

Does hapten exposure predispose to atopic disease? The hapten-atopy hypothesis

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Contact allergy data indicates that atopics have heightened oral tolerance to haptens (chemical allergens). We speculate here, that artificially increased oral exposure to chemicals compete with dietary proteins for the development of oral tolerance, predisposing to the acquisition of food protein allergy and representing one driver for the increasing prevalence of protein allergy and/or atopy. Hapten exposure via other surfaces such as the skin and airways might also be important in promoting atopic disease. Consistent with this hypothesis it is notable that over 40 years, with the huge increase in atopic disease, there has also been an increase in dietary hapten exposure through processed food, formula milk and oral antibiotic and drug use.

Introduction

Atopy is characterised by sensitisation to environmental proteins; definitions of atopy include sensitisation to two or more common protein allergens, as manifested by positive skin prick tests or positivity for antigen-specific immunoglobulin E (IgE) antibodies, in association with atopic disease such as dermatitis, asthma and hay fever [1]. A important influence on predisposition is heritable and susceptibility is usually associated with T helper cell (Th)2-biased immune responses. Atopic dermatitis is characterised by involvement in childhood, dry skin and an itchy eczematous rash of a flexural nature located at joints such as the elbow and knee [2]. The failure of tolerance to protein might be a prerequisite for subsequent sensitisation and allergy, such as to food protein [3] and indeed food protein allergy is often associated with atopic disease. We have recently shown that there is a negative association between the development of contact allergy to chemical allergens (haptens) that are encountered orally (and also via skin surfaces) and symptoms of atopic allergy [4] (Box 1). Haptens differ from protein allergens in that they are not allergenic when unbound, but upon binding to and altering the configuration of a peptide or protein, can render them allergenic [5,6] (Box 2). This observed negative association indicates that in atopics there is heightened oral tolerance to chemical haptens (contact allergens), in direct contrast to their known defective oral tolerance to food proteins. However, there was no observed

increase in tolerance to haptens that have no gastrointestinal exposure amongst atopics. One possible explanation is through some kind of inverted relationship between oral tolerance to chemicals and oral tolerance to proteins (i.e. they compete with each other). If this is true then maybe such 'competition' – associated with increased rates of dietary exposure to chemicals – could represent one driver for the increasing prevalence of atopic diseases (Figure 1a and 1b). We speculate that the increase in processed food and milk in western diets over the past 50 years, with artificially raised levels of chemical haptens, has shifted tolerance processes in the gut away from food proteins and towards chemical haptens, and that this has contributed to the rise in atopy seen over this period. The use of oral antibiotics (which can act as haptens in the gut) might also have had an important role.

Food protein allergy and atopic disease: association and predisposition

Protein allergy (and by inference, defective oral tolerance) to food predominantly occurs against an atopic background [3]. For instance, a population-based case-control interview and prick-test study, found food allergic subjects suffered significantly more frequently from urticaria, asthma, atopic eczema and especially hay fever than controls [3]. Other studies have shown a surprisingly high level of food allergy in atopics [7], in addition to a very high frequency of IgE food protein sensitization in infants with atopic dermatitis [8]. Furthermore, a murine model showed the induction eczema-like lesions in a third of food protein sensitized mice after low dose ingestion of small amounts of cow's milk and peanut allergens [9].

Food allergy can predispose to atopic disease in organs other than the skin, for instance, hen's egg sensitization is significantly related to the appearance of asthma, in a similar manner to the severity of atopic dermatitis [10]. Children sensitized to cow's milk proteins who also have atopic eczema are at higher risk of developing asthma [11]. This study also found that the introduction of formula milk during the first trimester of life increases the risk of developing asthma. These observations have been reinforced by experimental gastrointestinal allergy in mice to food protein (ovalbumin) enhancing subsequent atopic pulmonary responses to both specific (ovalbumin) and unrelated (house dust mite) allergens [12]. Additionally,

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Box 1. Haptens, contact allergens and allergic contact dermatitis

Haptens

Low molecular weight chemicals (usually less than 500 daltons), which are low reactive organic molecules that can bind to proteins and peptides, rendering them allergenic.

Contact allergens

Haptens which cause allergy through exposure ('contact') with the skin.

Allergic reactions to contact allergens occur as an inflammatory skin reaction to direct contact with the hapten.

Allergic contact dermatitis

The dermatitis reaction, which results from allergic reaction to a contact allergen (contact allergy).

Examples of common contact allergens include:

- Nickel: as many as 15% of adult women are allergic to nickel through sensitisation by ear-piercing
- Para-phenylenediamine: an aromatic amine used in the majority of permanent hair dye systems
- Fragrances: these are a group of aromatic chemicals found in perfumed water, toiletries and household products.

Although exposure to most contact allergens is solely on the skin, there are a few with both skin and gastrointestinal exposure. In these cases, clinical allergic inflammatory reactions have only been observed on the skin. They include:

- Fragrance chemicals such as eugenol, cinnamal and cinnamic alcohol which can occur in the diet both naturally and as an additive flavouring agent
- Preservatives such as sodium metabisulfite used in skin care products and as a food preservative
- The quinoline group of antimicrobials and preservatives. For example, ciprofloxacin, which is a commonly used antibiotic in humans; quinine, which is added to tonic drinks and thoxyquin, which is used in chicken feed and traces remain in the meat

several independent studies in children have shown positive associations between food protein allergy such as cow's milk and asthma or allergic rhinitis [13–17]. In many cases, these respiratory conditions were still present

Box 2. Immunological comparison of food protein allergens and haptens

Food protein allergens

- Water-soluble glycoproteins
- 10–70 kDa size
- Possess multiple IgE binding-epitopes
- Presence of linear or structural allergen-specific IgE binding epitopes
- Most are stable and resistant to food digestion

Haptens

- Agents that were originally defined as small molecules that can become sensitizing when they are bound to a protein. They are not allergenic on their own but covalently bind to and modify proteins and peptides rendering them 'foreign' and allergenic
- The main targets for hapten binding are amino acid side chains with nucleophilic properties. Strongest nucleophilic amino acids, and therefore targets, are lysine, cysteine and histidine
- Haptens can be derived from inert chemicals (pro-haptens) that are metabolised to active electrophilic chemicals in the skin and/or mucosa

after complete recovery from the food allergy. Another study showed that egg allergy in the first year of life was a predictor of not only asthma development but also reactivity to house dust mite antigen, which was again not dependant upon persistence of the egg allergy [18]. The inference is that early food protein allergy (and therefore defective food protein tolerance) can lead to the subsequent development of atopic disease, not only dermal but also respiratory. That there is not always a clear relationship seen in asthmatics at a later age might be related to the frequent resolution of food protein allergy [19]. In addition, subjects with defective tolerance to food protein early in life might not even necessarily develop food protein allergy, as this could depend upon quantitatively significant exposure of food protein on the skin for sensitisation [20].

Food exposure and reactivity during pregnancy might be important in determining subsequent food allergy and atopy in the offspring. Maternally delivered nutritive allergens, such as ovalbumin and β -lactoglobulin can be detected in cord blood and placental tissue [21], and foetal cord blood mononuclear cell reactivity to these agents has also been observed [22]. During pregnancy, there is a polarisation of T helper cells towards a dominance of Th2 in mother and foetus [23]. One could speculate that, if the neonatal immune system is not able to down-regulate the pre-existing Th2 dominance effectively, then an allergic phenotype might subsequently develop [23].

Dietary protein allergy, and by implication defective food protein tolerance, therefore not only co-exists with the presence of atopic disease but might also predate the actual development of atopic disease either directly or, perhaps more likely, by association with the development of an atopic (Th2) cytokine milieu. However, another human dietary tolerance mechanism, that of haptens, has also been characterised and has been shown to be operative in both mice and humans [24,25]. Before addressing the relationship between dietary hapten allergy or tolerance with atopic disease, one should address similarities and differences in oral tolerance pathways between protein and haptens.

Oral tolerance to dietary proteins and haptens: similar pathways?

Most food allergens are water soluble glycoproteins ranging from 10–75 kD that are relatively abundant in food and possess multiple IgE binding epitopes [5]. Many food allergens are stable proteins that are resistant to the effects of food processing and digestion, and have to be absorbed in a relatively intact form to be able to trigger an immune response [26]. Examples are ovalbumin (egg) and milk casein protein. Chemical haptens, by contrast, are low molecular weight (usually <500 D) and have the ability to bind with proteins or peptides, rendering them antigenic [6] (Box 2). Dietary haptens can be found in natural food-stuffs at low levels (e.g. diallyl disulfide, in garlic). They are also artificial additives in foods as preservatives, flavourings and colourings (e.g. sodium sulphite [E221] in carbonated drinks). The immunological mechanisms behind skin allergy to food and other proteins are different from the mechanism of allergy to haptens (allergic contact dermatitis). It could, therefore, be erroneous simply to assume that methods of oral tolerance to proteins and

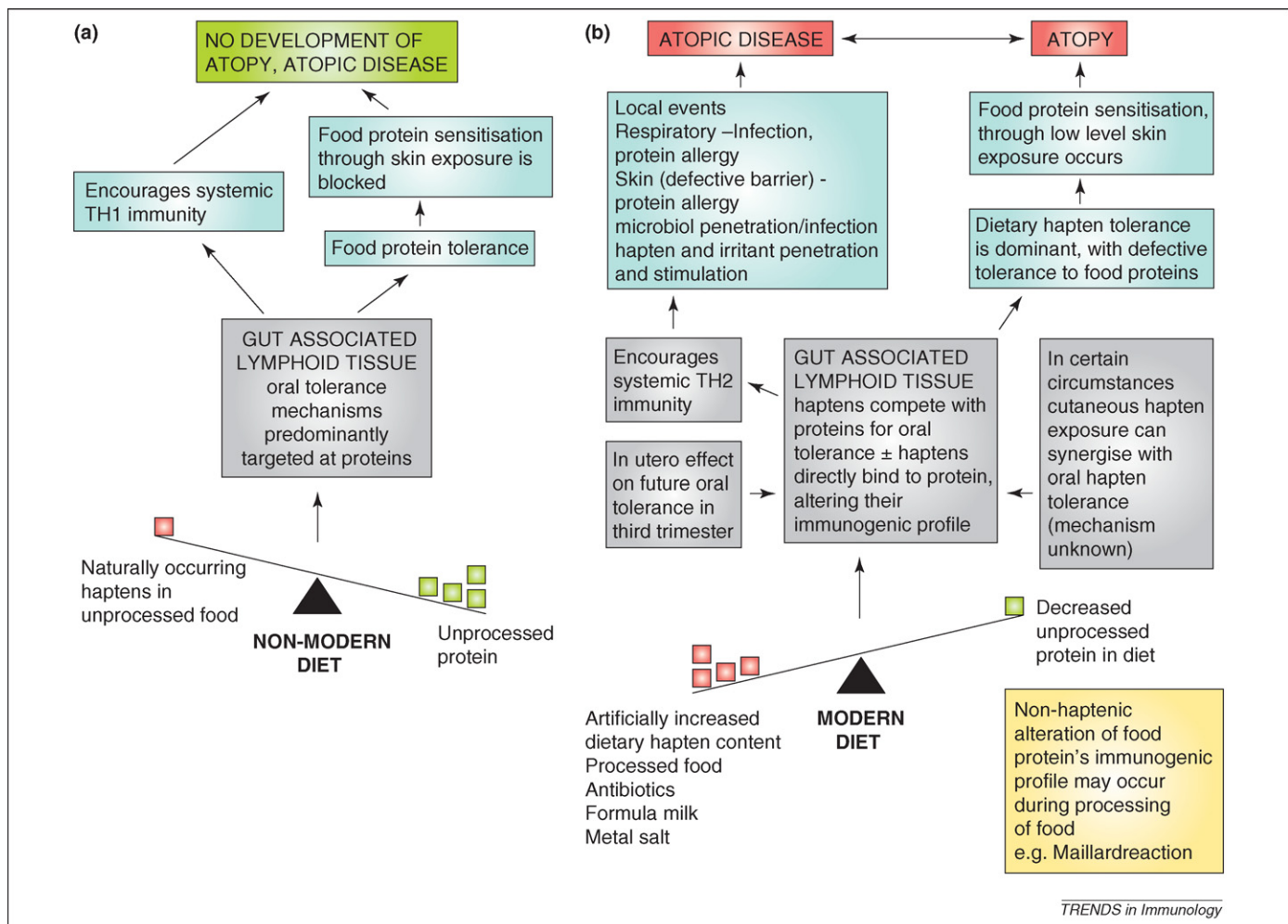


Figure 1. Proposed effect of artificially increased dietary hapten on oral tolerance. **(a)** In a non-modern diet most food is unprocessed and there is only a low level of naturally occurring hapten. Oral tolerance mechanisms are oriented towards protein. This encourages a Th1 immune response in humans. The efficient oral tolerance to food protein prevents allergic sensitisation from any subsequent low level cutaneous exposure to food protein. **(b)** In a modern diet there are artificially raised levels of hapten chemicals in processed food, antibiotics, other drugs and formula milk. Haptens compete with proteins for oral tolerance. Other forms of processing other than haptens (e.g. the Maillard reaction) can also alter protein immunogenic profile and thence tolerance. Maternal diet during pregnancy (including processed food) could also affect tolerance pathways. Under certain circumstances, cutaneous hapten exposure can synergise with oral hapten tolerance. Sensitisation to food protein from low level skin exposure might not then be blocked because there is defective protein tolerance. A dominant oral hapten tolerance mechanism encourages a Th2 immune response. Local events in the skin and airways can then trigger atopic disease.

haptens are similar, although in practice this is often assumed. A detailed review of similarities and differences between chemicals and proteins with respect to oral tolerance is beyond the scope of this article [27,28]. Nevertheless, it is clear that in both instances, various immuno-biological processes are involved [29–31].

The crucial site for oral tolerance to food proteins is postulated to reside in the Peyer's patches, whereas for dietary chemicals the crucial site is probably in the epithelial cell wall [32]. If oral tolerance pathways for food proteins and dietary chemical haptens are shared, then on a purely anatomical basis, haptens might have a competitive advantage because the epithelial cells are the first point of contact. In contrast to rodent studies, there is compelling evidence that in humans, the Peyer's patch T-cell response to dietary protein (β -lactoglobulin and casein of cow's milk) is of the Th1 type with IFN- γ and IL-12 expression, but negligible expression of Th2 cytokines IL-4, IL-5 or IL-10 [32]. It has been speculated that this difference found in humans compared to rodents could

be related to cholera toxins and other adjuvants used in rodent studies. The cytokine profile in humans after oral hapten tolerance has not been studied in depth.

Co-stimulatory signalling pathways (CD28, CTLA-4, B7) are involved in both allergic sensitisation and tolerance-induction to orally administered peanut proteins in mice [33]. Long-term anergy to food protein in orally tolerised mice is linked to decreased CD86 expression on B cells, favouring a Th1 shift [34]. It is presently unclear whether the same or different co-stimulatory pathways are necessary for oral tolerance to chemicals. Regulatory T (Treg) cells and TGF (transforming growth factor)- β seem to be necessary for both protein and hapten oral tolerance in mice [35–37]. Interestingly, a recent report described differences in human Treg cell function *in vitro*, depending upon whether the cells were derived from atopic or non-atopic donors [38]. It remains to be determined whether Treg cells involved in food protein and hapten tolerance behave differently. Interestingly, oral tolerance to nickel in mice is related to CD4⁺ and CD8⁺ Treg cells and $\alpha_E\beta_7$

integrin expression [31]. Expression of the Foxp3 transcription factor, which controls Treg cell development, also seems to be crucial for mechanisms of oral tolerance to protein [37]. Indeed, mutation of *FOXP3* in humans usually leads to very severe food protein allergy, raised circulating IgE and atopic dermatitis [39,40]. By contrast, FoxP3 expression is not emphasized or specifically mentioned in relation to oral tolerance to nickel [29,30].

Although pathways for dietary chemical and protein tolerance, therefore, seem to have some similarities, there is potential for biologically significant differences in immune responses within the gut-associated lymphoid tissue (GALT). There is certainly scope for potential interaction or competition between dietary chemicals and food proteins with respect to the induction of oral tolerance, particularly with respect to the cytokine milieu and behaviour of Treg cells. It is also possible that chemical haptens, through their ability to bind to soluble protein (or proteins and peptides within GALT) impact upon protein tolerance mechanisms.

Hapten allergy and atopic disease: any association?

Allergic reactions to chemical haptens occur, in the overwhelming majority of cases, as an inflammatory skin reaction to direct contact with the hapten (e.g. allergic contact dermatitis) (Box 1). Reactions to haptens on other epithelial surfaces have only rarely been described. For example, isocyanates in plastic manufacturing have been known to elicit allergic reactions through both the airways and the skin. However, there is experimental data to indicate that actual sensitisation primarily occurs through the skin [41]. Allergic contact dermatitis is characterised by a type IV delayed hypersensitivity response, and diagnosed by reproducing a small reaction to the chemical agent on the skin of the upper back (patch test). Examples of allergic contact dermatitis include reactions to nickel in jewellery, fragrance chemicals in perfumed products and para-phenylenediamine in hair dyes (Box 1).

Although there have been suggestions that atopics, through a Th2 cytokine shift, might sensitize less against contact allergens in general [42], most clinical studies show a similar incidence of allergic contact dermatitis between atopics and non-atopics [43–45]. Statistical analysis of population prick test (protein) and patch test (hapten) reactivity conclude that atopy and contact hypersensitivity operate as independent phenomena [46]. No significant difference was found between eczematous atopics, mucous membrane atopics and non-atopics in their capacity to be sensitized to hairdressing chemical allergens [47]. A large cohort of recently studied eczema patients showed that sensitization to contact allergens differs surprisingly little between atopic and non-atopic dermatitis patients [48]. However, these studies did not address allergy to the small number of haptens (contact allergens) with not only cutaneous but also dietary exposure (skin plus gastrointestinal [GI]), where efficiency of oral tolerance might influence allergy rates.

In a large epidemiological study, subjects who wore a nickel-containing dental brace before having their ears pierced subsequently had a significantly lower rate of allergy to nickel (40% lower) compared with those who had no dental brace [25]. Oral tolerance to contact aller-

gens with not only skin but also dietary exposure can, therefore, significantly lower contact allergy rates to that particular hapten. In groups who become tolerant to these haptens more efficiently one would expect to have lower contact allergy rates, and in groups with deficient tolerance to dietary haptens one would expect higher contact allergy rates.

Previous studies report no difference in the incidence of allergic contact dermatitis to fragrance chemicals between atopic and non-atopic dermatitis patients [48]. Allergic reaction to the mixture of chemicals used to screen for fragrance sensitivity is predominantly to those with little or no dietary exposure, such as to *Evernia prunastri* (oak moss). However, some fragrance chemical allergens, such as eugenol and cinnamal, are present in some foods and drinks as flavourings, in addition to occurring naturally in foods such as spices, fruits and bay leaves. When we analysed groups allergic to individual fragrance chemicals with significant dietary content (i.e. cinnamal, cinammic alcohol and eugenol), there was a highly significant reduced association with atopic dermatitis [49]. We have found similar reduced rates of allergy in atopic dermatitis subjects with respect to other skin plus GI haptens, including the garlic and onion hapten, diallyl disulfide [4]. These findings are also repeated when studied within one occupational group – caterers – in which one would expect significant handling of food matter. The finding that atopics have reduced sensitisation rates to haptens with dietary and skin exposure, is therefore novel and an unusual finding which would suggest that atopics are highly efficient at orally tolerising haptens in contrast to their known inefficiency at inducing oral tolerance to proteins.

The hapten-atopy hypothesis

Because atopy seems to be less common among those subjects displaying contact allergy to chemical haptens that are encountered in both the diet and skin, then a predisposition to atopy with a prevailing dominance of Th2-type immune responses might favour oral tolerance to chemicals. The corollary is that those who are not atopic, and who have preferential Th1 immune responses, better support tolerance to proteins compared with chemicals. Another explanation is that oral encounter with haptens might result in tolerance via elicitation of a Th2-type immune response that also then predisposes to defective oral tolerance to food proteins and to development of atopic disease at other sites with the required local stimulus. A final and more prosaic explanation is that this relationship is not causally linked but is merely an epiphenomenon.

Faced with an artificially high dietary chemical content, at some stage (probably early in life) the atopic gut could alter priorities of tolerance from protein (Figure 1a) to haptens (Figure 1b). An 'atopic' milieu, possibly through a Th2 cytokine shift, results. It has been proposed that the main route for sensitisation to food proteins, in the absence of adequate prior oral tolerance, is through the skin [20]. Defects in the skin surface barrier, either from genetic [50] or acquired [51] predisposition, could lead to penetration of proteins, haptens, irritants and microbes. Such local stimulus of the cutaneous immune system could thence lead to local atopic disease [52–54].

Opinion

Between 1964 and 1999, the incidence of UK childhood atopic dermatitis and asthma has increased by ~325% and ~500%, respectively [55]. This dramatic rise in atopic disease over the past 40 years coincides with a period when significant amounts of the average diet in the industrialized-world (modern) contained processed food with artificially high levels of chemicals in the form of preservatives, antioxidants, colourings, stabilizers and flavourings. Over this time period, consumption of some processed foods, such as biscuits, has not greatly altered, whereas consumption of others, like sausages, have moderately declined [56]. There are, however, notable increases in other processed foods (Figure 2). In 1964, average UK consumption of fresh green vegetable and potatoes was 393 and 1534 g/person/week, respectively. By 1999, this had declined to just 245 and 548 g/person/week, respectively. By contrast, consumption of processed vegetables and potatoes combined had risen from 300 g/person/week

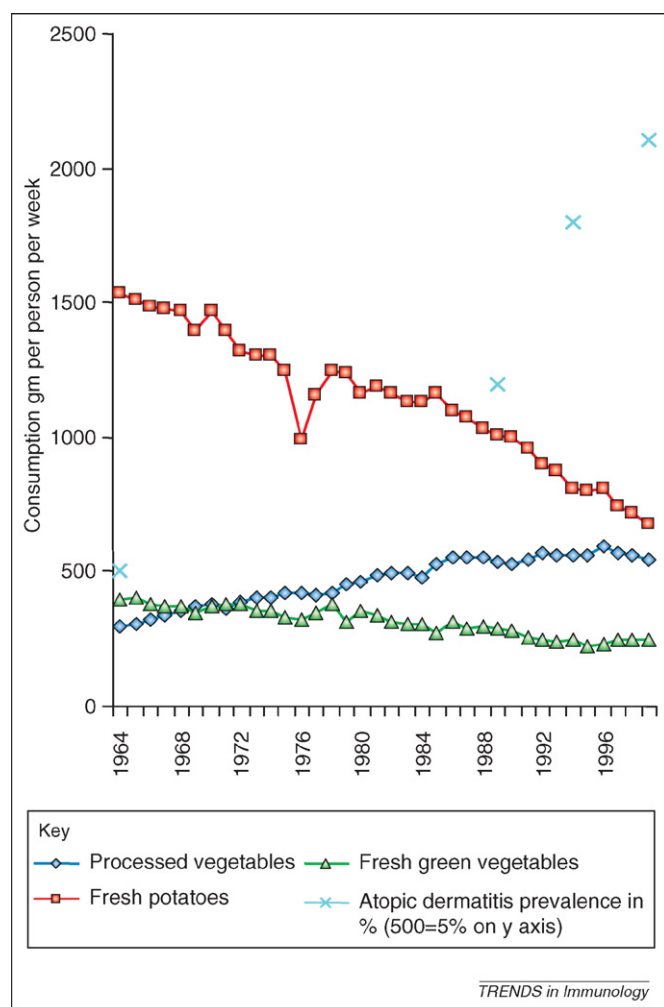


Figure 2. Changes in vegetable consumption 1964–1999. An example of changes in dietary habit coinciding with an increase in atopic disease. Between 1964 and 1999, atopic dermatitis amongst UK children increased by 325%. Over the same time period there has been a notable change in dietary habit with a shift away from unprocessed food towards processed food. A UK national food survey shows that between 1964 and 1999 there has been a 56% and 38% reduction in average UK consumption of fresh potatoes and fresh vegetables, respectively. Over the exact same period of time there has been an 83% increase in consumption of processed vegetables. Similar patterns of changes have been found in some other food groups such as dairy products. Between 1964 and 1999 there has been a 325% increase in incidence of childhood atopic dermatitis, (data reproduced, with permission, from DEFRA).

in 1964 to 548 per person week by 1999. During this time period there has also been a modest increase in personal consumption of fresh fruit. However, consumption of fruit juices (many of them processed) has increased by 1465%. Although in recent years there has been a concerted drive to remove additives from such fruit juice drinks, previously additives with haptenic potential, for example benzoic acid (E210), sodium benzoate (E211), potassium benzoate (E212), calcium benzoate (E213), sodium sulphite (E221), sodium metabisulphite (E223) and potassium metabisulphite (E224), were commonly found in these products. Interestingly, the recent drive by the food industry to minimise the use of some additives coincides with the observation by some authors that the increasing prevalence of atopic disease might have already peaked [57]. There has been a decline in the consumption of whole milk and unprocessed eggs; however, some of the decline in whole milk consumption has been compensated for by consumption of processed dairy products such as ‘fromage frais’ and yoghurts. Milk protein can be subjected to different forms of processing other than the addition of haptenic preservatives or flavours. Other processes include pasteurisation, enzymatic addition, hydrolysis and fermentation, some of which might also conceivably affect protein immunogenicity [58]. Milk proteins can also be found in a wide variety of ‘non-dairy’ processed food such as bakery products, pastry, chocolate, sausages, meatballs, processed ham, lollipops, hot dogs, frozen rice dessert and meringue [58].

In 1960, personal consumption of fresh white fish was greater than that of poultry. By 1996 poultry consumption was more than 12 times that of white fish. Much of the chicken produced is subject to intense farming methods with confined spaces and use of feeds with hapten additives such as the preservative and antimicrobial agent ethoxyquin [59,60]. However, it is less certain how this affects the structural nature of the protein in the food produced [59–61].

Geographical differences in atopic disease also coincide with consumption of processed food. For example, in the 1990s, atopic dermatitis was nearly four times lower in Romania compared to the UK [62] and during the same period consumption of processed food was significantly lower in Romania than in the UK [63]. Use of breast milk (with reduction or avoidance of chemical-containing formula milk) has been shown to be protective against development of atopy [64]. Accordingly, in a survey we found that formula milks contain, on average, 10 known haptens [65].

Processed food can alter proteins in different ways other than through haptens, which might not always be present. Interaction of protein with carbohydrate during food processing (the Maillard reaction) might restrict availability of some amino acids for immune-recognition and, thus, hinder specific tolerance induction [66]. Similarly, peanut allergens become less soluble with roasting, a process that increases the capacity of peanut-specific IgE binding to the protein. [67]

Cutaneous hapten exposure might also be important in the development of atopic dermatitis. Skin care products, containing haptens such as fragrance chemicals and pre-

servatives, have been commonly used over the past 40 years. Two animal models of atopic dermatitis have already been developed using repeated cutaneous application of haptens [54,68]. Cutaneous exposure to haptens might synergise with the effect of oral tolerance to haptens through an, as yet unknown, mechanism [69]. Because cutaneous haptens bind to skin self-proteins it is also possible that any local self-tolerance to cutaneous proteins could be disrupted. Hapten exposure in epithelial airways might also be relevant in the context of airborne chemicals present in the environment, for instance, passive cigarette smoke exposure is associated with the development of atopic asthma [70]. Although it is widely thought to be related to the irritant effect on the bronchial mucosa, nicotine has also been identified as a hapten [71].

One possible mechanism by which haptens could interface with protein tolerance is through their known ability to covalently bind to peptides and proteins and so alter their immunogenic profile [6,72,73]. The nature of these modifications is, however, understood most fully only in experimental systems for contact allergy [6,72,73]. The data so far is not yet sufficient to permit the predictive use of evidence of hapten peptide binding except for the lowest level of the identification of potential hazards. Given the evidence that contact allergens do bind to skin proteins, then it might reasonably be expected that these chemicals would also bind similarly to food proteins. Thus, it is noteworthy that when increasing amounts of whey (milk) protein is added to a flavoured drink, loss of taste of the (haptenic) flavouring agents citral and limonene is found to occur, strongly suggesting that direct hapten binding to soluble food protein does occur to a significant degree [74]. Amino acids with nucleophilic properties such as lysine and cysteine are thought to be targets for covalent binding of haptens [75]. These amino acids are also contained in postulated IgE epitope sites on, for example, proteins in cow's milk and hen eggs [76,77], which are probably important for oral tolerance.

The hygiene hypothesis, hapten-atopy hypothesis and other dietary hypotheses

A popular explanation of the recent rise in atopy is the hygiene hypothesis [78]. Its cornerstone is that changes in the type and level of stimulation from the microbial environment are associated with improvements in public health and hygiene and the use of antibiotics, and might have indirectly influenced the postnatal development of immune functions, so as to predispose to atopic disease. Although 'danger' signals (usually pro-inflammatory cytokine signals from bystander cells) are essential for cutaneous sensitisation to haptens (contact allergens) [79], oral tolerance to haptens occurs in the absence of 'danger' signals [80]. GI infections can deliver 'danger' signals, which could feasibly nullify hapten tolerance occurring at the epithelial cell surface. GI infections with hepatitis A virus [81], salmonella [82] or *Helicobacter pylori* [83] are associated with reduced subsequent development of atopic disease. Protein tolerance, occurring in the Peyer's patches away from the actual luminal surface, could conceivably be less prone to interference from infective events. By contrast, a protective effect from respiratory infection on the development of atopy is

much more strongly disputed [84]. Bronchitis seemed to increase the risk of atopic dermatitis development [85] and furthermore, children with repeated upper respiratory tract infections developed substantially more atopic asthma [86].

Although disputed, antibiotic use at an early age has been associated in several studies with an increased chance of subsequent development of atopic disease [87–89]. In the context of the hygiene hypothesis, this is explained by denying the host exposure to the fully developed bacterial infection. The hapten-atopy hypothesis would explain this, more directly, by an effect on the gastrointestinal immune system from the haptenic properties of antibiotics [90]. Certainly increased antibiotic use, both in humans and in farming livestock (the purpose of which includes increasing milk and meat yields) has coincided with the rise in atopic disease. In 1967, 168 tonnes of antibiotic were being injected or fed to livestock in the UK, compared with 240 tonnes to humans. By 1997, these figures had risen to 920 and 560 tonnes, respectively [91]. Erythromycin is a commonly used antibiotic in infancy, and is also recognized as a hapten [92]. Haptenic iron salts, such as ferrous salts are often given to pregnant women and it is known that oral tolerance pathways might be influenced in the last trimester by maternal diet [23].

There are other hypotheses on how modern diet might have encouraged allergy and atopic disease and these have been recently reviewed (e.g. see Refs [20,93]). The antioxidant hypothesis indicates that reduced antioxidant (from reduced fresh vegetables) could lead to reduced antioxidants in, for example, lung tissue leading to increased permeability of the mucosa to allergens, increased inflammation of the airways and increased prevalence of asthma with alteration of Th1–Th2 balance [94]. Another, the lipid hypothesis, claims that uptake of certain polyunsaturated fats in agents such as margarine, and decreased fats from fish and butter has led to a change in the lipid balance of membranes of inflammatory cells which could promote prostaglandins which then suppresses Th1 differentiation [95]. The vitamin D hypothesis [96] argues that vitamin D supplementation of food in western diet has led to excess vitamin D; alternatively, our largely indoor lives have led to deficient sun-induced vitamin D synthesis in the skin. Vitamin D can inhibit production of Th2 cytokines, but can also promote Treg cell development. Therefore, one can argue both ways. Although the hapten-atopy model is at variance, at least in part, with these alternate hypotheses, there is perhaps some synergism with the proposal that reduced dietary exposure to proteins such as peanuts can predispose to specific food allergy [20] because both elevate defective oral tolerance to protein in a primary role.

Conclusion

There is a paucity of knowledge in the immunology of some areas relevant to the hapten-atopy hypothesis. Direct experimental studies on the effect of hapten addition on oral tolerance to food proteins are required. It is not clear how hapten exposure on different epithelial surfaces, such as the skin and the gut, might synergise to promote atopy. Epidemiological work to link the more closely associated forms of hapten exposure to atopic disease, both geographically and over different periods of time, is required. The

'hapten-atopy hypothesis' might help explain (i) the close relationship between food protein allergy and atopic disease, (ii) the reduced frequency of allergic contact dermatitis in atopics to cutaneous haptens which also have gut exposure, (iii) the association of oral antibiotic use and the development of atopy, (iv) animal models of atopy based on hapten exposure and (v) the significant rise in atopic disease over the past 40 years. Multiple protein allergy (atopy), genetic influence, defective skin barrier (with atopic dermatitis) and a Th2 dominant immune system are all key associations of atopic disease. We suggest that elevated tolerance to dietary haptens, at the expense of food proteins, is a further key association that, together with the other associations, might lead to a unifying model of atopy.

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