

Gastrointestinal permeability in food-allergic eczematous children

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(Received 5 July 1982; accepted for publication 17 February 1983)

Summary

Gastrointestinal permeability has been studied in a group of clinically proven food-allergic eczematous children and compared with a control group using lactulose and L-rhamnose as probe markers. No significant difference was demonstrated in baseline permeability measurements between eczematous and control children using isotonic or hypertonic oral loading. Similarly after antigen-challenge permeability results showed no significant difference from the controls although two of the ten eczematous children challenged showed increased permeability to lactulose. These findings support the hypothesis that once sensitized the physiological absorption of dietary antigen may be sufficient to maintain an allergic response in the skin.

Introduction

Food allergy is now recognized to play a significant role in childhood atopic eczema (Atherton *et al.*, 1978; Juto, Enberg & Winberg, 1978). Although the mechanism of development is not clearly understood it has been suggested that potentially allergic individuals are sensitized by enhanced absorption of antigen across mucous membranes leading to excessive IgE production (Taylor *et al.*, 1973; Leskowitz, Salvaggio & Schwarz, 1972). In the food-allergic individual, sensitized gut mast cells are thought to release a variety of mediators following antigen challenge resulting in a local increase in gut permeability and a further increase in antigen absorption (Brostoff *et al.*, 1979; Pagnelli *et al.*, 1979).

We have studied gastrointestinal permeability in clinically proven food-allergic eczematous children before and after food challenge and compared them with a control group using lactulose and L-rhamnose as probe markers (Menzies *et al.*, 1979).

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Methods and patients

The assessment of gastrointestinal permeability

Oral loads were prepared each containing lactulose (2.5 g) and L-rhamnose (0.5 g) in 50 ml of solution. The loads were made up to 100 ml with 50 ml of water for baseline permeability measurements and with 50 ml of milk or 10 mg tatrazine dissolved in 50 ml of water for permeability assessment with an antigen challenge. The loads were made either isotonic (300 m.osm/l) or hypertonic (1500 m.osm/l) by adding dextrose monohydrate. Subjects were fasted overnight and for 2 hr after the ingestion of each sugar load. The entire loading solution was ingested within 5 min and a timed 5-hr urine save undertaken. The urine saves were preserved with thiomersalate (minimum 10 mg/100 ml urine) (Menzies *et al.*, 1979) and aliquots stored at -20°C for analysis. Urinary concentrations of lactulose and L-rhamnose were estimated using paper and thin-layer chromatography with direct densitometry and finally expressed as percentage of oral dose excreted (Menzies *et al.*, 1979). Controls and patients took both isotonic and hypertonic oral loads on separate occasions at least 4 days apart.

Patients

Ten children with active atopic eczema and clinically proven food allergy aged 2–9 years, mean 5.3 years, were investigated in the fasted state. Two children in this group and another eight children age range 1.5–13 years, mean 7.4 years, whose eczema was exacerbated by either tartrazine or milk challenge, were investigated further with a hypertonic load with either 50 ml of milk or 10 mg of tartrazine dissolved in water as an antigen challenge. None of these children were on an exclusion diet during the week prior to testing.

Controls

Ten healthy children (age range 2–9 years, mean 5.4 years) with no evidence of allergic disease were also studied.

Results

Permeability results were expressed as the urinary lactulose/L-rhamnose concentration ratio (Menzies *et al.*, 1979). Urinary excretion ratios of lactulose/L-rhamnose ranged from 0.04–0.07 and 0.04–0.09 in controls and 0.03–0.10 and 0.03–0.10 in eczematous patients following isotonic and hypertonic loads respectively (see Fig. 1). There is no significant difference between the results in these groups. All ten eczematous children challenged with either 50 ml of milk or 10 mg of tartrazine developed symptoms of increased itching 2–8 hr after challenge. The urinary excretion ratios in this group ranged from 0.1 to 0.15, two children showed an abnormally high permeability (0.15) but the overall results in this group were not significantly different from the non-challenged eczematous children or the controls.

Discussion

The concentration ratio of lactulose and L-rhamnose in urine collected after oral loading with mixtures of these sugars has proved a useful index of gastrointestinal permeability changes occurring in the neonatal period (Beach *et al.*, 1982), coeliac disease (Menzies *et al.*, 1979), after ingestion of hypertonic oral solution (Wheeler, Menzies & Creamer, 1978), and after intravenous cholecystokinin (Budillon *et al.*,

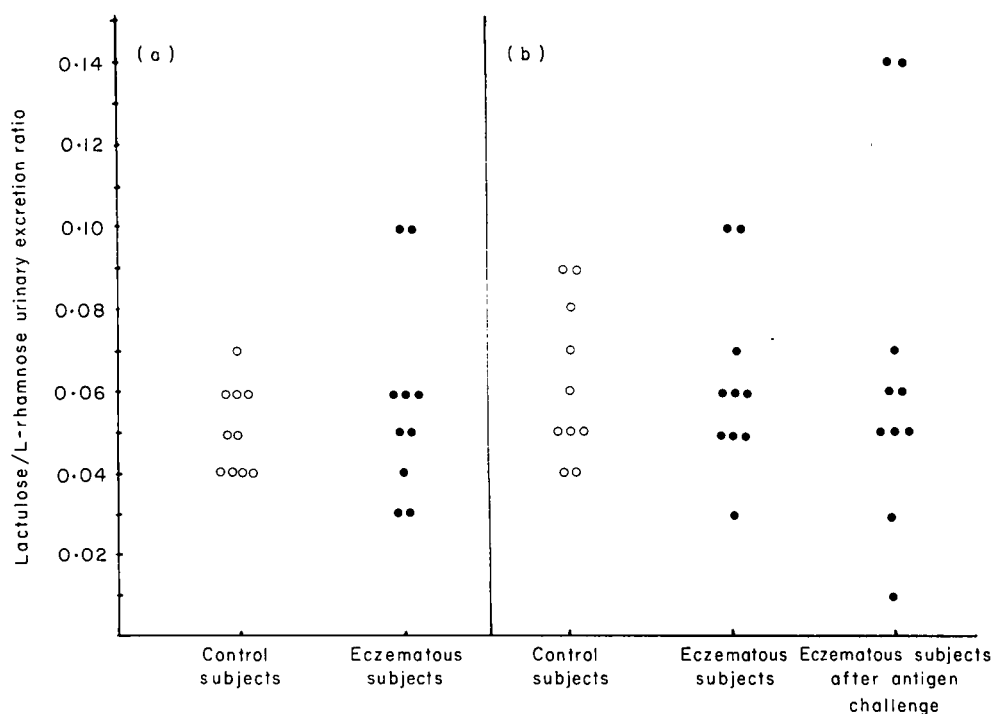


Fig. 1. Lactulose/L-rhamnose urinary excretion ratios in control and eczematous subjects after (a) oral isotonic and (b) oral hypertonic loading.

1980). These sugars are non-toxic, not hydrolysed by human digestion and are rapidly excreted in the urine (Menzies *et al.*, 1979). When gastrointestinal permeability is expressed in terms of the absorption of large and small molecules then errors due to irrelevant variables such as gastrointestinal motility, body weight and renal function are minimized.

The dietary antigens which may permeate the intestinal tract are in general proteins or polypeptides which are lipid insoluble and of high molecular weight. Other non protein polar molecules such as tartrazine (mol.wt 540) also appear to be associated with food allergy possibly because they act as haptens. Two routes have been postulated by which lipid insoluble molecules may permeate the gastrointestinal epithelium. Small polar molecules of mol. wt less than 180 daltons permeate a high frequency pathway through the enterocyte cell membrane (Höber & Höber, 1937; Fordtran *et al.*, 1965). Large molecules—e.g. dextran (mol.wt 3000) (Wheeler *et al.*, 1978) and inulin (mol.wt 5000)—are thought to permeate aqueous channels between adjacent enterocytes (Smulders & Wright, 1971). Larger molecules of dextran (mol.wt 15–1700) appear to pass through the same channels although their diffusion is restricted (van Of, de Jong & Segers, 1974). It is suggested that the dimension of this intercellular pathway in the rabbit gall bladder mucosa, approximates that of the albumin molecule (mol.wt 60 000) (van Of *et al.*, 1974). Dietary antigens may share the same pathway either intact or as fragments. The relative absorption of the polar sugars, lactulose and L-rhamnose (mol.wt 342 and 164 daltons respectively) indicates the relative contribution of these two pathways of permeation. If, as has been

suggested, there is an alteration in the barrier properties of the bowel in food allergy leading to enhanced absorption of food antigens or other large polar molecules this would be reflected in an increase in the lactulose/L-rhamnose ratio.

In coeliac disease the use of a hypertonic oral load has served to emphasize a permeability change not always demonstrated by isotonic loading (Menzies *et al.*, 1979). In this study we failed to demonstrate any consistent difference in permeability between eczematous children and the controls under isotonic or hypertonic conditions. After antigen challenge only two of the ten children showed a marked increase in permeability, one following 50 ml of milk, the other 10 mg of tartrazine.

In children with eczema associated with food allergy, no chronic increase in gastrointestinal permeability has been demonstrated in this study, and only two of ten children challenged showed an increase in permeability following an antigen challenge. It remains possible that changes in permeability too small to be detected by this method do occur. Alternatively, it has been suggested that excess absorption of antigen may occur on first exposure to the antigen in the early months of life due to a defect in IgA handling at mucosal level (Taylor *et al.*, 1973). Our finding of unimpaired gastrointestinal permeability in most eczematous children lends support to the hypothesis that once sensitized the physiological absorption of dietary antigen is sufficient to maintain an allergic response in the skin.

Our results are in marked contrast to the reported increase in absorption of polyethylene glycol 4000 (PEG 4000) in eczematous and food-allergic adults (Jackson *et al.*, 1981). However, there is an evident difference in the mucosal handling of the polyethylene glycols and the highly polar sugar molecules. In normal subjects the percentage absorption of PEG is up to 100 times that of sugar molecules of similar mol.wt (Wheeler *et al.*, 1978) and PEG absorption has been detected from the colon (Chadwick, Phillips & Hoffman, 1977) which is highly impermeable to polar molecules as small as urea (Billich & Levitan, 1969). In coeliac disease, where permeability to antigenic particles is thought to be increased (Walker & Isselbacher, 1974), percentage absorption of lactulose is increased (Menzies *et al.*, 1979) whereas that of PEG 400 is decreased (Chadwick *et al.*, 1977). These disparities have been ascribed to the higher lipid solubility of PEG (Wheeler *et al.*, 1978) which may therefore not be absorbed exclusively by the polar route but also by the lipophilic route through the cell membrane lipids. Furthermore, the distribution of the polyethylene glycols after absorption and their renal handling have not been fully established by intravenous loading in man (Blatzinger, Rominal & Ecknauer, 1981). The high urinary excretion of PEG 4000 in the latter 12 hrs of a 24-hr save in eczematous and food-allergic subjects may indicate an alteration in colonic permeability. Equally it may indicate differences in gastrointestinal transit or, perhaps less likely, changes in body fluid distribution or renal function.

Acknowledgments

R.C. Beach was supported by the Endowments Fund at St Thomas' Hospital. We thank Mrs Gale Willner for typing the manuscript.

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