Food-provoked eczema: A hypothesis on the possible role of systemic contact allergy to haptens present in both cosmetics and foods

Wyprysk prowokowany przez pokarmy: Hipoteza na temat możliwej roli układowej alergii kontaktowej na hapteny występujące w kosmetykach i pokarmach

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Abstract

Patients with eczema frequently associate relapses of their disease with ingestion of particular foods, however, the actual causation by food allergens can be confirmed only in a minority of them. In the present paper, a hypothesis is proposed on the possible causal link between eczema and food in cases not explainable by type I allergy to "classical" food allergens like egg, milk or peanut protein. It is proposed that eczema in such cases may be due to delayed-type allergy to haptens present in food – either natural components, contaminants, or food additives. A wide range of haptens are used in the production of both food and cosmetics. It is proposed that initial sensitization of the skin to a hapten may follow external exposure (e.g. from skin care products), while relapses in the course of eczema may be due to subsequent oral exposures to the same hapten from food (systemic contact dermatitis). This hypothesis also offers an explanation for cases of photoaggravated eczema by indicating on food haptens with photosensitizing properties. The proposed hypothesis is unifying recent scientific discoveries and clinical observations in the attempt at explaining cases of food-provoked eczema that could not be explained by the present mainstream views on food allergy. Nevertheless, it requires thorough verification through dedicated research aimed specifically at testing the proposed causal relationship between food-provoked eczema and haptens occurring in both cosmetics and foods. If confirmed, appropriate diagnostic methods (e.g. patch test panels with food haptens or specially devised in vitro tests) should be introduced into routine diagnosis of eczema. Furthermore, results of such studies will provide scientific evidence for possible restrictions on the use of food additives identified as potent sensitizers within the legal scheme of consumer protection policy.

Key words: eczema, food allergy, food allergens, haptens, food additives, cosmetic ingredients

Streszczenie

Chorzy na wyprysk często wiążą nawroty swojej choroby ze spożyciem określonych pokarmów, jednak faktyczny związek z alergenami pokarmowymi udaje się potwierdzić zaledwie w mniejszości przypadków. Niniejszy artykuł przedstawia hipotezę wyjaśniającą związek między wypryskiem a pokarmami w przypadkach, w których nie udaje się wykazać obecności alergii typu I na „klasyczne" alergeny pokarmowe, takie jak białka jaja, mleka, czy orzeszków ziemnych. Zgodnie z proponowaną hipotezą wyprysk w tych przypadkach może być wyrazem alergii opóźnionej na hapteny obecne w produktach spożywczych jako składniki naturalne, zanieczyszczenia lub dodatki spożywcze. Liczne hapteny są zarówno składnikami produktów spożywczych, jak i kosmetyków. W takich warunkach pierwotne uczulenie na hapten może następować na skutek kontaktu skórnego (np. produkty do pielęgnacji skóry), natomiast późniejsze nawroty wyprysku mogą być prowokowane przez spożycie tych samych haptenów w pokarmie (układowy wyprysk kontaktowy). Niniejsza hipoteza może również wyjaśniać przypadki wyprysku nasilanego przez światło wskazując na występowanie w żywności haptenów o właściwościach fotouczulających. Przedstawiona hipoteza łączy nowe odkrycia naukowe i obserwacje kliniczne w celu wyjaśnienia przypadków wyprysku prowokowanego przez pokarmy, których nie da się wyjaśnić w oparciu o obecnie obowiązujące wyobrażenia na temat alergii pokarmowej. Dla potwierdzenia proponowanego związku przyczynowo-skutkowego między haptenami obecnymi w kosmetykach i pokarmach a wypryskiem prowokowanym przez pokarmy niezbędne są jednak dedykowane badania naukowe. Jeśli zostanie on potwierdzony, niezbędne stanie się wprowadzenie stosownych metod diagnostycznych (np. serii testów płatkowych z haptenami pokarmowymi lub dedykowanych testów laboratoryjnych) do rutynowej diagnostyki wyprysku. Wyniki takich badań dostarczą ponadto podstaw naukowych dla przyszłych regulacji prawnych chroniących konsumentów przed narażeniem na dodatki pokarmowe o silnym potencjale uczulającym.

Słowa kluczowe: wyprysk, alergia pokarmowa, alergeny pokarmowe, hapteny, dodatki pokarmowe, składniki kosmetyków

Despite the fact that atopic eczema is associated by many patients with food allergy, experts have been aware for a long time that eczema lesions cannot be readily induced by provocation with food allergens [1]. Depending on the methodology, hypersensitivity to food allergens can be confirmed in 10% to 50% children with eczema [2-4]. In adolescents and adults, allergies to "classical" food allergens, such as hen's eggs and cow's milk are considerably less common and play a marginal role [3, 5]. Also, "elimination diets" aimed at curing eczema by excluding various "allergenic foods" remain ineffective in most cases, and the use of unjustified dietary regimens in infantile eczema has been criticized for more than five decades [6]. The simplistic approach "food allergy causes eczema" seems to be questioned in many ways, with recent evidence accumulating in favour

of the opposite causal relationship, i.e. infantile eczema being the predisposing condition for a subsequent development of food allergy, rather than its consequence. Lack et al. [7] have demonstrated that the use of skin care products with peanut oil is a strong risk factor for the development of food allergy to peanuts later in life. In a mouse model, application of peanut extract or ovalbumin A on the abraded skin (thus made penetrable to proteins) both provokes inflammatory skin response with clinical appearance of delayed-type hypersensitivity (eczema) and induces production of IgE specific to these allergens [8]. Similar processes seem probable in humans with eczema – a disease inextricably linked with disruption of skin barrier. Putting the above information together, only in a fraction of eczema patients hypersensitivity to "classical" protein food allergens can be confirmed as the cause of their disease. As a matter of fact, food allergy may be secondary to eczema in many patients. Allergies to food proteins do not seem to offer a plausible explanation for most of eczema patients, but many of them still insist that their skin problems are aggravated by ingestion of particular foods. In the present article, a hypothesis is proposed that links eczema provoked by food with food haptens, rather than "classical" protein food allergens.

Haptens in food

Haptens are small xenobiotic (exogenous) chemical molecules with molecular mass below 500 Dalton - a size that allows them to penetrate through intact skin [9]. The possibility of hapten penetration through intestinal mucosa becomes obvious once one realizes that many oral drugs are also haptens [10]. There are numerous haptens in food, some of which are natural components (e.g. nickel, cobalt, vanillin) or contaminants (pesticides, animal drugs, industrial chemicals), while others are purposefully added during food processing (preservatives, emulsifiers, colorants, flavour enhancers, antioxidants). Haptens are not immunogenic, due to the fact that they are too small to be recognized by the immune system's antibodies or receptors. However, haptens can form immunogenic complexes with body's own proteins. Strong (mainly covalent) chemical bonds with haptens distort spatial conformation of endogenous proteins to such extent that these are no longer tolerated as body's own structures but instead induce immune reactions.

Haptens typically cause delayed type hypersensitivity, which means that symptoms may appear one or even several days after the ingestion. Under such circumstances, it is difficult for the patient or even doctor to trace down the causal link between flares of eczema and ingestion of a culprit hapten in food. Moreover, various foods may contain the same haptens, regardless their kind, brand name or taste. For example, balsam of Peru - a well-known skin sensitizer may be found in chewing gums, alcoholic drinks, salad dressings, filled chocolates, soft drinks, and a range of other flavoured products. As a result, certain haptens may accumulate from various, seemingly unrelated foods in a hardly traceable way. This might also lend a possible explanation for patients, who declare that they can tolerate small amounts of processed foods, but experience flares of eczema after indulging themselves with more.

Breastfeeding and haptens

In spite of extensive research, there is still no definitive proof for the effectiveness of breastfeeding in the prevention of food allergy and eczema [11]. Sometimes, flares of eczema in children fed exclusively on mother's milk are explained by an alleged passage of allergens into mother's milk from food that she ingests. It seems rather improbable, considering the fact that "classical" food allergens are proteins and as such undergo hydrolysis into amino acids in the maternal gastrointestinal (GI) tract. Nevertheless, some mothers still insist that they see a connection between their food intake and child's eczema flares. The present hypothesis offers an explanation for this, by indicating on the possibility of the child being sensitized to haptens in maternal milk. Drug distribution studies demonstrate that non-protein drugs may be actively or passively transferred from mother's GI tract to breast milk, which most probably is also true for other haptens [12, 13]. In contrast to "classical" allergenic proteins, haptens (occurring in cow milk naturally or as contaminants) would be also resistant to hydrolytic processes during production of hypoallergenic milk formulas. It seems, therefore, that infants may become exposed to food haptens regardless the way of their feeding.

Photoaggravated eczema

Most patients with eczema respond well to sunlight, and phototherapy is among relevant therapeutic options for this disease. In a subgroup of patients, however, sun exposure causes relapses or aggravations of eczema. On the ground of the present hypothesis, this might be explained by the presence of photosensitizing haptens in food. An example of such photohapten might be 2-phenylphenol, a fungicide with known photosensitizing properties that is used in the production of citrus fruits. Citrus fruits are frequently accused of causing skin problems, therefore the possibility of hypersensitivity to 2-phenylphenol or other pesticides seems worthwhile a dedicated study. The underlying processes would probably be analogous to drug-induced photoallergy or phototoxicity [14-17].

The breach of tolerance to haptens

Each day we are exposed to dozens of haptens, however, we remain tolerant of most (if not all) of them, indicating that the preferred response of the immune system is tolerance. Immune tolerance is an active process mediated by specialized subsets of antigen-specific lymphocytes [18]. The stimuli turning immune tolerance into hypersensitivity remain unclear, possible factors of importance with this respect include co-existence of irritation or inflammation ("danger signals"), co-exposures, previous exposures, UV-irradiation, site and the route of primary exposure [19-22]. Evidence accumulated from numerous animal and human studies (reviewed recently in [23]) demonstrates that primary oral exposure to haptens can prevent subsequent development of contact sensitization through the skin. However, the surface of human body is exposed to haptens already in utero, while oral exposure to highly processed (thus hapten-rich) foods occurs later in the course of life. This could facilitate the early development of hypersensitivity to haptens through the skin, rather than tolerance through oral exposure. With this regard, another hypothesis - proposed by McFadden and colleagues [24] that links oral exposure to haptens with food allergy deserves a mention. According to the authors, "artificially increased oral exposure to haptens 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". In another words, the authors suggest that oral exposure to food haptens would facilitate the development of allergy to "classical" protein food allergens, while the hypothesis outlined in the present article points on haptens themselves as the possible sensitizers in eczema. These hypotheses do not necessarily exclude one another, but rather seem to look at one complex phenomenon from different perspectives. Furthermore, McFadden et al. stated that "hapten exposure via other surfaces such as the skin and airways might also be important in promoting atopic disease". In the present hypothesis, the route of hapten exposure is regarded as a decisive factors, which is outlined in the following paragraphs.

The possible role of cosmetics in food-related eczema

The second part of this paper is aimed at explaining why would intestinal exposure to haptens result in eczema, i.e. inflammation localized in the skin. Data on the bioavailability of oral drugs [25] demonstrate that once absorbed from gastrointestinal (GI) tract into the blood, haptens may circulate to various organs of the body, where they can ultimately bind to autologous proteins and turn them into immunogens. This opens the question, why would haptens absorbed from food cause eczema and not any other organ's disease? The skin is one of the organs richest in immunocompetent cells, which makes it a good target for allergic reactions. However, the same is true for the gut or respiratory tract, yet flares of eczema are rarely accompanied by GI or respiratory symptoms. One possible explanation could be that some haptens are capable of forming complexes only with proteins present exclusively in the skin, e.g. keratins. This may be true in some cases, but seems rather insufficient as a general rule. Other, perhaps more convincing explanation might be the organ specificity of sensitization processes, rather than haptens themselves. The central element of acquired immune response are lymphocytes – cells capable of recognising specific hapten-protein complexes (HPC) that recruit and orchestrate inflammatory actions of other cells (e.g. macrophages, neutrophils, eosinophils, cytotoxic lymphocytes). There is evidence that naïve lymphocytes acquire organ specificity at their first encounter with HPC fitting to their receptors, presented to them by antigen presenting cells (APC) that migrate into local lymph nodes from the sites of haptens' entry. It appears that next to HPC, signals characteristic of the exposed organ are transmitted to naïve lymphocytes, which determines the organ-specificity of daughter effector and memory cells. These signals could be molecules carried on the surface of an APC, chemokines or other factors dissolved in the lymph draining particular organs. Thus in case of hapten-protein complex presented by an APC from the skin, in the milieu of a lymph node flooded with the lymph from the skin, the antigen specific naïve T cell will ultimately undergo clonal expansion into skin-homing effector and memory lymphocytes [26-30]. Some of the daughter lymphocytes will settle in the skin, while other will circulate in the blood ready for rapid migration into the skin in case of re-exposure to the hapten. While the induction of contact hypersensitivity seems to require the epidermal route, subsequent elicitations of the disease in already sensitized subjects may follow systemic exposure to the hapten, e.g. by oral route. Hapten absorbed from the GI tract will distribute not only into the skin, but obviously also to another organs of the body, however, the skin will be most affected by the inflammatory response due to predominance of skin-homing effector lymphocytes. As a matter of fact, cases of eczema provoked by oral or parenteral exposure to haptens are well-known to clinicians and are referred to as "hematogenous allergic contact dermatitis", "hematogenous contact eczema", "systemic contact dermatitis" or "systemic allergic contact dermatitis" (SACD) [31-35].

In summarising, the occurrence of the same haptens in cosmetics and food might offer an explanation for cases of eczema provoked by food that could not be explained by type I allergy to protein allergens. According to the

present hypothesis, such patients may be sensitized to haptens – initially from cosmetics applied onto the skin (induction of hypersensitivity), with further relapses of eczema triggered by the same haptens absorbed from ingested food (elicitation of hematogenous eczema). As there are numerous haptens common to cosmetics and food products (table 1), these processes are very probable to occur in everyday life and deserve further studies. Repeated applications of cosmetics onto the skin seem a very effective way of inducing contact hypersensitivity to haptens, however, in small children the food might bypass the "cosmetic link", serving as a primary source of sensitizing haptens, as it is not unusual in children to have their food smeared over faces and hands during their meals.

Future outlook

The hypothesis presented in this paper requires thorough verification by the means of dedicated studies. One

Table 1. An overview of haptens that are both food additives and cosmetic ingredients (data extracted from [36])

Hapten	Occurrence in cosmetic products	Occurrence in food
2,6-di-tert-butyl-4-cresol	Antioxidant in cosmetics	Antioxidant in foods (beverages, gum, ice cream, fruits, cereals)
2-phenylphenol	Preservative in cosmetics	Agricultural fungicide for citrus fruits
2-tert-butyl-4-methoxyphenol (BHA)	Antioxidant in cosmetics	Antioxidant in foods (beverages, gum, ice cream, fruits, cereals)
Balsam Peru	Fixative and fragrance in perfumery	Flavour in tobacco, drinks, pastries, cakes, wines, liquors, spices, etc.
Benzoic acid	Preservative in perfumes, cosmetics and dentifrices	Preservative in foods (fats, fruit juices, etc.)
Benzyl alcohol	Enhancer and fixer in perfumery products	Food additive E1519. Natural occurrence in tea
Benzyl benzoate	Fixative in fragrances	In artificial food flavours
Benzyl cinnamate	Fixative in fragrances	Commonly used flavouring agent (sweet, floral, fruity)
Bithionol	Deodorant, antibacterial agent in soaps, and other cosmetics	Food additive, additive in animal feed and drinking water for farm animals
Butyl-4-hydroxybenzoate (Butylparaben)	Preservative in creams, lotions, ointments and other cosmetics	Preservative in foods (salad dressings, mayonnaise, spiced sauces, mustard, frozen dairy products, baked products)
R-(L)-carvone	Toothpaste, perfumery	Natural occurrence in lemon, orange, mandarin, grapefruit, clove oil, eucalyptus, juniper berry, lavender, marjoram, ginger grass, Scotch spearmint, garden mint, common spearmint
Cinnamic alcohol	Perfumed cosmetic products and deodorants	Natural occurrence in cinnamon
Cinnamic aldehyde	Deodorizers, toothpaste, detergents, soaps	Natural occurrence in cinnamon. Flavour in sweets, ice cream, soft drinks, chewing gums, cakes
Coumarin	Perfumes, soaps	Natural occurrence in strawberries
Captan	Preservative in soaps, shampoos, hair tonics	Preservative of fruits and other foods
Dodecyl gallate	Antioxidant in cosmetic creams and emulsions	Antioxidant in margarine
Ethyl-4-hydroxybenzoate (Ethylparaben)	Preservative in cosmetics	Preservative in foods (salad dressings, mayonnaise, spiced sauces, mustard, frozen dairy products, bakery products)
Eugenol	Perfume	Chemical intermediate and contaminant in vanillin
Farnesol	Perfume	Food flavour
Isoeugenol	Perfume	Chemical intermediate and contaminant in vanillin, food flavour
Juniper tar (Cade oil)	Perfume	Flavouring of meat and seafood (smoke note)
Methyl-4-hydroxybenzoate (Methylparaben)	Preservative in cosmetics	Preservative in salad dressings, mayonnaise, spiced sauces, mustard, frozen dairy products, baked products
Octyl gallate	Antioxidant in cosmetic products	Antioxidant in food products such as margarine and peanut butter
Olive oil	In emollients, soaps, other cosmetics	Used as food (salads, sardines, etc.)
Polyethyleneglycol (PEG 400)	Solvent and lubricant in cosmetics, detergents and soaps	Lubricant in food processing and packaging
Propolis	Flavour in toothpaste, mouthwashes	Flavour in chewing gum
Propyl gallate	Preservative and antioxidant in cosmetics	Food preservative and antioxidant (margarine, peanut butter, etc.)
Propyl-4-hydroxybenzoate (Propylparaben)	Preservative in cosmetics	Preservative in foods (salad dressings, mayonnaise, spiced sauces, mustard, frozen dairy products, baked products), mould control in sausage casings
Propylene glycol	Vehicle in cosmetic bases, present in cleansing creams, suntan lotions, perfumes	Solvent for colours and flavours in food
Sodium benzoate	Common preservative in cosmetic products	Preservative in food products (drinks, jams, jellies, pickles, syrups, etc.)
Sorbic acid	Preservative in cosmetics	Mould and yeast inhibitor and fungistatic agent for foods, especially cheese
Titanium oxide	Mineral sunscreen agent, pigment and thickener in cosmetic and skin care products, toothpaste	Food additive E171, white colouring agent in food
Tocopherol (Vitamin E)	Antioxidant in many cosmetics, often labeled as tocopherol acetate, tocopheryl linoleate or tocopheryl nicotinate	Natural occurrence in vegetable oils (soybean), nuts, seeds. Widely used as an antioxidant in foods
Trans-anethole	Perfume in soaps, dentifrices, etc.	Flavouring agent in foods
Vanillin	Perfume	Flavouring agent in beverages, confectionery and other foods

such study should focus on the prevalence of contact hypersensitivity to food additives among patients with food-provoked eczema. Such patients should be tested with an array of haptens used as food additives or naturally occurring in foods. Cosmetic ingredients with recognised sensitizing potential that are also used as food additives (table 1) seem very promising candidates for such studies, however, other food-specific haptens – either natural, contaminants or additives – should also be taken into consideration. After confirming the role of hypersensitivity to food haptens in food-provoked eczema, appropriate diagnostic methods (e.g. patch test panels with food haptens or specially devised in vitro tests) should be introduced into routine diagnosis of eczema patients. Furthermore, results of such studies will provide scientific evidence for possible restrictions on the use of food additives identified as potent sensitizers within the legal scheme of consumer protection policy.

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