

Oral tolerance to contact allergens: a common occurrence? A review

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Experimental and clinical oral tolerance to contact allergens has been reported sporadically, most notably in respect of nickel, and is generally assumed to be an uncommon phenomenon. There has recently been increased understanding of the immunological mechanisms inducing and maintaining oral tolerance. There are several contact allergens, including fragrance, antioxidant, and preservative chemicals, to which subjects are exposed through both cutaneous and oral routes. We examine the possibility that oral tolerance to contact allergens may be more common than previously thought. Animal models of oral tolerance to contact allergens indicate that cutaneous exposure to small, subsensitizing doses of contact allergens might negate any subsequent attempts to induce tolerance by oral administration. Extrapolating these observations to common human practises raises the possibility that application of contact allergens (fragrances, preservatives and antioxidants) in consumer products used by children could prevent or inhibit the later acquisition of specific tolerance resulting from 'natural' dietary exposure after weaning. Existing data on formaldehyde may conflict with this theory, though this could be explained by allergen specificity. We propose that further work in this area is needed.

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Although it is sometimes assumed that largest body surface area is the skin, the area of gut mucosa is, in fact, far larger. The small intestine alone (1) is estimated to have an area of approximately 300 m². Whilst the skin is equipped to mount cutaneous immune responses against potentially hostile encounters (and thereby skin sensitization), the maintenance of normal gastrointestinal function is dependent upon being unresponsive to 'foreign' antigens including, importantly, food and commensal bacteria. Contact allergens are small molecular weight chemicals that are able to gain access to the viable epidermis. They are haptens, and as such must form stable associations with proteins in order to trigger cutaneous immune responses and cause the acquisition of sensitization.

Contact allergens embrace a wide range of chemistry and include metals, fragrances, preservatives, plant products, medicaments, and resins. Some attempts at inducing tolerance to skin contact allergens through oral/gastrointestinal expo-

sure, including with urushiol (2), were largely unsuccessful. However, it is clear that oral tolerance is not restricted to rodents, nor is it an experimental artefact, because oral tolerance to both proteins (3) and chemical allergens (4) has been reported.

Against this background, we argue here that oral tolerance to contact allergens may not be an uncommon occurrence, and may confer important health benefits.

Nickel and Other Metals

Despite widespread exposure, only a minority of subjects acquire skin sensitization to nickel. It is debatable whether sensitization to very high concentrations of nickel could be induced in most or all people so exposed. The presence of trace amounts of nickel in foods may be relevant to sensitization. The average adult human daily dietary intake of nickel has been estimated at 0.1–0.5 mg in populations in Europe and North America (5).

Intake has been declining in the UK since 1976, and intake in children is higher than that in adults (6). Oral exposure to nickel in patients already sensitized can affect coexistent dermatitis; either increased amounts of oral nickel intake causing exacerbation (5, 7), or reduction of intake causing reduction of hand dermatitis in nickel-allergic patients (8, 9).

It has been shown experimentally that oral/gut exposure to nickel may lead to tolerance and resistance to the subsequent acquisition of skin sensitization. Oral administration of nickel and chromium to various animal species results in specific immune non-responsiveness to subsequent induction of cutaneous allergic contact hypersensitivity (10). Such oral tolerance, found to be dependent upon the dose given orally, was antigen specific and persistent. In orally tolerised guinea pigs, subsequent cutaneous contact boosted tolerogenic signals, supporting the view that oral tolerance results from active antigen-specific immunosuppression (11). Oral administration of nickel to animals that had already acquired skin sensitization resulted in, at best, only partial and transient desensitization. Even non-sensitizing epicutaneous contact (rubbing against nickel cages) was considered to prevent the subsequent induction of oral tolerance (11, 12).

In humans, there is similar evidence for immunological interaction between the gut and skin. Potentially tolerising (oral nickel contact via orthodontic braces) as well as sensitizing (ear piercing) events were studied retrospectively in 2176 patients (13). Ear piercing strongly favoured development of nickel-allergic contact dermatitis. More importantly, patients having had oral contacts with nickel-releasing appliances (dental braces) at an early age showed a reduced frequency of nickel hypersensitivity but only if the oral contact with nickel had preceded ear piercing. The findings of this study were confirmed subsequently in a large Danish study of 1501 school-children aged between 12 and 16 years (14). Nickel allergy was found most commonly in girls with pierced ears but application of dental braces (oral nickel exposure) prior to ear piercing (cutaneous nickel exposure) was associated with a significantly reduced prevalence of nickel allergy.

On one part of the Norwegian–Russian border, there was a long episode of nickel contamination of drinking water supplies caused by emissions from 2 local nickel factories on the Russian side. The general adult population had similar rates of ear piercing on both sides of the border and was patch tested to nickel. Only 7.2% of the Russian women who had drunk nickel-contaminated water were sensitized to nickel, compared with

27.5% of the Norwegian women (15) who were not exposed to high levels of nickel in drinking water. This again suggests that oral exposure to nickel may lead to tolerance.

The potential mechanisms for such oral tolerance to chemical allergens are starting to be elucidated. Using the contact allergen 2,4-dinitrofluorobenzene (DNFB) in mice, naturally occurring CD4⁺ CD25⁺ regulatory T cells are critical for the development of oral tolerance. Adoptive transfer of CD4⁺ CD25⁺, but not of CD4⁺ CD25[−], T cells was shown to prevent contact hypersensitivity completely. *In vivo* depletion of CD4⁺ CD25⁺ cells by antibody treatment in normal mice impaired oral tolerance, and CD4⁺ CD25⁺ T lymphocytes were shown to inhibit interferon-gamma (IFN- γ) production *in vitro* (16). Nickel-sensitive and non-sensitive subjects were investigated by *in vitro* proliferation assays. When CD4⁺ CD25⁺ cells were depleted, nickel-specific responsiveness was strongly increased both in allergic and non-allergic individuals. CD4⁺ CD25⁺ cells from nickel-allergic individuals showed only a limited capacity to suppress effector T-cell responsiveness, suggesting that their regulatory role is impaired in nickel-allergic individuals (17). When stimulated with nickel, some CD25⁺ cells were found to upregulate expression of CTLA-4, which is induced by T-cell receptor (TCR) triggering, suggesting that a minority of CD25⁺ T regulatory cells (Tregs) could specifically recognize metal (18). Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation by competing with CD28 for binding to the B7 family of costimulatory molecules expressed on antigen presenting cells. CTLA-4 expression is higher on CD25⁺ T cells compared with that in the CD25[−] counterpart, and it can be involved in the suppressive activity of Tregs (19). Skin-homing Tregs CD4⁺, cutaneous lymphocyte antigen (CLA)⁺, CD25⁺ differ in their suppressive properties to nickel compared with CD4⁺ CLA[−] CD25⁺ lymphocytes, being much more efficient in regulating nickel-specific T-cell responses (18).

Nickel-challenged skin of non-allergic individuals showed significant mononuclear infiltrate; about 20% of the T cells were CD25⁺; these were anergic on rechallenge with nickel and they strongly suppressed nickel-specific activation of blood-derived CD4⁺CD25[−] T cells. It is possible that Tregs may play a part in downregulation at the skin-draining lymph node site, as more than 50% of Tregs express the chemokine (CHC motif) receptor CCR7 which is involved in T cell homing to peripheral lymph nodes (18, 20). However, earlier animal studies showed clearly that oral/gut

exposure can also mediate suppression (11). In general terms, different mechanisms of oral tolerance may occur depending upon the dose of allergen. Thus, low doses of antigen result preferentially in the generation of antigen-specific regulatory cells secreting down-modulatory cytokines such as transforming growth factor β and interleukins 4 and 10 (IL-4 and IL-10). In contrast, high doses of orally administered antigen result in anergy and the deletion of specific effector T cells in the gut (21). Suppression of cutaneous delayed-type hypersensitivity to nickel by oral exposure can be transferred by CD8⁺ cells (12). Oral tolerance (to proteins) can be prevented by depleting $\gamma\delta$ T lymphocytes and cannot be induced in γ TCR-deficient mice (22). It is not yet clear what role, if any, $\gamma\delta$ T lymphocytes play in regulation of immune responses to nickel and other contact allergens. In oral tolerance of nickel in mice, it has been shown that Fas ligand-expressing invariant natural killer T cells promote tolerance induction by eliciting apoptotic death of antigen-carrying, effete B lymphocytes (23). Cutaneous nickel exposure occurs in the context of 'danger' signals, with the hapten itself inducing proinflammatory cytokines from keratinocytes (24), whilst these signals may be absent in oral tolerance (25). Collectively, these reports suggest that the induction and maintenance of tolerance to nickel and other antigens are probably associated with more than one, and probably several, immunoregulatory mechanisms.

Such mechanisms may include oral tolerance (e.g. nickel as described above); local immunosuppression (e.g. by ultraviolet irradiation of skin); or low zone tolerance. This latter phenomenon (also described as contact tolerance) has been well described in murine models and is achieved by epicutaneous application of very low doses of antigen. Reports of antigens that can effect this include 2,4,6-trinitrochlorobenzene (26), which is chemically related to DNFB.

Plant Products

Chrysanthemum is part of the compositae family of plants which make up 10% of plants worldwide. It is a common allergen in Europe, North America, India, and the Middle East. The rate in Danish contact clinics is 4.3%. Compositae allergic contact dermatitis (ACD) is screened for by patch testing with the chemical sesquiterpene lactone (contained in all compositae plants), which is included in most standard series. However, in some countries in the Far East, such as Japan, chrysanthemum allergy is thought to be rare (27). We compared the rate of chrysanthemum allergy in our London contact clinic with a contact

dermatitis clinic in Singapore (Mak, accepted by *Contact Dermatitis*). When comparing strong allergy (++ or +++ reactions to sesquiterpene lactone) to chrysanthemum, there is a 15-fold higher prevalence in London compared with that in Singapore. Why is there a discrepancy?

The statistically significant difference in sensitization rates to sesquiterpene lactone mix 0.1% petrolatum between the 2 populations studied here may be related to the widespread ingestion of chrysanthemum tea among all age groups in the Singaporean population.

Particularly popular in the Far East, chrysanthemum tea is a herbal infusion made from dried chrysanthemum flowers. Dried, yellow flowers are steeped in boiling water, often with the addition of rock sugar. The resulting drink has a floral aroma and is reputedly a powerful aphrodisiac. Chrysanthemum tea is widely available as a beverage in many Asian restaurants and from supermarkets in canned form. Ingestion of chrysanthemum tea is probably much less commonplace in a European population. We postulate that ingestion of chrysanthemum tea by the predominantly Chinese population of Singapore since childhood may have induced oral tolerance, or at least diminished responsiveness to sesquiterpene lactone in a substantial proportion of the population, resulting in the lower sensitization rate. Cytokine analysis in sesquiterpene lactone-reactive T-cell lines showed IFN- γ and IL-4 production, suggesting that T-cell lines were not exclusively Th1 types (28). This obviously has implications for oral tolerance.

Consumer Fragrance Chemicals

Whilst there are no experimental data showing a role for oral tolerance with consumer fragrance chemicals, we speculate that there are possibilities for oral tolerance in this category. Reactions to fragrance and preservative chemicals present in toiletries and personal care products have become a major problem. Contact allergy to these chemicals is usually seen from teenage years onwards. Many of the fragrances commercially used in perfumes/skin-care products and identified as causes of allergic contact dermatitis are also found in foods. For example, isoeugenol and eugenol are aromatic constituents in some foods, citrus essential oils contain citral, which may be metabolized to hydroxycitronellal and geraniol is contained in maize. Bay leaves are commonly used in cooking and contain linalool, isoeugenol, and eugenol. Cinnamic aldehydes are found in large quantities in various spices such as cinnamon and Indian bay leaf. Isoeugenol, eugenol, citral, hydroxycitronellal, and cinnamic aldehyde are all well recognized

and common contact allergens. A few fragrance allergens, such as evernia prunastri, are only uncommonly found in food items. Of the commercial fragrances, chloroatranol, contained in evernia prunastri, is perhaps one of the most potent sensitizers (29) in consumer products, as measured by human dose–response elicitation studies.

There have been no studies, to our knowledge, of the effect of oral exposure to fragrance chemicals upon risk of developing skin sensitization. There is only one report that characterizes T-cell responses to fragrances in respect of allergic contact dermatitis to fragrance. 32 patients allergic to at least one of the 8 fragrance chemicals used in screening eczema patients by patch testing (eugenol, isoeugenol, evernia prunastri, cinnamic aldehyde, cinnamic alcohol, alpha-amyl-cinnamic aldehyde, hydroxycitronellal, and geraniol) were studied and T-cell clones established from them. CD4+ and CD8+ clones were established, and produced Th1 type cytokines (IL-2 and IFN- γ), whereas, in contrast, Th2 cytokines (IL-4 and IL-10) were virtually absent (30). Of particular interest, however, was the observation of 14 positive lymphocyte transformation tests to fragrance chemicals showing negative patch tests to that particular fragrance on patch testing. No further comment was made about this observation, though it is similar to observations made with regard to nickel T-cell reactivity in some nickel patch test-negative subjects.

One possible route for oral exposure to fragrance chemicals is through toothpastes, where common/allergenic flavour/fragrance chemicals are used such as cinnamic aldehyde, anethole, and spearmint. Cinnamic aldehyde is a moderately or potent sensitizer [human class 2, as estimated by the mouse local lymph node assay (31)] and is now only used in some toothpaste ranges. Incidence of allergic contact dermatitis to cinnamic aldehyde has decreased and this may be related to its reduced use in skin products. Spearmint is a weak sensitizer but the fragrance chemical anethole, however, is a potent sensitizer, yet it is relatively unknown as a contact allergen. The use of anethole and spearmint in toothpaste is widespread; these agents are only rarely reported as contact allergens in toothpaste.

Anethole is used in aniseed and cake flavouring as well as in most toothpastes and in some soaps. There is only one case report of anethole as a contact allergen and this was in a food-handler (32). Human gastrointestinal exposure should be extremely common. In the guinea pig maximization test, anethole was found to be a moderate to potent sensitizer, equivalent to cinnamic aldehyde (David Basketter, pers. comm.). In contrast,

human maximization tests to anethole produced no sensitization at all (33). Anethole does not seem to be used at high levels by the fragrance industry. Despite all this indirect evidence, suggesting that oral tolerance may be important in fragrance allergy, sensitization potencies in humans may be very different from those in animals. Another possibility is that oral exposure to allergens may neither sensitize nor tolerize, i.e. the oral route of exposure may be immune-neutral.

Preservatives and Antioxidants

Again, there is no direct evidence linking oral tolerance to preservatives and antioxidants, however, there is some circumstantial evidence. Parabens and propylene glycol are used extensively in foodstuffs, skin-care products, and topical medicaments. Parabens is classed as a non-sensitizer in animal predictive tests (34) but is well known to cause allergic contact dermatitis, albeit uncommonly. Likewise, propylene glycol is found extensively in foodstuffs, skin-care products, and medicaments. Several animal predictive studies in animals failed to induce skin sensitization; human maximization tests did not elicit sensitization but the modified Draize test in humans (which allows for perturbation of the skin) did show reactions in a minority of subjects (35).

Sodium metabisulfite is an antioxidant found extensively in foodstuffs, skin-care products, and topical medicaments. It is classified as a non-sensitizer in animal predictive tests but in a recent survey, when added to a standard series of patch test allergens used to screen eczema patients, was found to be frequently positive and usually caused through medicament exposure (36).

Propyl gallate is an antioxidant that is also found in food but unlike parabens, propylene glycol, and sodium metabisulfite, it is limited to fatty food such as chewing gum, bakery goods, frying oils, and sauces and is thus unlikely to be found in animal feed. Predictive tests found all gallates to be moderately strong sensitizers (37). However, despite its widespread use in the cosmetic industry, propyl gallate is a surprisingly uncommon sensitizer clinically (38).

Kahn et al. were able to induce oral tolerance to propyl gallate in guinea pigs through gastric feeding. They speculated that the low frequency of contact sensitization is through tolerance induced by constant oral exposure in humans through food containing propyl gallate. We have also recently reviewed our data on propyl gallate sensitivity in the contact clinic and also found a surprisingly low prevalence rate, which may be rising (Perez, submitted). Recent work has shown that

the number of skin-care products containing propyl gallate reduced in 2002 compared with that in 1981. The concentrations used in skin preparations have decreased considerably over the same period (39). This suggests that skin exposure is unlikely to be increasing and this raises the possibility that oral tolerance may be decreasing, perhaps due to reduced oral intake of propyl gallate.

Factors mitigating against gut exposure having an influence on cutaneous contact sensitization would include the potency of formaldehyde. Formaldehyde is found in certain foodstuffs in significant amounts (40). Some foods are also subject to treatment with formaldehyde. Free formaldehyde may be found in milk and is formed in the gut (41). Consumer products used by children commonly contain formaldehyde, or formaldehyde releasers. Hence, both oral and epicutaneous contact with formaldehyde occur at an early age. Yet, formaldehyde is a frequent and potent cutaneous sensitizer on experimental testing (42). This may be explained in a number of ways:

- (1) Epicutaneous contact may negate subsequent tolerising signals from oral consumption (like in the models suggested above).
- (2) Simultaneous oral/epicutaneous contact may lead to conflicting sensitization or tolerance signals, leading to no net change.
- (3) Other data suggest that tolerance is an antigen-specific process. Formaldehyde may not effect tolerizing signals like other chemicals (e.g. via gut metabolism, adaptive evolutionary responses etc.).

Allergens with Little or No Gut Exposure

Among examples of common contact allergens with little or no oral/gut exposure are the permanent hair dye allergen *para*-phenylenediamine (PPD), the plant allergen primin, the fragrance allergen evernia prunastri, and epoxy and acrylate resins. Of the fragrance allergens, evernia prunastri is perhaps the most potent, both clinically and on animal testing. PPD is one of the most potent contact allergens clinically (in terms of prevalence) and experimentally (e.g. guinea pig maximization test, human maximization test, and the mouse local lymph node assay). All subjects in a human maximization test became sensitized (43), and in animal predictive assays, PPD is one of the most potent contact allergens with an EC₃ of 0.06% (44).

Primin is classified as a strong sensitizer, as are epoxy and acrylic resin. These allergens also appear to be the most difficult with which to patch test. Most of the common active sensitizers have

little or no gut exposure in humans (45). However, this observation may be due to other factors, such as for instance, innate allergenic potency.

Gut Conditions May Influence the Development of Oral Tolerance or Gut Sensitization

Inflammatory bowel disease causes intense inflammation and ulceration of the gut mucosa. One might speculate that such conditions might shift the balance from tolerance to sensitization, as antigens could more readily breach gut integrity, migrating to mucosa-associated lymphoid tissue (46). Some data suggest that nickel sensitivity is increased in patients with Crohn's disease (47), a finding that may be explained by a breakdown of tolerance.

Analysis

In the context of skin sensitization, tolerance to contact allergens, and skin–gut interactions, the following aspects would be involved:

- (1) Skin sensitization to contact allergens.
- (2) Tolerance to contact allergens through repeated low dose/zone epicutaneous exposure. This has been described in animal experiments and involves down-modulatory cytokines (IL-10) and generation of CD8 + effector cells by CD4+ regulatory T cells (26). Low zone tolerance has not yet, however, been described in humans or in a clinical context.
- (3) Sensitization to contact allergens through oral/gut exposure. This has been described mainly in oral exposure to dental allergens (such as gold), which are subsequently positive on skin patch testing. It may be increased by gut inflammation and ulceration.
- (4) Oral tolerance to contact allergens.

The work of van Hoogstraten et al. (10) has clearly shown that oral tolerance is a real phenomenon to common contact allergens in guinea pigs. In trying to assess its possible relevance to contact allergens in a clinical setting one should remember some of their main findings:

- (1) Not all animals could be orally tolerised to contact allergens.
- (2) Oral tolerance was dose dependent.
- (3) Oral tolerance could only be successful if there was no pre-existing cutaneous exposure, even at subsensitizing doses.
- (4) Tolerance was antigen specific.
- (5) Tolerance was most successful through the oral mucosa.

- (6) In tolerized subjects, cutaneous exposure may boost the tolerogenic signal.

There are strong and consistent epidemiological data to show that oral tolerance to nickel is a real clinical phenomenon. There has also been accompanying immunological data to suggest nickel tolerance exists as a clinical phenomenon. Other instances where there is indirect evidence for oral tolerance to contact allergens in a clinical setting is with propyl gallate, and to the plant allergen sesquiterpene lactone amongst chrysanthemum tea drinking populations. What do these groups have in common? All these groups would have been exposed to the allergen through oral exposure from an early age; however, until recently, nickel piercing does not usually occur until adolescence; the toiletry agents containing propyl gallate (lipstick and female cosmetic) are not usually worn until adolescence; and repeated manual handling of plants such as chrysanthemum is usually an adult experience. These examples therefore would be in keeping with the observation from animal experiments that for oral tolerance to be successful, oral/gut exposure must precede cutaneous exposure.

Anethole is used in many toothpastes, so oral/gut exposure should occur from an early age; it is present in aniseed and cakes but would be unlikely to be present in guinea pig/mice feed; it is relatively unknown clinically as a contact allergen. Whilst in animal predictive tests it is a relatively potent sensitizer, in human tests it is non-sensitizing. Although these observations may arise by chance, it could be in keeping with oral tolerance being most effective through the oral mucosa.

With regard to other fragrances and preservatives there is at present no evidence to suggest that oral tolerance exists; however, as these agents should commonly be present in food, there may be a possibility of oral tolerance. Unlike nickel, propyl gallate, and sesquiterpene lactone, cutaneous exposure to many fragrance and preservative products may occur through application consumer products used by children. This could negate oral tolerance and this would be in keeping with animal experiments showing that initial cutaneous exposure may negate any subsequent tolerance from oral exposure. Therefore, any pattern of oral tolerance may not be so obvious in this group, and would perhaps only occur in some or even few individuals, if it did, indeed, occur at all.

Another confounding factor in sensitization/tolerance in babies is that allergens are present in breast milk. Indeed, recent evidence suggests that previous guidelines (for mothers to avoid common food protein allergens whilst breast-feeding

infants prone to food allergy) have no real evidence base (48). Reduced exposure to peanut may increase the risk of sensitization (49). The development of sensitization or tolerance may depend on a number of factors: genetic background; nature and dose of antigen; frequency of administration; age (maturity versus immaturity) at first antigen exposure; immunological status of the host (e.g. viral infection); or the dietary exposure of the mother and antigen transmission via breast milk (50).

Although animal predictive assays have clearly been shown to be generally highly reliable predictors of chemicals, which can cause human sensitization, occasional anomalies do exist. One is the classification of some weak human allergens as non-sensitizers, when some of these agents obviously do cause skin sensitization. Often this may arise due to the experimental problem of detecting very weak allergens, such as chemicals, which sensitize normally only in the context of medicament dermatitis (where the allergen is rubbed onto already inflamed skin). However, in certain cases, an alternative explanation could be prior oral exposure influencing predictive testing. Laboratory animal diet for guinea pigs/mice meets nutritional guidelines but to our knowledge is not standardized in a manner, which would limit the content of certain plant-derived fragrances and preservative antioxidant chemicals, which might be expected to be present. There may well be merit in further analysis/research concerning animal diet and its contribution to oral tolerance, particularly when the animals are used for predictive sensitization tests.

Demonstrating the presence of oral tolerance to consumer allergens may have important practical applications, particularly in respect of the first months prior to weaning, as cutaneous contact to allergen in skin-care products may negate naturally occurring oral tolerance.

A review of the current literature shows there is some evidence to suggest that oral tolerance may be a much commoner phenomenon than previously thought. Future work could explore the following:

- (1) The presence of Tregs in the blood and patch test-negative skin of individuals, in certain groups (e.g. patch test-negative sesquiterpene lactone subjects who have drunk chrysanthemum tea from a young age).
- (2) Local lymph node assays on certain antigens in which there is oral/gut exposure in humans, e.g. anethole. Assays could be performed on animals with gut exposure only, oral mucous-membrane exposure and no oral exposure

(e.g. fragrance chemicals considered as weak allergens).

- (3) Screening of eczema patients to contact allergens with both oral and gut exposure to ascertain more accurate prevalence data in humans, i.e. to ascertain the prevalence of cutaneous sensitization to potent contact allergens on a background of extensive oral/gut exposure.
- (4) Experimental studies of induction of oral tolerance proven by unresponsiveness to subsequent attempts to sensitize. The endpoints should be previously documented immunological parameters.

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