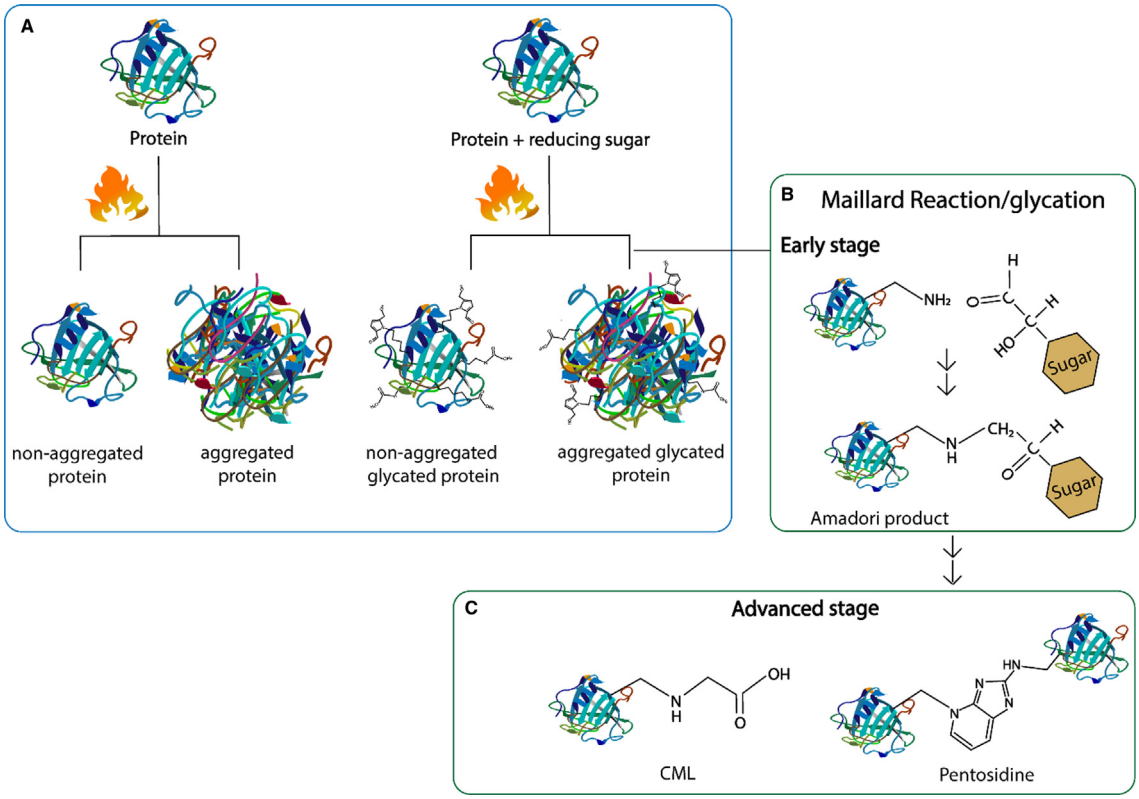

Fig. 1 Structural changes of protein upon heating with and without reducing sugars. (A) protein aggregation, (B) Early Maillard reaction, (C) Advanced stage of the Maillard reaction. N^{ε}-carboxymethyl lysine (CML) and pentosidine are shown as representatives for linear and cross-linking, heterocyclic advanced glycation end products, respectively.

Influence of AGEs on the innate and adaptive immune system

To bring about the effector phase of food allergy, the specific epitopes of dietary proteins need to be recognized by epitope-specific immunoglobulins E (IgE). Such epitope-specific immunoglobulins are formed during the sensitization phase of IgE-mediated food allergies. During the sensitization phase, APCs present fragments of allergens to T-cells and subsequently produce pro-inflammatory cytokines to induce an adaptive response. The immunogenicity of proteins, including MR-modified ones, is dependent on their ability to induce adaptative T and B lymphocyte responses. This can take place only if the AGE-modified protein (or peptide) is recognized, internalized and processed by antigen presenting cells (APC) followed by presentation of specific antigen/peptides. The digestibility of MR-modified food proteins is impaired as reported in the case of β-lactoglobulin (Zenker et al., 2020b) increasing the chance of interaction of larger particles with immune cells. Internalization of these particles may be mediated via specific receptors. To date, several AGE receptors have been identified, including: RAGE (Xue et al., 2014; Palanissami and Paul, 2018; Zenker et al., 2019), oligosaccharyltransferase complex protein 48 (AGER1) and 80 K-H protein (AGER2) (Li et al., 1996) as well as galectin-3 (AGER3) (Vlassara et al., 1995; Teodorowicz et al., 2021). Additionally, several AGE receptors have been identified that belong to the heterogenous scavenger receptor family, including: class A type I and II (SR-AI/II), class B type I (SR-BI), CD36 (Teodorowicz et al., 2021; Ohgami et al., 2001a,b; Nishinaka et al., 2020) and lastly Toll-like receptors (van Zoelen et al., 2009; Hall and Agrawal, 2016, Paz et al., 2017). Principles of binding of food derived AGEs to the receptors expressed on APCs has been well described in a number of reviews (Pinkas and Aschner, 2016; Asadipooya and Uy, 2019; Briceno Noriega et al., 2022, Twarda-Clapa et al., 2022). Such a binding may result in both activation of a number of pro-inflammatory pathways and internalization of the ligands thus activating innate but potentially also adaptive immunity. The best studied interaction of AGEs with the immune system is via the Receptor for Advanced Glycation End products (RAGE) (Palanissami and Paul, 2018). The interaction of food derived AGEs with RAGE has also been shown for glycated whey proteins (Teodorowicz et al., 2021; Liu et al., 2016a,b) as well as for roasted peanuts (Moghaddam et al., 2014). Activation of RAGE leads to an intracellular signaling cascade, resulting in the induction of pro-inflammatory cytokines, inflammation, and oxidative stress (Kierdorf and Fritz, 2013) but RAGE was also shown to mediate phagocytosis (Jones et al., 2013; Yang et al., 2022). Smith et al., proposed so called false alarm hypothesis postulating that a crucial role of RAGE signaling in development of a food allergy. It has been proposed that dAGEs through interaction with receptors might induce alarmin signaling pathways and to skew an immunological reaction toward allergic responses in certain subjects that have a genetic and environmental predisposition (Rider et al., 2017; Smith et al., 2017). Although RAGE is highly

expressed on DCs, macrophages, T lymphocytes and B cells Currently, there an evidence that AGEs trigger food allergy through interaction with RAGE needs to be better support by the scientific data.

Internalization of food-derived AGEs may be mediated through such a receptors as galectin-3 and the receptors from the scavenger family which has been demonstrated in a number of *in vitro* studies (Teodorowicz et al., 2021; Zhu et al., 2001; Ilchmann et al., 2010; Heilmann et al., 2014). Additionally some data suggest that dietary AGEs may contribute to chronic states of inflammation within the human body in the same way as shown for endogenous AGEs (Byun et al., 2017; Di Pino et al., 2017; Gugliucci, 2017; Sergi et al., 2021). Realizing that dietary AGEs reach the local gut immune system as well as the circulation, it cannot be excluded that via interaction with e.g. RAGE they contribute to the low grade chronical inflammation and a number of non-communicable diseases including allergy (Smith et al., 2017). However, the contribution of dietary AGEs (dAGEs) to oxidative stress and inflammation needs to be better documented in human studies and may depend on many factors such as studied population (health status, age, gender etc.), study design, duration of an intervention and importantly, the type of diet (and AGEs) used in the intervention study (de Courten et al., 2016; Di Pino et al., 2017; Linkens et al., 2022).

To sum up, current literature shows that MR can alter the internalization of dietary proteins by APCs however how this affects the cellular signaling and T-cell activation varies depending on the protein and the conditions of a treatment and will be discussed in the subsequent paragraphs.

Influence of Maillard reaction (glycation) on immunogenicity of food proteins

Ovalbumin (OVA)

There are a few studies describing an effect of glycation on immunogenicity and allergenicity of OVA, however the outcomes are not always corroborating. Rupa et al. studied the effect of glycation of OVA with a number of sugars: D-mannose, D-glucose, glucomannan, and galactomannan on allergenicity of OVA in BALB/c mice model. This intervention study showed that OVA glycated with mannose but not other sugars decreases such parameters as histamine and mast cell protease concentration, serum anti-OVA antibody as IgG, IgG1, IgG2, and IgE and the production of less IL-4 and IL-17. Exposure of mice to OVA glycated with other sugars did not led to any significant change in any of parameters mentioned above. A series of *in vitro* experiments revealed that mannosylated OVA showed reduced uptake by DCs, reduced DCs maturation, T-cell activation, and type-2 response (Rupa et al., 2014). These outcomes contradict the results of other studies by Heilmann et al. (2014) and Ilchmann et al. (2010). Ilchmann et al. showed that myeloid DCs take up OVA glycated with glucose through receptor-mediated endocytosis involving SR class-A type I and type II, and the production of IL-4 was enhanced by OVA-specific $CD4^+$ T-cells (Ilchmann et al., 2010). Heilmann et al. used OVA as a model to identify specific glycation structures that may have allergenic potential by inducing T-cell immunogenicity in murine subjects. Their research is among a handful of studies attempting to identify AGEs structures responsible for activating T-cell immunity by modifying OVA specifically with CEL, CML, and pyralline (Pyr). The T-cell immunogenicity of variously glycated-OVA was evaluated by co-culturing OVA-specific $CD4^+$ T-cells from mice with bone marrow-derived DCs. Pyr-modified OVA (Pyr-OVA) showed higher production of IL-2, IL-17A, and IFN-y than native OVA, indicating an increased $CD4^+$ T-cell immunogenicity. Additionally, the scavenger receptor (SR) was involved in the uptake of Pyr-OVA by bone marrow dendritic cells (BMDCs). Thus, this study demonstrated that pyralline could induce enhanced allergen uptake by DCs through its association with SR class A (SR-A), resulting in increased $CD4^+$ T-cell activation and IgE production (Heilmann et al., 2014). The discrepancy in the obtained results per study may be caused by differences in the treatment conditions used. Ma et al. showed nicely how various parameters of the glycation affect the IgG binding to the modified OVA. These parameters included temperature (60−100 °C), time (10−120 min), pH (2.0−10.0), glucose/lysine ratio (1−100), and OVA concentration itself. The study found that the Maillard reaction can have a positive or negative effect on the IgG-binding capacity of OVA which depending on the conditions applied varied between 62% and 124%. This study clearly demonstrates that heat induced structural changes determine the IgG binding which can be masked by sugar structures. However immunogenicity measured by IgG binding does not well reflect immunogenicity of OVA measured by uptake by immune cells and further possible activation of T-cells. Nevertheless also these parameters depend on the conditions of the glycation including the sugar type like demonstrated by Rupa et al. (2014).

β-Lactoglobulin (BLG)

One of the most common causes of cow's milk allergy is β-lactoglobulin (BLG), which is the most abundant whey protein and is not present in breast milk (Golkar et al., 2019). Several studies have been conducted to understand the importance of heat and Maillard reaction induced changes in the immunogenicity and allergenicity of BLG (Perusko et al., 2018; El Mecherfi et al., 2019; Kurpiewska et al., 2019; Zenker et al., 2019; Deng et al., 2020; Shao et al., 2020; Teodorowicz et al., 2021; Jia et al., 2022). More intense local immunologic response toward heated BLG compared to its native form was observed in the mucosa of rats (Rytkönen et al., 2002). Also Maillard reaction was shown to modulate the immunogenicity of BLG as well as its binding to the receptors expressed by APCs (Chun et al., 2016; Zenker et al., 2020a; Teodorowicz et al., 2021). Other studies investigating the immunogenicity of BLG showed enhanced recognition and uptake of heat induced aggregates of BLG as well as glycated BLG, pointing at the structural changes as the most relevant features determining the binding of BLG to APCs (Teodorowicz et al., 2021; Deng et al., 2019; Zenker et al., 2019). Those structural features are heat-induced formation of aggregates, formation of β-sheets structures, increased hydrophobicity and changes in the charge of a protein. These opposing results create the question: is there any effect of glycation of BLG on its immunogenicity or is this driven mainly by structural, heat-induced changes? Although this question is still not fully answered, the importance of glycation *in vivo* was suggested by a study showing that glycated aggregates of β-lactoglobulin are less sensitive to digestion

and therefore maintain their binding capacity to RAGE and Gal-3 (Teodorowicz et al., 2021). Also CML modified BLG was shown to bind to the receptors present on antigen presenting cells (Zenker et al., 2020a). However, also the conditions of glycation of BLG (dry vs. wet environment) seem to have a key role in determining the structural changes and therefore immunogenicity (Zenker et al., 2019).

Moving a step further to the T-cell responses, pasteurization-induced aggregates of BLG were shown to play a role in allergic sensitization in mice by increased uptake via Peyer's patches resulting in higher production of Th2-associated antibodies and cytokines (Roth-Walter et al., 2008). Similarly, cross-linked BLG has been found to be increasingly endocytosed by dendritic cells, leading to the development of a Th2-associated environment in a food allergy-murine model (Stojadinovic et al., 2014). However, there are also studies showing that heat treatment and glycation do not lead to an activation of T-cell immunity (Perusko et al., 2018). Perusko et al. showed that glycation of BLG significantly enhanced the receptor-mediated endocytosis in BMDCs in a murine model. However, even though glycated BLG underwent greater degradation by lysosomal enzymes, it exhibited reduced capacity in induction of T-cell response in the co-culture of BMDCs with BLG-specific $CD4^+$ T-cells (Perusko et al., 2018). These diverse results illustrate the complexity of the problem and the need for standardization of the studies performed on effect of glycation of BLG in order to obtain conclusive results.

Nuts

Nuts as the top of the list of eight big allergens are relatively well studied in terms of the role of processing as well as glycation in sensitization and elicitation of food allergy. Studies performed on peanuts emphasized a role of processing-induced aggregation in the sensitization process. Guillon et al. highlighted the role of processing-induced aggregation of Ara h 6. The authors demonstrated that native monomeric Ara h 6 extracted from raw or roasted peanuts was unable to induce sensitization in mice while extracts from roasted or fried peanuts were shown to do so. This phenomenon was explained by aggregation of Ara h 6 either with itself or with other proteins including Ara h 1 monomers forming structures with MW above 260 kDa. These aggregates were characterized by high immunogenicity and allergenicity of Ara h 6 leading to the induction of specific IgG1 and IgE in mice. Authors suggest that the aggregation of Ara h 6 with glycosylated Ara h 1 can play a crucial role in sensitization of aggregated Ara h 6. Also interaction with the matrix compounds may take a part in formation of immunogenic structures, therefore MR may be an important factor increasing immunogenicity of aggregated Ara h 6 (Shreffler et al., 2006; Guillon et al., 2016). These results are in line with earlier studies showing formation of high immunogenic aggregates in roasted and processed peanuts (Schmitt et al., 2010). Moghaddam and colleagues demonstrated that BALB/c mice primed subcutaneously with soluble fractions of peanut protein extract from raw or dry roasted (DR) peanuts show enhanced peanut-specific IgG titers in DR-primed groups. These results were confirmed in intragastric gavages of DR and raw peanut extracts showing 100-fold higher IgG titers, enhanced titers of anti-peanut IgE as well as functional basophil degranulation in DR group. Moreover, mesenteric lymph node cells from DR but not raw peanut protein-primed mice proliferated robustly in response to raw and DR peanut extract with the dominance of IL-4 and IL-5 over IFN-γ and TNF-α. The authors suggested that the observed increased immunogenicity of DR peanut antigens can be explained by selective targeting, activation and presentation of antigen via binding to AGE receptors on DCs (Moghaddam et al., 2014). To sum up in case of peanuts the aggregation plays a critical role in sensitization process. As discussed before on the example of BLG the glycated aggregates had lower digestibility and were recognized by receptors like RAGE and Galectin-3 (Teodorowicz et al., 2021) which may be a principle of generation of immune response also for roasted peanuts.

Immunogenicity and allergenicity of glycated proteins: Other examples

DCs are crucial immune cells involved in regulation of immune responses including initiation of food allergies. DCs express a number of receptors recognizing and binding AGES, such as RAGE, Galectin-3, SRAI and CD36. However, the influence of dAGEs on DC-differentiation and capacity to present antigen to T-cells remains unclear. For example, Ge et al. reported maturation and activation of human monocyte-derived DCs stimulated with glycated bovine serum albumin (BSA). Additionally, BSA-AGEs enhanced the capacity of DCs to stimulate T-cell proliferation and the production of IFN-γ and IL-12 but also expression of SR-A and RAGE (Ge et al., 2005). On the other hand, Price et al. showed that AGE-modified peptides lead to reduced expression of CD83 in peripheral blood DCs lowering the maturation and therefore the capacity of DCs to stimulate primary T-cell proliferation (Price et al., 2004). This incompatibility of the results may be caused by differences in the structure of AGEs used for DC-stimulation as well as the type of the DCs used in the studies. Therefore, more standardized set up of the studies on activation of DCs by AGEs is needed in order to better gain insight into the role of AGEs in initiation of food allergies.

Allergic elicitation and the Maillard reaction

IgE-avidity and severity of the allergic reaction

Foods are, in almost all cases, heated before being consumed. Heating of proteins in the food, and hence also of allergens, may lead to altering the 3-dimensional folding of their amino acid chain and therefore possibly their interaction with IgE-type antibodies, in the case of allergens and potentially altering the initiation as well as the elicitation of an allergic reaction. When such heating has taken place in the presence of reducing sugars, on top of changes in 3D-structure, relevant amino acid residues, i.e. lysine and/or arginine, may participate in the Maillard reaction and become glycated, another physicochemical heating-related structure change in allergens that may affect their interaction with their respective IgE antibodies. Here, the focus will, as sec as possible, be placed on the effect of *glycation* on allergenicity, i.e. IgE-binding (Verhoeckx et al., 2015), and not on the impact of changes in protein conformation.

The severity of an allergic reaction is determined by a multitude of factors. These may be related to the allergenic protein (such as protein type, dose, the matrix in which it is embedded and the processing to which it has been subjected), to the host (e.g. age, threshold dose, co-morbidities, cofactors such as medication or exercise), as well as to the IgE-response of which also the strength of the interaction between IgE and the corresponding allergen, i.e. the avidity, is of importance (El-Khouly et al., 2007; Santos, 2020). Hence knowledge of the, also food processing-related, factors that are of importance for this allergen-IgE-interaction is relevant for the development of safer foods from a perspective of allergenicity management. Much, but not all, of the research that will be discussed here was performed with firstly isolated and then glycated allergens, after which their allergenicity was evaluated. An approach to work with isolated allergens may lead to a 'clean' picture of the events at the molecular level of such individual allergen. However, as foods are not consumed, and in practice also not processed, as isolated proteins/allergens, such an experimental set-up will not take into account whether food matrix-related events, such as protein-protein or protein-lipid interactions play a relevant role. The, in number less, studies that do make use of more complex preparations do suggest, however, that afore-mentioned interactions do contribute to eventual allergenic properties of allergens.

Impact of glycation of allergens from animal-derived foods

Egg: Ovalbumin and ovomucoid

The, for analysis of glycation effects, by far most studied egg-derived allergen is Gal d 2 (ovalbumin), which is, with approx. 54% abundancy, the major allergen from egg white (Mine and Rupa, 2004).

In all studies, glycation of Gal d 2 led to a reduced capacity to bind to (human) IgE, as evidenced by various types of ELISA and/or dot-blot tests (Yang et al., 2020a; Cherkaoui et al., 2022; Wang et al., 2022b; Zhang et al., 2022; Yu et al., 2023). In no study, a mediator release assay (MRA) was applied. Degree of glycation and extent of reduction of IgE-binding depended on the type of sugar used (Wang et al., 2022b). MS-analysis of glycated (glucose) Gal d 2 showed that structural modifications of residues in or near known human linear IgE epitopes, such as C121, K123, S169, K190, K207, H332 and C368, were most relevant for reduction of IgE-binding.

Also for ovomucoid, glycation with FOS or GOS (fructo-, resp. galacto-oligosaccharides) reduced IgE-binding (attributed to epitope masking), and β-hexosaminidase release from LAD-2 cells, but glycation with mannosan was reported to increase both these parameters with a few percent. Glycation with mannosan may have been somewhat less effective, possibly explaining these opposite effects (Ma et al., 2021).

Milk: Whey proteins and caseins

The most abundant allergens in milk are the whey proteins α-lactalbumin (Bos d 4) and β-lactoglobulin (Bos d 5), and the 4 caseins (α_{S1}, α_{S2}, β and κ (resp. Bos d 9−12); resp. 1−1.5, 3−4 and 27−34 g L^{-1} in cow's milk (Monaci et al., 2006)).

Caseins

The caseins are, probably resulting from their intrinsically unordered structure, most processing resistant and hence also most recalcitrant allergens. Although quite some literature on its role in allergenicity of milk is in place, they appear least studied with respect to IgE-binding and glycation, despite their ubiquitous presence e.g. in, heavily processed and glycated, products such as infant formula. Perhaps this is because they are not always easy to handle due to their physico-chemical properties and micellar aggregation.

The consensus, though based on limited literature, seems that glycation of caseins does not have a strong, if any, effect on their IgE-binding capacity. Such is suggested in the review by Bu et al. (2013), referring to rather old and hardly-retrievable primary sources. The observation is, however, in line with Yousefi et al. (2017) in a more recent paper, for β-casein that indeed seemed to be effectively glycated with glucose, although it is unclear whether an appropriate control (i.e. not just native protein, but heated in the absence of sugar) was used.

Whey: α-lactalbumin

Glycation of purified α-lactalbumin led to reduced IgE-binding and mediator release from KU-812 or RBL-2H3 cells in all consulted studies (Li et al., 2019; Liu et al., 2020; Wang et al., 2021a, 2022a; Bu et al., 2022), regardless of sugar (allose, mannose, glucose, galactose or lactose) that was used, or of glycation protocol. It is of note that in most studies native α-lactalbumin, and not α-lactalbumin heated in absence of sugar, was used as control, making it uncertain whether reduced IgE-binding was totally ascribable to glycation or to (partial) protein unfolding. Because α-lactalbumin was found glycated at K13, K16, K94, K98, and K108 (K98 claimed to be particularly important (Li et al., 2019)), but also phosphorylated at Y18, S22, Y103, and S112, resp. acetylated at K13, T33, S34, T38, S47, K62, S69, S70, K108, and K114, it was concluded that not only masking of its linear epitopes explained the decrease in IgE-binding, but also their modification. The decrease of allergenic reactivity of α-lactalbumin induced by glycation, phosphorylation and acetylation was supposed not only to depend on epitope shielding effects, but also the change of conformational structure (Wang et al., 2021a). High pressure microfluidization pre-treatment was, strongest at 110 MPa, found to amplify the reduction in IgE-binding (Li et al., 2019).

Gastric or duodenal digestion was reported to increase IgE-binding (Wang et al., 2021a, 2022a), to be explained by higher accessibility of epitopes and/or of unshielding of epitopes (Monaci et al., 2006; Wang et al., 2021a).

Whey: β-lactoglobulin

Also for glycation of isolated β-lactoglobulin, in all reports a decreasing effect of glycation on IgE-binding or mediator release (KU812, RBL-2H3, RBL-hεIa-2B12, RS-ATL8) was claimed for a variety of sugars (lactose, galactose, glucose, arabinose) (Bu et al., 2010; Perusko et al., 2018; Shao et al., 2020, 2021; Bosman et al., 2021; Wang et al., 2021b). Reduction of allergenicity was amplified by prior treatment such as ultrasonication (Shao et al., 2020) or high-temperature (180 °C) spray drying (Yang et al., 2020a). Also in these reports, it is not always clear which contribution to reduced IgE-binding is delivered by conformational changes or by glycation.

High temperature spray drying was claimed to lead to protein aggregation, hence shielding of epitopes and decreased free amino group content. Glycated Lys side-chains were detected by MS, mostly in the known epitope regions (Gasparini et al., 2020; Yang et al., 2020a).

Fish: Parvalbumin

The most studied, again purified, allergen from fish (*Scophthalmus maximus*, *Gadus chalcogrammus* or the recombinant form from *Hypophthalmichthys molitrix*) is parvalbumin (Zhao et al., 2017; Zhang et al., 2021a; Wu et al., 2022). Wu et al. (2022) claimed a reduced mediator release (β-hexosaminidase, IL-4, IL-13, histamine, tryptase) from KU812 cells, a process that could partly be attributed to the heating process itself, but was amplified by glycation with glucose. Glycation also led to parvalbumin aggregation, but to aggregates of maximally approx. 70 kDa that could still migrate into an SDS-PAGE-gel. Zhang et al. (2021a) described IgE-binding by glycated parvalbumin to depend on the type of sugar used, glucose and fructose giving higher IgE-binding compared to heated-only control and in particular ribose and galactose, but also lactose, leading to reduced IgE-binding. Of note is that ribose and galactose gave considerably higher glycation levels (50−75% reduction in free NH_2-residues, vs. 20% after glycation with glucose in (Zhang et al., 2021a)). Zhao et al. (2017) also reported decreased IgE-binding (in dot blots) by r-parvalbumin and mediator release (β-hexosaminidase, histamine, IL-4, TNF-α) by RBL-2H3 cells after glycation (to 80% of free NH_2-residues) with glucose. Glycation also occurred in epitopes of parvalbumin, as evidenced by LC-MS/MS, and glycation also led to aggregation, albeit again to not very large aggregates (maximally ca. 70 kDa).

Arthropods and mollusks: Tropomyosin

The, exclusively, at the molecular level studied allergen from arthropods and mollusks is tropomyosin. And also here applies that glycation by a variety of sugars (even methylglyoxal (Yang et al., 2023) or oligosaccharides (Zhang et al., 2020)) and glycation methods leads to decreased IgE-binding and response in MRAs, regardless of the source (crab, shrimp, squid or clamps) of tropomyosin (Nakamura et al., 2006; Zhang et al., 2018, 2019, 2020, 2021b,c; Bai et al., 2021; Liu et al., 2021; Han et al., 2022; Lv et al., 2022; Yang et al., 2023). Although glycation at epitopes was demonstrated via LC-MS/MS (Nakamura et al., 2006; Han et al., 2022; Lv et al., 2022; Yang et al., 2023), it is not always clear which part of the reduction in allergenicity is due to structural changes and which to glycation, because in many cases the control was native, and not heated-in-absence-of-sugar, tropomyosin. Liu et al. (2021) worked with whole shrimp meat that was glycated with galactose. Glycation occurred on epitopes, did not result in aggregation as shown in western blots, and digestion (in particular duodenal) destroyed IgE-binding as evidenced in dot blots for both tropomyosin and sarcoplasmic calcium-binding protein.

Impact of glycation of allergens from seed- or nut-derived foods

Seeds and nuts are, almost by definition, worthwhile to consider in detail due to the presence of pan-allergens such as albumins and cupins (Mills et al., 2004).

Peanut and hazelnut: 7S-globulins and 2S-albumins

Important allergens from peanut are the 7S-globulin Ara h 1 and the 2S-albumin Ara h 2. Vissers et al. (2011) studied the effect of heating of these proteins in the absence resp. presence of glucose on their allergenicity with both an inhibition ELISA and with β-hexosaminidase release from RBL-2H3 cells. Heating resulted in decreased allergenicity for both Ara h 1 and 2 compared to their native forms, an effect that was considerably stronger for Ara h 1 when this protein was glycated. Allergenicity assessment with RBL-2H3, however, showed increased allergenicity for Ara h 1 but the opposite for Ara h 2. Shi et al. (2020) also reported higher degranulation of (albeit non-specified) RBL-cells by AGE-Ara h 1 than by non-heated Ara h 1. Glycation of Ara h 1, but not of Ara h 2, led to the formation of large aggregates as measured with differential light scattering (approx. 10.3 nm for native Ara h 1 versus 560 nm for aggregated Ara h 1.

The observations on Ara h 1 were confirmed for the 7S-globulin from hazelnut, Cor a 11, by Iwan et al. (2011). IgE-binding aggregates were also observed in the glycated soy protein extracts confirming the role of aggregates in the generation of an (allergic) immune response (Briceno et al., 2023). The last study illustrates a lack of correspondence between IgE binding tests and functional assays, indicating a need to include functional assays, next to the IgE binding tests, in the studies on allergenicity of MRPs to be able to work toward conclusions on clinical relevance of an allergen.

Aggregation could explain the observed phenomena; aggregation may shield IgE-epitopes in IgE-binding tests, leading to decreased responses, but sufficiently large aggregates may be better able to bind multiple receptor-bound IgE-molecules simultaneously, hence facilitating their crosslinking on effector cells (Fig. 2). 'Sufficiently large aggregates', in this context, could be estimated from a number of assumptions.

- Assuming a diameter of 12−15 μm and a spherical shape for typical basophils leads to an estimate of 450−700 μm^2 for their surface (Tigner et al., 2023)
- A typical basophil to contain 6000−600,000 FcεRI-receptors with IgE bound to it, out of a total of 29,000−680,000 FcεRI-molecules (Knol, 2006)
- From this, assuming an equal distance between FcεRI-bound IgE-molecules, an average distance between these of 27−275 nm can be calculated; and even larger for allergen-specific IgE, in case of a polyclonal palette of IgE
- This calculation is based on quite a few assumptions, which admittedly are to be taken with due reservation. As a rough estimate, however, this estimation does suggest that molecules like trimeric Ara h 1 of approx. 10 nm in diameter, or less well aggregating Ara h 2 resp. animal proteins with aggregates of maximally 70−80 kDa, being smaller than native Ara h 1, would less effectively, or at lower velocity, crosslink than aggregates of approx. 560 nm. In such situation, even one aggregate of such size would be able to induce degranulation under proper circumstances, assuming the claimed required 100 cross-links for at least 100s (Knol, 2006) to be correct.

Complex heated preparations from peanut

Adding to these observations is a study by Kroghsbo et al. (2014) in which Brown Norway rats were orally sensitized with either roasted or blanched peanuts or peanut butter, and MRAs (RBL-2H3) were performed with the resulting sera. Regardless of the product that was used for sensitization, an extract from roasted peanut was the superior inducer of β-hexosaminidase release in these assays, although no details, beyond being >200 kDa, were given on the likely present aggregates in such peanuts, nor on glycation characteristics on the proteins that were present in the preparations. Intraperitoneal sensitization of rats with purified or processed (heated or glycated with glucose) Ara h 1 showed glycated Ara h 1 to the least effective IgE inducer, and also the least effective cross-linker for rat-serum loaded RBL-2H3 cells. However, the sera with which the RBL-cells were loaded were not standardized for IgE-titers, so whether this lower β-hexosaminidase release was due to the lower IgE-titer or due to protein characteristics is unclear. Also, no data on glycation or aggregation levels were shown.

The importance of intermolecular interactions for both sensitization as well as for the quality of the resulting IgE is further illustrated by Moghaddam et al. (2014). Balb/c mice were sensitized with either raw or dry roasted (DR) peanuts. DR peanuts were found to be more immunogenic and the resulting sera being more effective in an MRA. Also in this study, no details on e.g. aggregation or glycation were presented. Roasting conditions were much more harsh (160 °C 20 min) than those used by Kroghsbo et al. (150−160° 3−5 min (Kroghsbo et al., 2014)).

Discussion and conclusions

The overall picture that emerges from the above presented studies is that glycation of allergenic proteins leads to a reduction in their allergenicity, allergenicity in this review interpreted as the capacity of such proteins to interact with IgE in either IgE-binding tests

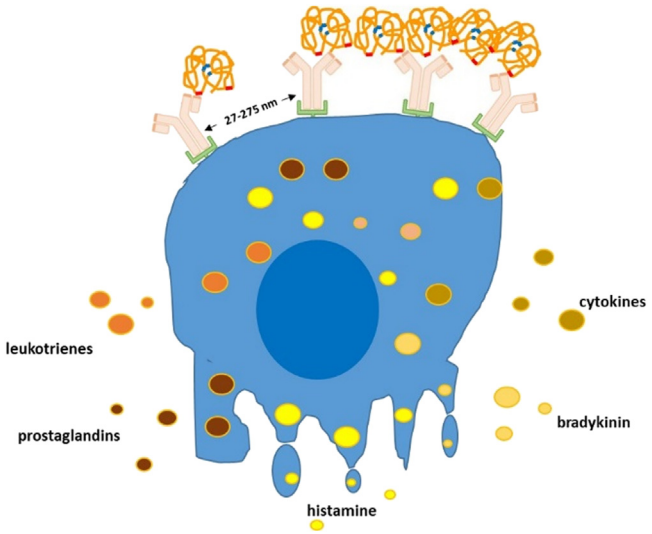

Fig. 2 Graphical image of (faster) cross-linking by aggregates than by smaller allergens.

such as dot blots, Western blots or various types of ELISA. This may sound reasonable, as modified proteins would have, perhaps, changed epitopes compared to the native ones. However, in food allergy the key issue would be which form of the protein is the primary sensitizer. As observed in the pollen-fruit syndrome, the explanation for higher avidity of IgE for Bet v 1 than for Mal d 1 and other fruit-contained PR-10 proteins is that the primary sensitizer leads to the production of the highest avidity IgE (Kleine-Tebbe et al., 2017; Pomés et al., 2018). Extrapolating this, and assuming that most, if not all, of the proteins that are discussed above are consumed after the food that they are contained in has been processed (often meaning heat-treated) and the ubiquitous (or at the least in sufficient dose for a glycation reaction) presence of reducing sugars in such foods, it could be hypothesized that glycated, anyway heat-processed, forms of such proteins are primary sensitizers, rather than their native forms, and should give rise to highest avidity IgE. Such hypothesis is to be rejected, however, based on the results presented here.

The observed decreased allergenicity could be understood via a number of molecular mechanisms, such as e.g. modification of IgE-binding epitopes or peritopes through glycation, which seems confirmed in a number of studies (Zhao et al., 2017; Liu et al., 2020; Yang et al., 2020b; Wang et al., 2021b; Cherkaoui et al., 2022; Han et al., 2022; Zhang et al., 2022), or aggregation of allergens leading to shielding of epitopes, making fewer available for IgE-binding (Bu et al., 2010; Zhang et al., 2019; Wang et al., 2021b; Lv et al., 2022; Wu et al., 2022).

Applying another, and more physiological relevant, method for allergenicity assessment, i.e. some form of mediator release assay using basophils or mast cells, leads to a similar conclusion, at least for the allergens of animal origin: glycation appears to decrease their allergenicity. However, this picture changes a bit when seed or nut-derived allergens, and in particular 7S-globulins, are analyzed with respect to the impact of their glycation. This may be explained to be the consequence of (strong) aggregation, leading to hiding of epitopes inside the aggregate making these inaccessible for IgE-binding, but creating sufficiently large aggregates to simultaneously crosslink multiple FcεR-bound allergen-specific IgE on the surface of effector cells, leading to enhanced mediator release. Concluding from the (scarce) descriptions of aggregation behavior of animal-derived allergens, it seems that the aggregates formed thereout are relatively small compared to the ones formed from e.g. 7S-globulins (Iwan et al., 2011; Vissers et al., 2011; Zhao et al., 2017; Shao et al., 2021; Wang et al., 2021a; Wu et al., 2022; Yang et al., 2023).

There are several limitations to the evaluated literature that hamper their potential physiological relevance. Firstly, in many reports purified allergens have been used for the studies. This allows a more precise description of glycation and aggregation behavior, but ignores potential effects from the food matrix on their molecular properties upon heating, which seem to do play a role (Kroghsbo et al., 2014; Moghaddam et al., 2014). In real life, allergens are eaten nor processed in their purified form, so matrix effects likely do bear strong physiological relevance. In addition, if aggregation explains part of the decreased allergenicity in IgE-binding tests, such by consequence hidden epitopes may be re-exposed e.g. upon digestion (Zhang et al., 2019; Wang et al., 2021a, 2022a), making the supposed decreased allergenicity a bit a fata morgana, and efforts to technologically aggregate proteins to shield epitopes may turn out to be useless under physiological conditions.

Another important limitation is the lack of clinical data. Allergenicity changes have been described in terms of (simple) IgE-binding tests, or MRA-tests. This allows precise descriptions and relatively quantitative descriptions of effects, but what such effects might mean in clinical practice and which promise they hold, remains to be established. The often used remark that 'glycation may be used to prepare less allergenic foods' is hence to be taken with some skepticism and remains to be tested and demonstrated in a clinical setting.

Summary and overall conclusions

As reviewed above, a number of studies have shown that MR effects immunogenicity and allergenicity of food proteins both in terms of sensitization and elicitation phase, however the results of different studies are often diverse. The outcomes depend highly on the structural arrangements of the epitopes, thermal stability of allergens but also on the conditions of MR itself like types and concentrations of reducing sugars, food matrix composition and treatment conditions itself (temperature, pH, duration and moisture). To induce an allergic immune response, the MR-modified protein needs to be recognized and taken up by APCs and presented subsequently to T cells (as shown in **Fig. 3**). Several studies have identified RAGE and other receptors expressed by APCs as the receptors recognizing glycated food proteins. Based on current knowledge it can be hypothesized that binding of AGEs to RAGE will not lead directly to an activation of T-cells or T-cell skewing but rather to the re-programming of the cell via activation of the particular signaling pathways like NF-kb. Binding of AGEs to the receptors like galectin-3 or/and receptors from scavenger family results in internalization of the ligand, which may directly lead to antigen presentation and activation of food protein-specific T-cells (see **Fig. 3**). Importantly, heat and MR-induced aggregation of allergens seems to be a key factor enhancing both the sensitization capacity of allergens and the elicitation phase in terms of IgE binding. However, when isolated allergens are studied, glycation seems to decrease IgE-binding but matrix components are very relevant for the immunological effects, as they also interact with allergens upon heating. Moreover, simple IgE binding tests cannot fully predict clinical relevance of an allergen. Therefore functional assays like degranulation assays and basophil activation assays (BAT) are needed to obtain a more objective picture on the allergenicity of a specific protein. In conclusion, heterogeneity of AGEs formed upon different conditions and from different proteins as well as the diversity of their receptors are a challenge to draw clear conclusions and to build a predicting model relating condition of MR, structure of the allergen and its immunogenicity/allergenicity. Therefore joined efforts are needed in order to find a pattern between structure of AGEs, conditions of MR and immunogenicity of glycated proteins on the level of both innate and adaptive immunity.

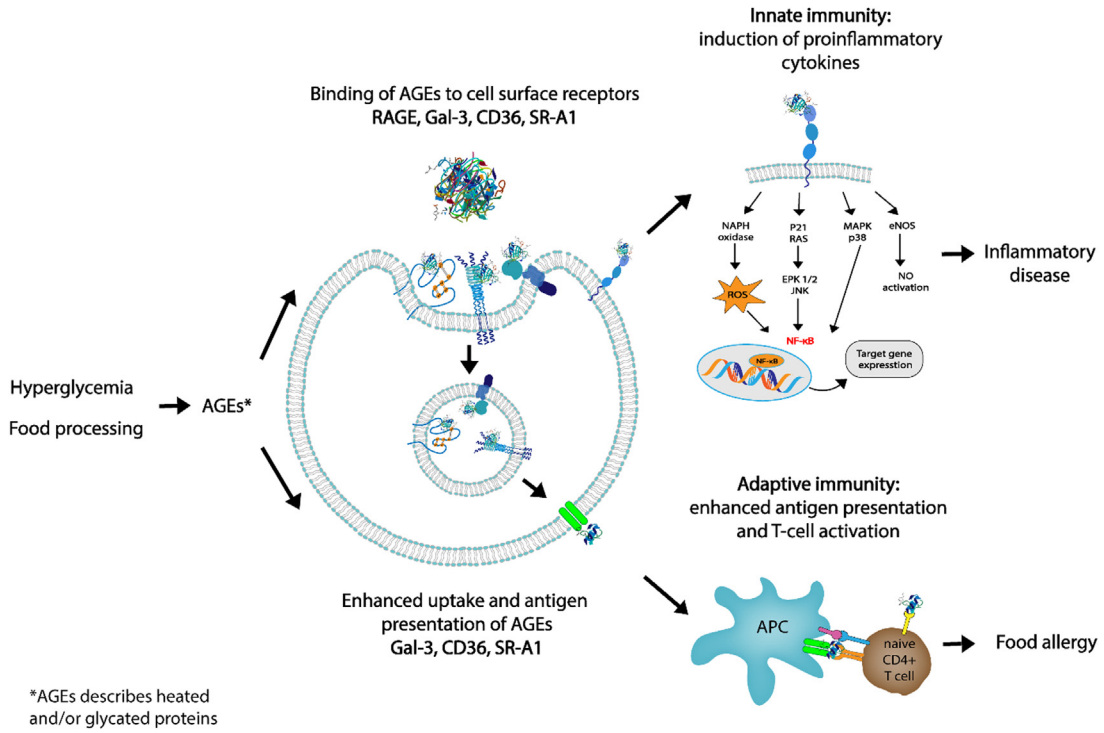

Fig. 3 Role of dietary advanced glycation end products (AGEs) in innate and adaptive immunity. By targeting AGE receptors dAGEs may influence innate immunity via interaction with RAGE or by binding to AGE receptors which internalize the ligands: galectin-3 (Gal-3), CD36, and scavenger receptor class A type I (SR-A1). Presentation of antigen to T-cells may facilitate the T-cell activation and skewing possibly leading to the allergic responses. In that way dAGEs may contribute to both innate and adaptive immunity.

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