



Perspective

An evolutionary perspective on intestinal lymphatic fat absorption, the industrialization of food, and allergy



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Introduction

The gastrointestinal system absorbs nutrients while coexisting with normal microbiota but excluding pathogens. Therefore, there is a close evolutionary relation among the digestive, metabolic, and immune systems,¹ which is particularly so regarding fat metabolism.² There also is a close relation between allergens and lipids, with more than half of major allergens being lipid binding.³ Nevertheless, although dietary fat has been implicated in vascular and inflammatory diseases, the possible role of the absorption of fats into the intestinal lymphatic system has not been emphasized regarding allergy. Furthermore, this lipid-absorptive system is now confronted with a diet of mechanically processed foods, the lipid components of which have been fractionated, concentrated, emulsified, and otherwise radically modified from the state present during the gastrointestinal and immune systems' evolutionary selection.

Dietary Lipids

Fatty acids comprise a hydrophilic carboxyl (COOH) group attached to a hydrophobic linear hydrocarbon chain and are categorized according to their number of carbons as short-chain (<6 carbons), medium-chain (6–12 carbons), or long-chain (>12 carbons) fatty acids. Fats are tri-esters of the tri-alcohol glycerol with 3 fatty acids (ie, triglycerides). Fats that are liquid at room temperature are called oils. Most foods, including peanuts, egg, and milk, contain predominantly long-chain fatty acids.

There is an important distinction between the absorption of long-chain fats and the absorption of other food products. Digested proteins, carbohydrates, and short- and medium-chain triglycerides are primarily absorbed into the portal circulation, passing through the liver and then rapidly into the systemic circulation. In contrast, long-chain triglycerides are absorbed into the lacteals and formed into lipoproteins such as chylomicrons, which then

spend approximately 4 hours in contact with the mesenteric immune system before reaching the systemic circulation through the thoracic duct.⁴

Absorption of Proteins in Association with Fats

These distinct pathways of absorption are exploited in pharmaceutical design, where drug peptides are associated with lipids to cause intralymphatic, rather than hepatic portal, absorption.⁵ Lipids likewise affect food allergen absorption in quantity and route. A murine model showed 4-fold higher plasma levels of major soybean allergen Gly m Bd 30K after soymilk was coadministered with 30% corn oil and 6-fold higher levels with 30% corn oil plus an emulsifier.⁶ Coadministration of long-chain triglycerides, but not medium-chain triglycerides, increased the absorption of labeled ovalbumin, which could be tracked through mesenteric lymph nodes and which ultimately stimulated a stronger peripheral T-cell response.⁷ The medium-chain triglyceride coconut oil decreases systemic allergen absorption but increases Peyer patch absorption and IgE formation.⁸

The association of allergenic proteins with fats also affects their transcutaneous absorption, of relevance to the Lack hypothesis linking food sensitization to cutaneous allergen absorption.⁹ Most proteins, large and hydrophilic, cannot passively traverse the intact stratum corneum, which allows penetration only by small lipophilic molecules. However, transdermal protein absorption does occur through intact skin when proteins are associated with lipids.¹⁰ It is noteworthy that many allergenic foods, including egg, soy, seeds, fish, and milk, are themselves emulsifiers,¹¹ and that emulsifiers are frequently added to processed foods.

Isoprostanes and Phytosterols—the Ingestion of Plant-Derived Inflammatory Mediators

Prostaglandins are produced by the enzymatic action of cyclooxygenase on arachidonic acid in animal cell membranes, whereas isoprostanes are inflammatory mediators formed by the non-enzymatic peroxidation of arachidonic acid. Isoprostanes are

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present in the exhaled breath condensates of patients with asthma and in their urine after allergen challenge.¹² Plants lack arachidonic acid, but contain 18-carbon linoleic and α -linoleic acids, the peroxidation of which yields the plant analogs of the isoprostanes, the *phytoprostanes*. Pollen-associated phytoprostanes activate human dendritic cells and inhibit dendritic cell interleukin-12, thus promoting a T-helper type 2 (T_H2) response.¹³

High concentrations of free and esterified phytoprostanes form in vegetable oils by auto-oxidation. Phytoprostane levels in opened bottles of room-temperature vegetable oil increase 10- to 20-fold over 18 days, despite the absence of rancidity.¹⁴ High levels of E1 or F1 phytoprostanes are found in linseed, olive, soybean, rapeseed, walnut, and grapeseed oils. Ingestion of olive and soybean oils causes detectable free F1-phytoprostane levels in urine¹⁴; supplementation with 9 g/d of flaxseed oil leads to significantly increased plasma F1-phytoprostane levels.¹⁵

The Modern Diet and the Industrialization of Food

It has been said, “Nothing in biology makes sense except in the light of evolution.” In that light, it would be expected that the interrelated digestive, metabolic, and immune systems, having evolved over millions of years, would be affected by sudden changes in their fuel source. Until only 600 years ago, two thirds of the human population was still living in hunter-gatherer societies, eating the “Paleolithic diet” of fruits, berries, shoots, flowers, buds, young leaves, meat, marrow, organ meats, fish, shellfish, insects, larvae, eggs, roots, bulbs, nuts, and non-grass seeds.¹⁶ In contrast, the current Western diet obtains three fourths of its calories from grass seeds (grains), dairy products, refined vegetable oils, and refined sugar—none of which were available during the vast majority of human evolution.¹⁶ The mechanical modification of foods has occurred in a little over 100 years and greatly accelerated in the last 50 to 60 years.

The “Refining” of Plant Oils

Given the present ubiquity of vegetable-derived salad and cooking oils, it is easy to forget that these oils were not part of the human evolutionary diet, in which foods were consumed whole. Industrialization has allowed oils to be separated from seeds, nuts, and other plant parts by mechanical extraction with steel rollers or screw-press or by solvent extraction. The per-capita intake of these oils has increased steadily in the past century, and approximately exponentially since 1950, to more than 50 lb per person yearly (Table 1; Fig 1), a trend increased by the awareness of the negative health effects of solid hydrogenated *trans*-fatty acids. Approximately 25% of dietary essential fatty acids are now ingested as refined oils rather than in whole foods.

This has led to a dramatic change in the ratio of pro-inflammatory ω -6 to ω -3 fatty acids, from approximately 2:1 in the ancestral diet to approximately 20:1 in the current Western diet.¹⁷ Perhaps equally important, however, is the presence in vegetable

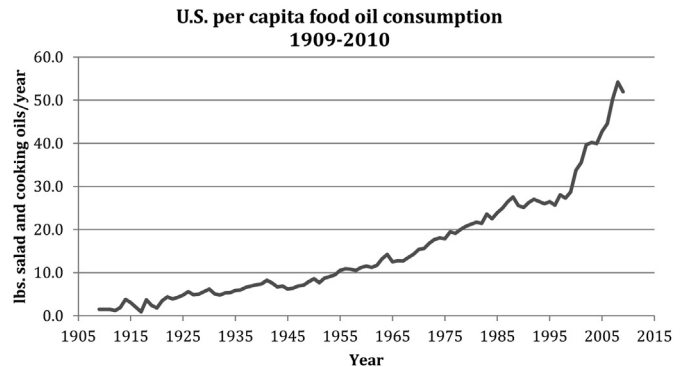


Figure 1. US per-capita availability of salad and cooking oils, 1909 through 2010. Data were adapted from: Food Data Consumption Spreadsheets: Fats. United States Department of Agriculture Oil Crops Yearbook. Washington DC: USDA Economic Research Service; 2012.

oils of high levels of T_H2-inducing phytoprostanes. Separated plant oils are thus fundamentally different from whole plants, which have evolved antioxidants that minimize oxidative damage, making the intact plant much less susceptible to proinflammatory auto-oxidation. In this light, it is hardly surprising that experimental supplementation of diets with additional refined oils has generally not been beneficial, regardless of the position of their double bond.

Concern over possible allergic consequences of ingesting separated plant oils has been limited to assuring that the allergenic protein is not present in sufficient amounts to elicit reactions in already-sensitized individuals. However, the evolutionary novelty of using concentrated plant oils as a food source, the presence of spontaneously forming and T_H2-promoting phytoprostanes, the increased transdermal absorption of these oils, and the ability of these oils to increase the intralymphatic absorption of protein allergens raise questions as to their possible role in inducing or promoting allergic sensitization. Simply put, corn oil does not equal corn, and olive oil does not equal olives.

Transformation of Peanuts into Peanut Butter

The industrial revolution led to a method for creating peanut butter by milling roasted peanuts between heated rollers, creating a product that, in addition to being high in advanced glycation end products, is concentrated (45 peanuts into 1 oz of peanut butter), fractionated (into oil), and emulsified. Peanut butter consumption has increased dramatically since 1950, with the average American child now eating 1,500 peanut butter and jelly sandwiches through high school.

A study performed more than 30 years ago showed that fecal fat excretion decreased (and intestinal absorption presumably increased) on changing from ingesting whole peanuts to an equal weight of peanut butter and yet again to an equal weight of peanut oil—the peanut butter and peanut oil resulting in a hyper-absorption of fat.¹⁸ Clearly an issue for atherosclerosis, this might also be relevant to allergic sensitization and tolerance. From the absorptive, metabolic, and immunologic viewpoints, peanut butter does not equal peanuts.

Homogenization of Bovine Milk

Natural cow's milk is 3.8% fat by weight, a suspension of fat globules in water. These fat globules comprise triglycerides surrounded by a membrane of phospholipids and protein. Homogenization forces the milk under pressure through extremely narrow tubes, producing a decrease in the average fat globule diameter from 3.3 to 0.4 μ , with a 600-fold increase in the total number of fat globules, and an almost 10-fold increase in their total surface area,

Table 1
US per-capita availability of salad and cooking oils^a

Year	US per-capita intake (lb)
1910	<1.5 ^b
1930	<6.2 ^b
1950	<8.6 ^b
1970	15.4
1990	25.1
2010	53.5

^aData adapted from: Food Data Consumption Spreadsheets: Fats. United States Department of Agriculture Oil Crops Yearbook. Washington DC: USDA Economic Research Service; 2012.

^bBefore 1965 “salad and cooking oils” were not recorded separately but only as part of “other edible fats and oils.”

from 0.08 to 0.75 m²/mL of milk.¹⁹ This large increase in total surface area produces surface forces that cause casein, whey, and other proteins to adhere to the surface of the new smaller globules¹⁹—with implications for the intralymphatic absorption and immunologic presentation of those proteins.

Homogenization increases allergenicity in murine models. Intraperitoneally sensitized mice experience anaphylaxis when challenged intravenously with homogenized but not with raw milk; decreasing the fat content of homogenized milk lessens its ability to induce anaphylaxis.²⁰ Homogenized milk also induces greater sensitization than raw milk.²¹ The clinical relevance of this in humans is unclear, because a small study of 5 children 12 to 24 months old with existing cow's milk allergy showed reactions in all 5 children to skin tests and challenges with both raw and homogenized milk.²² However, in each of the 4 of the 5 patients in whom wheal size differed, the reaction was greater to homogenized milk; and in the 3 of 5 patients in whom challenge reactions differed, the provoking dose was lower and/or the time to onset was shorter with homogenized milk. Importantly absent are human studies of the possible effect of homogenization on primary milk sensitization.

Although the transcutaneous absorption of allergenic proteins from homogenized vs raw cow's milk has not been studied, modifications aimed at increasing the transcutaneous absorption of protein drugs have indicated that the smaller and more lipophilic the particle, the better is its transdermal absorption.

Intramuscular Fat in Beef Grated by the US Department of Agriculture

Cattle are ruminants (ie, natural grass feeders). However, modern feedlot cattle are confined and fed grain rather than grass, resulting in meat with an abnormally high ω -6 to ω -3 ratio and with fat within the muscle tissue, the “marbling” necessary for US Department of Agriculture Prime, Choice, or Select status. Grain-fed beef contains twice the fat of game animals, which lack marbling.¹⁷

Commins et al²³ described urticaria or anaphylaxis occurring 4 hours after the ingestion of beef or other mammalian meat in patients with IgE antibodies to the carbohydrate allergen “alpha-gal.” This 4-hour interval correlates with the time course of intralymphatic passage of absorbed fats from the lacteals to the systemic circulation,⁴ suggesting that the alpha-gal was absorbed as a glycolipid. Anecdotal reports have suggested that at least some patients with alpha-gal allergy can tolerate wild venison (T. Platts-Mills, personal communication, 2014), and several patients have reported an apparent relation between the fat content of the meat and the occurrence of symptoms.²⁴ If confirmed, these observations would support speculation that the unnaturally high fat content of feedlot beef is leading to the increased intralymphatic absorption of the fat-linked carbohydrate allergen.

Possible Implications for Oral Immunotherapy

Humans do not normally ingest allergens; they ingest foods containing allergens. Food components including fats can be adjuvants required for protein sensitization.²⁵ Therefore, it may be counterproductive to focus only on allergenic proteins—as in oral immunotherapy trials using partially defatted peanut flour, egg white powder, or non-fat powdered milk—thereby unintentionally decreasing any adjuvant or intralymphatic-absorptive effect of fat. Similarly, the fat content of peanut challenges affects the timing and severity of the clinical reaction.²⁶

Overview

The absorptive and immunologic functions of the gastrointestinal tract evolved together. The physical form in which a food is ingested and the differential absorption of long-chain fatty acids and associated peptides into the lymphatic system rather than into

the portal circulation could have relevance for the understanding of food allergy. The industrial fractionation of foods, the timing of which corresponds to the increasing prevalence of food allergy, creates components that were never ingested during the majority of human evolution and which therefore warrant further scrutiny for possible causality. The separation of vegetables and seeds into oils, which are excessively absorbed and which auto-oxidize and spontaneously produce phytoprostanes that have been shown to skew towards T_H2; the homogenization of cow's milk into abnormally small particles with abnormal surface proteins and increased allergenicity; the mechanical degradation of peanuts into oil-rich and excessively absorbed peanut butter; and the change in meat from lean game into “marbled” feedlot beef have the potential to increase allergic sensitization. Conversely, attempts at inducing tolerance in already-sensitized patients should consider the possibility of different immunologic effects of defatted proteins and the corresponding whole foods.

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References

- [1] Shulzhenko N, Morgun A, Hsiao W, et al. Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut. *Nat Med*. 2011;17:1585–1593.
- [2] Wang Y, Li J, Tang L, et al. T-lymphocyte responses to intestinally absorbed antigens can contribute to adipose tissue inflammation and glucose intolerance during high fat feeding. *PLoS One*. 2010;5:e13951.
- [3] Thomas WR, Hales BJ, Smith W-A. Structural biology of allergens. *Curr Allergy Asthma Rep*. 2005;5:388–393.
- [4] Labbe SM, Grenier-Larouche T, Croteau E, et al. Organ-specific dietary fatty acid uptake in humans using positron emission tomography coupled to computed tomography. *Am J Physiol Endocrinol Metab*. 2011;300:E445–E453.
- [5] Wasan KM. The role of lymphatic transport in enhancing oral protein and peptide drug delivery. *Drug Dev Ind Pharm*. 2002;28:1047–1058.
- [6] Weangsriripana T, Moriyama T, Kageura T, Ogawa T, Kawada T. Dietary fat and an exogenous emulsifier increase the gastrointestinal absorption of a major soybean allergen, Gly m Bd 30K, in mice. *J Nutr*. 2005;135:1738–1744.
- [7] Wang Y, Ghoshal S, Ward M, de Villiers W, Woodward J, Eckhardt E. Chylomicrons promote intestinal absorption and systemic dissemination of dietary antigen (ovalbumin) in mice. *PLoS One*. 2009;4:e8442.
- [8] Li J, Wang Y, Tang L, et al. Dietary medium-chain triglycerides promote oral allergic sensitization and orally induced anaphylaxis to peanut protein in mice. *J Allergy Clin Immunol*. 2013;131:442–450.
- [9] Fox AT, Sasieni P, du Toit G, Syed H, Lack G. Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol*. 2009;123:417–423.
- [10] Russell-Jones G, Himes R. Water-in-oil microemulsions for effective transdermal delivery of proteins. *Expert Opin Drug Deliv*. 2011;8:537–546.
- [11] Mills ENC, Jenkins JA, Alcocer MJC, Shewry PR. Structural, biological, and evolutionary relationships of plant food allergens sensitizing via the gastrointestinal tract. *Crit Rev Food Sci Nutr*. 2004;44:379–407.
- [12] Zanconato S, Carraro S, Corradi M, et al. Leukotrienes and 8-isoprostane in exhaled breath condensate of children with stable and unstable asthma. *J Allergy Clin Immunol*. 2004;113:257–263.
- [13] Traidl-Hoffmann C, Mariani V, Hochrein H, et al. Pollen-associated phytoprostanes inhibit dendritic cell interleukin-12 production and augment T helper type 2 cell polarization. *J Exp Med*. 2005;201:627–636.
- [14] Karg K, Dirsch VM, Vollmar AM, Cracowski J-L, Laporte F, Mueller MJ. Biologically active oxidized lipids (phytoprostanes) in the plant diet and parenteral lipid nutrition. *Free Radic Res*. 2007;41:25–37.
- [15] Barden AE, Croft KD, Durand T, Guy A, Mueller MJ, Mori TA. Flaxseed oil supplementation increases plasma F1-phytoprostanes in healthy men. *J Nutr*. 2009;139:1890–1895.
- [16] Lindeberg S. Paleolithic diets as a model for prevention and treatment of Western disease. *Am J Hum Biol*. 2012;24:110–115.
- [17] Cordain L, Watkins BA, Florant GL, Kehler M, Rogers L, Li Y. Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. *Eur J Clin Nutr*. 2002;56:181–191.
- [18] Miller J. Absorption of peanuts. *N Engl J Med*. 1981;304:359.

- [19] Goff D. Homogenization of milk and milk products. Dairy Science and Technology, University of Guelph; 2010. <http://www.foodsci.uoguelph.ca/dairyedu/homogenization.html>. Accessed August 1, 2012.
- [20] Poulsen OM, Hau J, Kollerup J. Effect of homogenization and pasteurization on the allergenicity of bovine milk analysed by a murine anaphylactic shock model. *Clin Allergy*. 1987;17:449–458.
- [21] Nielsen BR, Poulsen OM, Hau J. Reagin production in mice: effect of subcutaneous and oral sensitization with untreated bovine milk and homogenized bovine milk. *In Vivo*. 1989;3:271–274.
- [22] Host A, Samuelsson EG. Allergic reactions to raw, pasteurized and homogenized/pasteurized cow milk: a comparison. *Allergy*. 1988;43:113–118.
- [23] Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol*. 2009;123:426–433.
- [24] Crawford N, Bauer B, Taylor J, Bird H. Ticked off carnivores. Tick bites likely cause allergy to red meat. *University of Virginia Magazine*. 2011;2012. Available at http://uvamagazine.org/articles/ticked_off_carnivores. Accessed August 25, 2014.
- [25] Mirotti L, Florsheim E, Rundqvist L, et al. Lipids are required for the development of Brazil nut allergy: the role of mouse and human iNKT cells. *Allergy*. 2013;68:74–83.
- [26] Grimshaw KEC, King RM, Nordlee JA, Hefle SL, Warner JO, Hourihane JOB. Presentation of allergen in different food preparations affects the nature of the allergic reaction—a case series. *Clin Exp Allergy*. 2003;33:1581–1585.