Food intolerance and allergy in gastro-intestinal disorders

Keith LE Dear

Approximately 60 tonnes of food passes through the gastrointestinal tract in an average lifetime. With a surface area second only to the respiratory tract, it is surprising that adverse reactions to food do not occur more frequently.

The concept of dietary modification to improve symptoms is not new. As far back as 1771, Sir George Bates presented a patient to the Royal College of Physicians whose abdominal symptoms improved on a diet of 'sea biscuits and salt meat'. Although the mechanisms of food-induced injury are well characterized for conditions such as food allergy and coeliac disease, there is increasing evidence that diet may play a role in other gastrointestinal conditions, such as irritable bowel disease, Crohn's disease and, to a lesser extent, ulcerative colitis. The following is a review of the mechanisms involved in food allergy and food intolerance and the possible role diet may have in gastrointestinal diseases.

FOOD ALLERGY

Food allergy affects 4–6% of children and up to 2% of adults. A limited number of foods are responsible for the majority of allergic reactions, notably milk, eggs, peanuts and seafood. Most true food allergies are mediated via a type 1 hypersensitivity reaction, with pre-sensitized immunoglobulin (Ig) E antibodies on the surface of mast cells binding the food allergen, resulting in mast cell degranulation (*Figure 1*). Release of proinflammatory mediators from mast cells, such as histamine, proteases, heparin proteoglycans and chemotactic factors, results in increased bowel wall permeability, increased mucus production, inflammatory cell infiltrate and stimulation of pain fibres. This results in pain, diarrhoea, nausea and vomiting together with non-gastrointestinal symptoms, e.g. asthma, rhinorrhoea, urticaria and even angio-oedema.

Food allergy is diagnosed by a history of recurrent symptoms on exposure to a particular food in association with evidence of an immunological reaction. Such reactions are demonstrated by use of skin prick tests or measurement of food allergen–IgE complexes by either a radioallergosorbant test (RAST) or an enzyme-linked immunosorbant assay. A true food allergy should be confirmed by a double-blind food challenge.

Despite its prevalence, food allergy is a relatively uncommon cause of gastrointestinal symptoms. Bentley et al (1983) demonstrated food allergy by immunological tests in only three out of 27 irritable bowel syndrome (IBS) subjects, all of who had a history of atopy. Petitpierre et al (1985) highlighted the importance of an atopic history, demonstrating that nine out of 14 patients with food-related symptoms were considered atopic by classical criteria (personal and family history, atopic symptoms, positive immediate skin tests and RAST).

Sometimes foods appear to provoke symptoms only after a period of time, from hours to days, which are therefore difficult to detect clinically by use of food histories or double-blind challenges. Such reactions usually are not IgE-mediated but may be associated with IgG antibodies, in particular IgG4. IgG receptors have also been demonstrated on mast cells and basophils.

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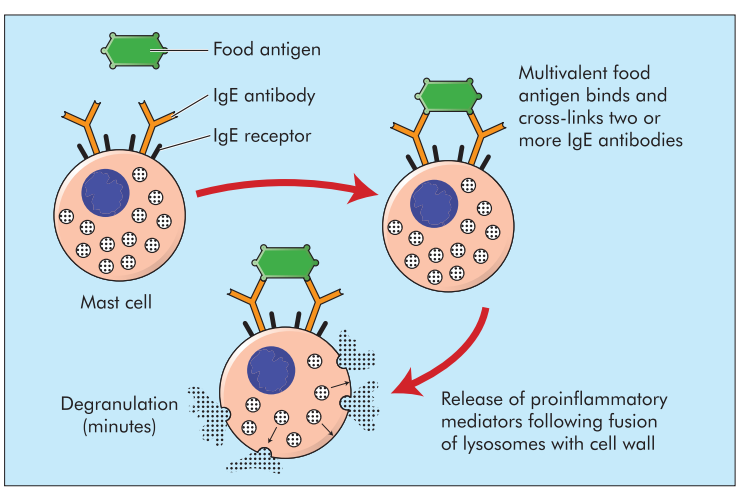

Figure 1. Schematic depiction of the immunogenic events in an immunoglobulin E (IgE)-mediated inflammatory response.

FOOD INTOLERANCE

Although true food allergy is relatively uncommon, many individuals complain of symptoms provoked by certain foods without evidence of an immunological basis. These individuals are often described as being food intolerant. Food intolerance occurs in up to 50% of IBS subjects among whom the incidence of classical IgE immunological reactions to food is low (Nanda et al, 1989). Moreover, Dainese et al (1999) demonstrated no significant difference in the prevalence of positive skin prick tests to common intolerant foods between IBS subjects with food intolerance and those without. Such food reactions may lead to a wide variety of gastroenterological and non-gastroenterological symptoms (*Table 1*).

Prolonged remission can be achieved in such patients by use of an 'exclusion diet', avoiding foods that commonly provoke symptoms in IBS subjects (*Table 2*). Initially, diets composed of lamb, rice and pears were used to induce remission (Bentley et al, 1983), although others have used less restrictive initial diets (Nanda et al, 1989). A single food is then reintroduced to the diet every 24–48 hours. Any food provoking symptoms is avoided and intolerance to that food is confirmed by repeat exposure, preferably double-blinded.

TABLE 1.
Analysis of presenting symptoms suffered by 122 patients subsequently found to be food intolerant

Symptoms	% of subjects presenting with symptom
Abdominal pain	73
Diarrhoea	60
Tiredness	42
Headaches	38
Constipation	22.5
Abdominal distension	21.5
Migraine	11
Atopy	10

From Hunter et al (1985)

TABLE 2.
Foods commonly implicated in food intolerance

Food	% subjects reacting	Food	% subjects reacting
Cheese	35.2	Tea	17.6
Onions	35.2	Soft fruit	7.7
Milk	31.9	Yeast	5.5
Wheat	29.7	Tomatoes	5.5
Chocolate	27.5	Fish/shellfish	2.2
Coffee	24.2	Colourings	2.2
Egg	23.3	Pork	2.2
Nuts	18		

From Nanda et al (1989)

MECHANISMS OF FOOD INTOLERANCE

There are several non-immune mechanisms by which food may precipitate symptoms. Food constituents may have a direct toxic effect, such as vasoactive amines in cheese, wine, avocados and bananas, oxalates in rhubarb and alkaloids in mushrooms. Additives also may have toxic effects, such as monosodium glutamate, benzoate, nitrites and colouring agents. However, many of the exclusion diets used contain considerable amounts of such bioactive ingredients, and therefore other pathogenic factors in food must exist.

DISACCHARIDASE DEFICIENCIES

Gastrointestinal enzyme deficiencies are a relative common cause of gastrointestinal symptoms, with lactose intolerance occurring in up to 25% of IBS subjects, although only approximately half of such patients respond to lactose restricting diets (Verria et al, 1995). However, many of the studies demonstrating food intolerance in IBS have specifically excluded lactose intolerance.

Similarly, Rumessen and Gudmand-Høyer (1988) demonstrated fructose malabsorption to occur in up to half of IBS subjects. This was exacerbated by addition of other non-absorbed sugars, such as sucrose, leading to a worsening of symptoms. However, the same authors showed that malabsorption of fructose also occurs in healthy individuals without gastrointestinal symptoms. Therefore, symptoms provoked by malabsorption of sugars in IBS may be the result of a reduced sensory threshold for colonic distension. Such hyperalgesia is commonly seen in IBS (Whitehead et al, 1990).

PROSTAGLANDINS

Administration of prostaglandins PGE_2 and $PGF_{2\alpha}$ provoke gastrointestinal symptoms, such as nausea, vomiting, colicky abdominal pain and bloating. Food intolerant subjects have been shown to have a rise in both serum and stool PGE_2 and $PGF_{2\alpha}$ following exposure to the intolerant food. Moreover, use of non-selective prostaglandin inhibitors has been demonstrated to be associated with an improvement of symptoms, together with a reduction of prostaglandin levels (Buisseret et al, 1978). Such alteration in prostaglandin production in food intolerant subjects has not been consistently found by others (Alun Jones et al, 1982).

BACTERIAL FLORA

Diet has a direct effect on the composition of an individual's gut flora. Chemically refined diets

lead to a loss of highly sensitive anaerobes in the faeces, in particular *Bifidobacteria* and anaerobic cocci. Abnormalities of the faecal flora can be demonstrated in many patients with IBS, in particular a reduction in *Bifidobacteria* spp. and an increase in facultative species, such as *Pseudomonas* spp. and *Enterobacteriae* spp. (Balsari et al, 1982). However, owing to the vast number of species within the gut and inter-individual differences, accurate characterization of any changes of gut flora is difficult. Food intolerant IBS subjects have also been demonstrated to have quantitative differences in bacterial activity, with greater rates of bacterial fermentation resulting in the production of greater volumes of the gaseous products of fermentation, hydrogen and methane. Reduction of the rate of fermentation in such individuals can be achieved using an exclusion diet and is associated with an improvement of symptoms (King et al, 1998).

Therefore, food intolerance in IBS may be secondary to changes in the gut flora, leading to increased rates of fermentation. It is interesting that many of the proven risk factors in IBS have potential to alter gut bacteria, such as gastroenteritis and antibiotics. Hydrogen produced by fermentation is usually utilized by other species of bacteria, such as methanogenic and sulphur-reducing species, but may occur at such rates to overcome utilization by other sources, leading to distension of the bowel and painful symptoms. The rectal hyperalgesia frequently demonstrated in this condition can be induced following repetitive distension of the colon (Munakata et al, 1997) and may be a consequence of increased fermentation rates. Such findings may also explain why fibre supplementation may actually worsen symptoms in many IBS subjects, leading to increased rates of fermentation. Indeed, many subjects appear to improve on fibre-restricted diets (Woolner and Kirby, 2000).

ALTERATIONS IN CYTOKINES

Abnormalities in cytokines have been demonstrated following food challenges in food intolerant individuals, resulting in an increased production of pro-inflammatory cytokines associated with the T helper 1 and T helper 2 pathways (interleukin (IL)-4, tumour necrosis factor (TNF)-α and interferon (IFN)-γ) and a decrease in the anti-inflammatory cytokine IL-10. Such changes were observed without evidence of a type 1 hypersensitivity reaction (Jacobsen et al, 2000). Certain bacterial species can induce changes in cytokine production within the gut. Therefore, changes in cytokine production following a food challenge may result from selective stimulation of groups of bacteria by the food that in turn stimulate the host's cytokine response.

FOOD INTOLERANCE IN CROHN'S DISEASE

Since IBS affects approximately 12% of the population, most cases of food intolerance are included within this broad category. However, food antigens have been demonstrated to play a part in other gastrointestinal disorders, most notably Crohn's disease. Several authors have demonstrated the efficacy of elemental diets in inducing remission in Crohn's disease. Such diets contain food elements in their basic format – protein as amino acids, carbohydrate as maltodextrins and sugar, fat as small quantities of defined oils, with the addition of vitamins and minerals.

It was initially believed that such diets lead to remission by avoiding antigenic whole proteins, although it has been subsequently shown that feeds containing oligopeptides or even whole proteins are equally as effective (Royall et al, 1994). However, elemental feeds are absorbed in the proximal bowel and minimize the intestinal contents reaching the colon, reducing bacterial numbers and hence bacterial antigens. Intestinal contents, of which bacteria comprise the major part, appear essential for the development of Crohn's disease since recurrent anastomotic disease may be prevented by diverting the faecal stream via formation of a proximal ileostomy. However, ulceration reoccurs within 6 months of closing the proximal stoma (Rutgeerts et al, 1991).

Although approximately 80% of patients respond to elemental diets, the majority of patients relapse once they start a normal diet. Teahon et al (1990) reported that only 38% remained in remission at 3 years following restarting a normal diet. Prolonged remission may be achieved by use of similar exclusion diets as used in IBS. Alun-Jones et al (1985) were able to maintain seven out of ten individuals in remission by use of such diets compared with none out of ten in patients fed a standard diet.

MECHANISMS OF FOOD INTOLERANCE IN CROHN'S DISEASE

The mechanism of food intolerance in this disorder is unclear, although raised levels of IgE have been demonstrated in active disease, with evidence of mast cell degranulation implying that classical food allergy may play a role. However, Jewell and Truelove (1972) demonstrated that immunological reactions to milk proteins, one of the most commonly recognized intolerant foods, did not occur any more commonly in inflammatory bowel disease than in controls.

Cellular mechanisms may also be altered in Crohn's disease, with altered tolerance to luminal antigens resulting in an inflammatory response rather than a suppressor response. The importance of a TGFβ-mediated suppressor response has been demonstrated in the trinitrobenzenesulphonic acid (TNBS)-induced murine model of colitis, where upregulation of the suppressor system by oral administration of TNBS-haptenized proteins has been shown to prevent colitis in mice following TNBS rectal infusion. If the same is repeated with anti-TGFβ, then colitis ensues, demonstrating the pivotal role of TGFβ (Kapikaan and Chanock, 1996). Impaired suppressor responses may play a role in food reactions in Crohn's disease, although there is no evidence yet to support this.

FOOD INTOLERANCE AND ULCERATIVE COLITIS

Several authors have demonstrated a subset of colitics who appear to respond to a milk-free diet and in whom reintroduction of milk precipitated symptoms. Raised antibodies to milk have been demonstrated in such individuals, but there appears to be no correlation between antibody titres and the severity of disease. Others have reported a ten-fold higher incidence of infantile cow's milk sensitivity in those who subsequently develop colitis, suggesting such sensitization may initiate the development of autoantibodies against the colonic mucosa. However, the majority of patients with ulcerative colitis show no improvement with dietary modification.

CONCLUSIONS

Diet has been demonstrated to play a role in many gastrointestinal disorders as well as in many non-gastrointestinal disorders, such as rheumatoid arthritis, asthma and dermatitis, all of which may improve on exclusion diets. Although disease mechanisms are well established in classical food allergy, the mechanisms involved in food intolerance are less clear. There is increasing evidence that diet may be beneficial in food intolerant individuals by altering the gut flora and influencing colonic fermentation. As such, diet provides a non-toxic treatment for individuals with a wide range of conditions. **HM**

KEY POINTS

- A diagnosis of food allergy requires a history of recurrent symptoms on exposure to the food allergen in conjunction with evidence of an immune response to that food.
- Food allergy is mediated by an immediate type 1 immunoglobulin (Ig) E immune response, although delayed IgG-mediated reactions may occur.
- Although food allergy is common, it is a relatively unusual cause for gastroenterological symptoms in the community.
- Food intolerance accounts for up to 50% of gastroenterological symptoms fulfilling the criteria for irritable bowel syndrome, and prolonged remission may be achieved by dietary restriction.
- Food intolerance is not immune mediated but may occur owing to the influence of diet on the composition of the gut flora.
- Food also appears to play a role in the pathogenesis of Crohn's disease, and similar dietary restrictions may result in prolonged remission in many patients.
- Milk-free diets may benefit a minority of patients with ulcerative colitis, although there is no evidence to suggest an immune response to milk in this condition.

Table 1 *is reproduced by kind permission of the authors and publishers.*
Conflict of interest: none.

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