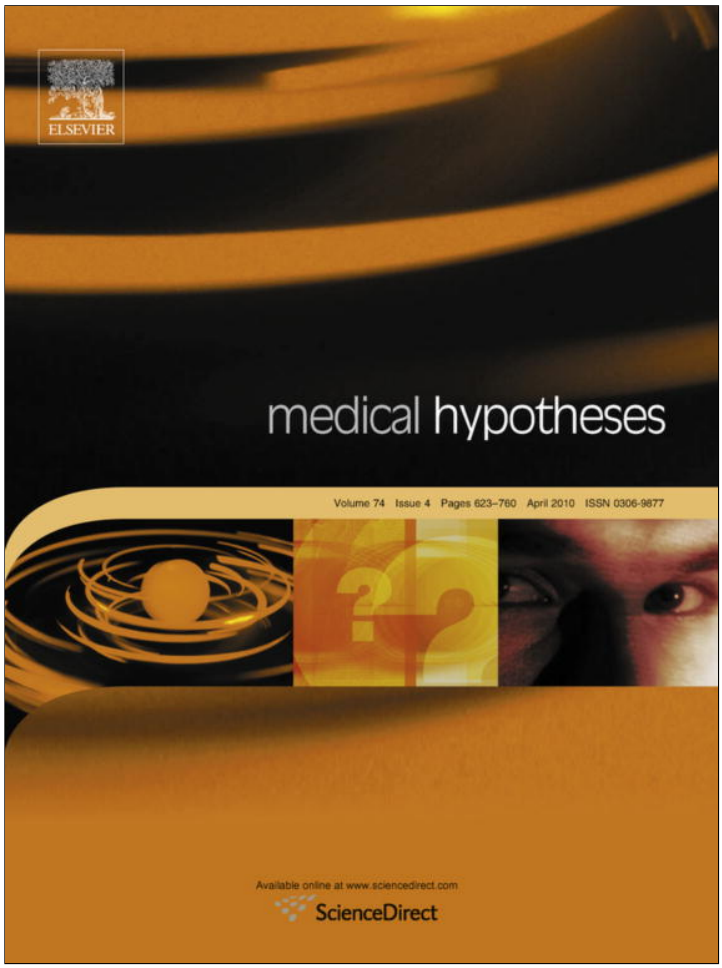

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Does milk increase mucus production?

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SUMMARY

Excessive milk consumption has a long association with increased respiratory tract mucus production and asthma. Such an association cannot be explained using a conventional allergic paradigm and there is limited medical evidence showing causality. In the human colon, β-casomorphin-7 (β-CM-7), an exorphin derived from the breakdown of A1 milk, stimulates mucus production from gut MUC5AC glands. In the presence of inflammation similar mucus overproduction from respiratory tract MUC5AC glands characterises many respiratory tract diseases. β-CM-7 from the blood stream could stimulate the production and secretion of mucus production from these respiratory glands. Such a hypothesis could be tested in vitro using quantitative RT-PCR to show that the addition of β-CM-7 into an incubation medium of respiratory goblet cells elicits an increase in MUC5AC mRNA and by identifying β-CM-7 in the blood of asthmatic patients. This association may not necessarily be simply cause and effect as the person has to be consuming A1 milk, β-CM-7 must pass into the systemic circulation and the tissues have to be actively inflamed. These prerequisites could explain why only a subgroup of the population, who have increased respiratory tract mucus production, find that many of their symptoms, including asthma, improve on a dairy elimination diet.

Introduction

Excessive milk consumption has a long association with increased respiratory tract mucus production and asthma. However while large proportions of the population believe this [1–3], the published medical evidence documenting these links is limited. People who believe that milk increases mucus production have more respiratory tract symptoms, consume less milk and complain that milk increases throat secretions [1]. Such an association cannot be explained using a conventional allergic paradigm.

'Conventional' food allergy mechanisms

Immunologically, allergy is subdivided into four classes. The best known, where there is little dispute is the Type I, or immediate hypersensitivity, reaction due to the presence of IgE antibodies against the offending food. Most of the controversy in food allergy relates to Type III allergic reactions involving food IgG immune complexes. T-cell mediated reactions can also be involved. Cases of asthma-like symptoms resulting from consumption of, or exposure, to dairy foods have only occasionally been reported.

Milk challenge and asthma

Although several studies have examined the effect of dairy exposure on bronchoconstriction, none have shown any major effect. For instance, Woods et al. found no bronchoconstrictive effects when subjects were exposed to 300 ml of UHT milk compared to a rice milk placebo [4]. Haas et al. exposed patients with asthma or healthy controls to whole milk, skim milk, or water. No differences in expiratory flows were found. However, diffusing capacity did decrease after ingestion of whole milk, but not after skim milk or water. The decrease was attributed to differences in fat content [5]. Nguyen in a double-blind, placebo-controlled crossover study of atopic adults with mild asthma found no evidence for cow's milk induced bronchoconstriction before and after ingestion of either cow's milk or a placebo [6].

Milk exclusion and asthma

In contrast, a number of studies have suggested that the exclusion of milk products from the diet may improve asthma symptoms. In the 1950s, Rowe and Rowe suggested that a variety of foods could contribute to asthma and found that in asthma patients, symptoms often improved on an exclusion diet [7,8]. With the development of effective medications for asthma treatment these observations were neglected.

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Pinnock et al. found that when milk was excluded from the diet, symptoms of cough and nasal congestion improved particularly at night. This was an unblinded study and recording bias was used to explain the effect [9]. More recently, in a single blind prospective study 22 children with asthma (13 in the experimental and 9 in the control group) received an egg and milk free diet for eight weeks. The children of the experimental group exhibited distinctly decreased IgG antibody concentrations toward ovalbumin and beta lactoglobulin. In 5 children in the experimental group, the peak expiratory flow rate was increased markedly when compared to children in the control group [10].

Similarly, in a double-blind controlled trial looking at the role of exclusion diet in childhood migraine, Egger et al. found that asthma symptoms and eczema also improved [11]. In another double-blind crossover study chronic constipation was found in a number of children to be due to cow's milk. Those children who had a response also had a "higher frequency of coexistent rhinitis, dermatitis and bronchospasm" [12]. These observations would suggest that in some situations a cow's milk exclusion diet can be beneficial.

Stimulation of mucus production

The two main mucins produced in the respiratory tract are MUC5AC and MUC5B. In airway tissues from healthy individuals, goblet cells typically express MUC5AC, while glandular mucosal cells typically express MUC5B. MUC5AC and MUC5B are present at lower levels in mucus from normal airways than in sputum from patients with asthma, bronchitis or cystic fibrosis [13]. Similar observations have been made in chronic rhinosinusitis and nasal polyposis [14]. Mucus overproduction is now recognized as a characteristic of asthma [15]. Inflammation is a necessary prerequisite for MUC5AC production. Specifically, inflammatory/immune response mediators cause airway remodeling including goblet cell hyperplasia, which is also responsible for MUC5AC production [16]. Cytokine mediated inflammation, particularly via IL13 upregulate mucin gene expression and mucus production [17].

An additional protein that has been shown to specifically increase MUC5AC production is β-casomorphin-7 (β-CM-7). β-CM-7 belongs to the opioid peptide family and is derived from the breakdown of A1 milk. Milk is comprised of a mixture of water, fat, protein, lactose and minerals. Cow's milk contains six major proteins – four casein proteins make up 80% of milk proteins, the other two are whey proteins. Most allergies to milk are associated with these proteins. The casein proteins are further subdivided into three types α-, β-, and γ-. The most common proteins in cow's milk are β-casein A1 and β-casein A2. Milk high in β-casein A1 is being referred to as 'A1 milk' while milk high in β-casein A2 is being called 'A2 milk.' An enormous number of variables can influence the final composition including the breed of cow and stage of lactation [18]. In the human colon β-CM-7, has been shown to stimulate mucus production from gut MUC5AC glands [19]. However, no studies have examined the relationship between the specific composition of milk consumed with respect to mucus production and asthma.

Proposed mechanism of respiratory tract cells exposure to milk protein

The evidence suggests that some food derivatives can pass into the systemic circulation. In healthy individuals, despite high stomach acidity and enzyme activity in the small intestine, 2% of ingested food is absorbed through the intestines in a form that is sufficiently immunologically intact to produce food allergy [20]. In a variety of situations such as during trauma, larger macromolecules have been shown to enter the portal circulation. Stress and the subsequent release of corticotrophin releasing factor (CRF) increases gastrointestinal mucosal permeability. In rat, CRF increased ion secretion and mucosal permeability to macromolecules [21]. This provides a physiological explanation for the increased intestinal permeability observed after trauma and burns [22]. Increased intestinal permeability with subsequent leakage of macromolecules has also been observed with the prolonged use of many non-steroidal anti-inflammatory drugs [23]. Increased intestinal permeability is well recognized in Crohn's disease, however there is considerable debate as to which comes first – the inflammation or the increased permeability [24]? Up to a fifth of clinically healthy relatives of Crohn's disease patients also have an increased gut permeability implicating both genetic and dietary factors in its aetiology [22]. In infants and young children who have a more immature mucosal barrier; a greater percentage of food is also absorbed intact [25]. Therefore, in situations involving increased intestinal mucosal permeability, milk proteins could find their way into the systemic circulation to stimulate respiratory tract mucus production.

Hypothesis

The hypothesis is that A1 milk increases mucus production in the respiratory tract in a sub-population of people who have increased intestinal permeability. Specifically, β-CM-7, acts via μ-opioid receptors on goblet cells, to upregulate MUC5AC gene expression and increases mucus secretion. This would occur only in specifically primed tissues and only when β-CM-7 was able to pass into the systemic circulation.

Evaluation of the hypothesis

Using nasal brushings of normal and asthmatic patients, μ-opioid receptors expression would be examined using western blotting and dual immunofluorescence labelling [19]. To establish whether β-CM-7 modulates mucin production in human respiratory tract mucosa – a respiratory tract mucin secreting goblet cell line would be obtained. β-CM-7 would be added to goblet cell cultures at a range on concentrations. MUC5AC mRNA expression would be assessed at several different time points following treatment. Mucus secretion would be assessed using ELISA's. Controls will comprise untreated cells or cells treated with μ-opioid antagonists. The second component of the hypothesis would be to identify the presence of β-CM-7 in plasma from asthmatic patients [25].

Consequences of the hypothesis

The belief that excessive milk consumption causes excessive mucus production is common, however such an association cannot be explained using a conventional allergic paradigm. Mucus overproduction from MUC5AC glands is characteristic of many respiratory tract diseases [15]. β-CM-7 from A1 milk could potentially increase mucus production from these glands.

This association many not necessarily be simply cause and effect. For this to occur there needs to be a number of prerequisites. The person may have to consuming A1 as opposed to A2 milk, β-CM-7 has to be passing into the systemic circulation and the tissues have to be actively inflamed. These prerequisites could explain much of the confusion in the "milk-mucus" literature. This would explain why a sub group of patients have found that their asthma or rhinitis symptoms improve on a dairy free diet.

Conflict of interest statement

None declared.

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