Antigen absorption: food, fire or fuel?

KR Kamath, MD, FRACP, DCH

Department of Gastroenterology, Royal Alexandra Hospital for Children, Sydney, Australia

The epithelium of the gastrointestinal tract is constantly exposed to varieties of antigens. In healthy individuals, only small amounts of ingested dietary antigens are absorbed. The normal immune response to absorbed food antigens is one which, without causing disease, breaks down tolerance to a specific antigen. Breakdown in tolerance may result in a spectrum of clinical problems, including food allergy, food sensitive enteropathy and food intolerance ("fire"). When food-sensitive enteropathy is subclinical, continued ingestion of the offending food antigen may result in development of tolerance and resolution of the enteropathy. The development of tolerance to a specific food antigen under these circumstances may be prevented by briefly excluding the antigen from the diet, substituting it with a different antigen and then reintroducing the first antigen. In this situation, the second food antigen not only prevents the mucosal reaction expected if the infant had been continuously fed the food containing the first antigen, but frequently prevents the lesions when the first antigen is reintroduced ("fuel"). While genetic constitution seems to be the major player in the heightened IgE response/secretion in atopic subjects, the pathophysiology of food-specific enteropathy in food sensitive children is less well understood. Complex interactions between environmental factors such as breast feeding and host factors such as the integrity of the absorptive gut epithelium and its immunomodulatory responsiveness at the time of introduction of novel food antigens seem to be important in its genesis as well as its tendency to be a transient disorder of infancy.

Introduction

The gastrointestinal epithelium is repeatedly exposed to a variety of dietary, microbial and other antigens from the immediate post-natal period. Although adverse reactions to food antigens are uncommon, there is now a great deal of both in vivo and in vitro evidence which indicates that small amounts of antigens gain access to the tissues after penetrating the gastrointestinal epithelium in children as well as in adults. In normal hosts the entry of such antigens into the intestinal mucosa may be followed by various consequences and results in a state of immunological tolerance. Antigen entry into the intestinal mucosa may, however, have a significant pathogenic role in a variety of human disorders, including food allergy, coeliac disease and transitory food sensitive enteropathies (FSE) in children. This review will address the physiology and development of the effects of antigen absorption and the immunological response of the normal host to the absorbed antigen, and discuss the complex interplay between food antigens, antigen absorption and abnormal immunological responses to the antigens in the pathogenesis of transient FSE in children.

Antigen absorption in the normal host

The intestinal lumen of the exclusively breast-fed infant contains only trivial amounts of foreign dietary antigens, presumably from foods consumed by the mother. In contrast, the gut lumen of the formula-fed infant is exposed to varieties of food proteins which are potential sources of numerous foreign antigens. The normal gastrointestinal tract is endowed with a highly efficient machinery to minimise entry of food antigens into the mucosa and body tissues (Tables 1 and 2). Furthermore, the small amounts of food antigens which normally gain access to tissues across the absorptive epithelium, usually fail to evoke adverse local or systemic effects, thanks to an ingenious and efficient immune system.

Table 1. Intestinal barrier for antigen absorption: non-specific mechanisms

A. Mucin layer

B. Digestive

C. Structural

Table 2. Intestinal barrier for antigen absorption: non-specific mechanisms

Non-specific mechanisms which minimise antigen absorption

The normal gastrointestinal tract has a very efficient digestive system which ensures an almost complete enzymatic breakdown of ingested proteins into non-antigenic peptides and amino acids. The extent to which different food proteins are degraded and rendered either non-antigenic or immunogenic is a function of intestinal functioning. It is shown that some dietary proteins are degraded incompletely in immature animals, compared with mature animals, resulting in immunogenicity to enterocyte.

Correspondence address: K. Ramamoorthy, Department of Gastroenterology, Royal Alexandra Hospital for Children, PO Box 3515, Parramatta, NSW 2124, Australia. Tel: +61-2-845-3999 Fax: +61-2-845-3970.
microvillus membranes. In the human, the mucosal barrier absorption by histologically normal intestinal mucosa in childhood has been shown to be a normal phenomenon in the gut lumen. In keeping with the observation that the gut lumen is the site of origin for many infections, increased macromolecular absorption has also been demonstrated in premature infants.

A critical determinant of macromolecular absorption is the structural integrity of intestinal epithelium. A study using intestinal organ culture showed increased number of enterocytes permeable to macromolecules in histologically abnormal mucosa compared with normal mucosa. Increased mucosal permeability to large molecular weight (4000 kDa) polyethylene glycol has been found in patients with food allergy and atopic dermatitis, or atopic dermatitis alone. These patients had mucosal histological abnormalities that were not known as morphological studies had not been carried out. Finally, increased macromolecular absorption has also been observed in severely malnourished children. From these aforesaid studies, it is clear that antigen absorption is a normal physiological phenomenon and that increased antigen absorption is a consequence of either intestinal immaturity or increased passive permeability of damaged enterocytes.

Some children with food induced disorders such as cow’s milk allergy (CMA) and coeliac disease have been known to develop intestinal symptoms when they consumed the offending foods and would either spit out or vomit the food if forced to ingest them. Although such a “protective” behaviour might help prevent the child from future exposure, with consequent decreased antigen absorption, it might also contribute to serious nutritional consequences such as failure to thrive, impaired growth and malnutrition.

Table 2. Intestinal barrier for antigen absorption: specific mechanisms

| A. | Secretory immunoglobulin A (sIgA) |
| B. | Human milk IgA (Breast-fed infants) |

Specific mechanisms which minimise antigen absorption

In addition to the non-specific intestinal mechanisms which mitigate against excessive entry of antigens into the epithelium and lamina propria discussed above, the gastrointestinal tract mounts a significant local immune response to dietary antigens through the gut associated lymphoid system. (GALT) T lymphocytes have been shown to migrate into human fetal intestine at about 12-14 weeks gestation, and their numbers increase gradually thereafter. By about 20 weeks of gestation, these T-cells are capable of responding to luminal stimuli by the production of cytokines such as interleukin-2 (IL-2) and interferon gamma. However, GALT is capable of responding to food antigens by production and secretion of secretory immunoglobulin A (sIgA) to the epithelial luminal surface. This response aids in diminishing antigenic absorption by increasing the ability of brush border peptidases to completely hydrolyse antigenic peptides into non-antigenic molecules. The sIgA response, however, is not developed in premature infants until about 35 weeks gestation.

Maturatiom of the sIgA response occurs throughout infancy and early childhood. A recent study which measured salivary IgA in infants showed that sIgA increased more rapidly in the first six months after birth in infants who were exclusively breast-fed than in those who were exclusively bottle-fed. Human milk contains soluble factors mitogenic to B-cells. These factors include 2’,5’-oligoadenylates, IL-6 (IL-1β), IL-13. IL-6 has been shown to stimulate IgA synthesis by human appendix B-cells. Further, recent study by Ramaswamy et al in which targeted disruption of the gene that encodes IL-6 in mice resulted in greatly reduced numbers of IgA-producing cells at mucosa, the mucosal defect in IgA secretion as well as antigen-specific IgA antibody production could be restored by IL-6 expression. Local application of IL-6 induced a significant increase in vifucanina virus. These interesting observations suggest a convincing physiological role for human milk in regulating antigen absorption by the infant gut when the gastrointestinal tract is most vulnerable to immunopathologic insults due to enhanced absorption of luminal antigens.

Normal response to absorbed dietary antigens

The small quantities of food antigens that are normally absorbed evoke local as well as systemic immune responses which may promote or inhibit antigen absorption. The mechanism of these responses has been the subject of considerable interest. The molecular and cellular mechanisms of these responses are still largely unresolved. Because the mucosal immune system is highly efficient and exquisitely adapted to the gut environment, the immune response to dietary antigens is a complex and highly regulated process. The gut immune system is designed to prevent the entry of harmful antigens into the body, while allowing the passage of beneficial antigens that are essential for normal gut function.

Adverse gastrointestinal reactions to food antigens

Normal antigen absorption followed by the development of food sensitivity is not a common event. Small and major intestinal, maturational process which is susceptible to complex modulatory effects of genetic and environmental influences. Failure of development of tolerance or the loss of development of tolerance after it has already been established is a potential threat, albeit small, associated with repeated food consumption. Considering the fact that all ingredients for a potentially serious and even lethal adverse reaction to food are present in close proximity within the gut micro-environment, it is, food antigens in the human, antigen processing cells in the mucosa and T-lymphocytes in the epithelium and lamina propria, it is indeed surprising that food sensitive gastrointestinal disease does not occur in all individuals. Fortunately, such reactions occur in less than 10% of the population. Not unexpectedly, they are more common in young infants in their first few weeks and months of life than in older children and adults. The clinical spectrum of food-induced immunological disorder is indeed quite wide, and at least one half of affected children show predominantly gastrointestinal symptoms. With the exception of IgA mediated reactions, convincing evidence for causal relation between any immune reaction to food antigens and adverse clinicopathological disorders has not been established. Further discussion of various immunopathological and non-immunological mechanisms through which food antigens contribute to the development of adverse reactions to foods is beyond the scope of this review. An excellent recent review of food allergy in children is provided by Stern.

A list of common and some uncommon gastrointestinal manifestations of food protein-induced adverse reactions in children is shown in Table 3. Among the various features listed, bloody diarrhea due to colitis in infants less than three months of age deserves special mention. It is particularly, though not exclusively, seen in entirely breast-fed infants and is a transient disorder with spontaneous remission in the majority of cases. Clinically, the early age at which it usually occurs, the self-limiting nature of the illness and the fact that it resolves without sequelae make the diagnosis of this entity relatively straightforward.

The European Society for Paediatric Gastroenterology and Nutrition has established a working group for the diagnostic criteria for food allergy. Recommendations of this expert group should be of further interest to those interested in food allergy.

Table 3. Gastrointestinal manifestations of adverse reactions to food antigens

| A. | Acute |
| B. | Chronic |

Food sensitive enteropathy (FSE)

Small intestinal mucosal (enteropathy) is now a well-recognised histopathological feature of gastrointestinal adverse reactions to food in children. While cow’s milk protein (CMP) and soy protein have been shown to be the most common antigens involved, FSE has been shown in documented to be related to egg, rice, fish, gluten and other food antigens. With the exception of IgA-sensitive enteropathy (coeliac disease) FSE caused by other dietary antigens is usually a transient disorder affecting children in the first 2-3 years of life. The enteropathy resolves completely when offending antigens are excluded from the child’s diet but it recurs if the antigen is reintroduced into the diet within a few weeks or months. After prolonged periods of exclusion, however, usually 12 months or more, the enteropathy does not recur and the child remains tolerant to the food protein(s) thereafter. In contrast, classic coeliac disease is a chronic, relapsing and permanent lifelong phenomenon. The immunological mechanisms that result in failure of development of tolerance or, less commonly, breakdown in established tolerance to food protein and FSE are not well understood. Immunonegativity of the antigens, structural integrity of the gut epithelium, lamina propria factors such as microbial flora and the mucosal immune system appear to be crucial in the development of food-induced gastrointestinal immuno-reactivity during critical, particularly vulnerable periods of life, such as infancy and during recovery from acute viral gastroenteritis. All have been considered to be important. The intestine of young infants seems to be particularly vulnerable to disturbances of regulatory mechanisms which normally prevent immunopathologic damage due to antigen entry into the mucosa. The histological and immunopathological lesions of the mucosa in FSE have all the hallmarks of damage caused by abnormally activated T-lymphocytes. The remarkable similarities in immunopathological lesions seen in the mucosa of human foetal intestinal explants which have been exposed in vitro to various lamina propria mitogens to FSE induced in the rat suggest that the lesions seen in FSE lend strong support to this hypothesis. Recent studies which employed sophisticated molecular genetic techniques to selectively inactivate IL-10 gene and create spontaneous nontolerogenic IL-10 precursor cell line and secretion have thrown further light on immunological mechanisms which may be relevant to FSE. In this IL-10 "knock-out" mouse model, the small bowel lesions resulting in impaired growth and anemia consequent to malabsorption bear remarkable similarity to FSE in infants. A role for luminal antigen stimuli in the immunopathology of the small intestinal lesions of this mouse model became apparent when it was observed that the lesions attenuated when the mutants were cared for in a specific-pathogen-free environment. Uncontrolled antigenic stimuli in IL-10 deficient mice may have been responsible for enhanced stimulation and activation of T-helper cell subset 1 (Th-1). IL-10 is known to suppress the macrophage-dependen activation of Th-1 cells and natural killer cells (NK). Enhanced production of cytokines by Th-1 cells and NK, and the specific effects of these cytokines on enterocytes such as ablation of cell proliferation of LMW in their support, and the role of IL-10 in the prevention of the plaste of normal development of B-lymphocytes into antibody producing plasma cells under the influence of Th-2 cells and lamina propria antigens entering the mucosa, may account for the observation. The chain of events starting with antigen entry into the mucosa, followed by dysregulated and enhanced activation of T-cells which culminates in the development of food protein sensitivity, tolerance, and culminating in a clinical syndrome of FSE with chronic diarrhea, malabsorption, failure to thrive.
micrivial membranes. In the human, the macromolecular absorption by histologically normal intestinal mucosa in childhood has been shown to be a "normal phenomenon". In adults, in keeping with experimental work in immature animals, increased macromolecular absorption has also been demonstrated in premature infants.

A critical determinant of macromolecular absorption is the structural integrity of intestinal epithelium. A study using intestinal organ culture showed increased number of enterocytes permeable to macromolecules in histologically abnormal mucosa compared with normal mucosa. Increased mucosal permeability to large molecular weight (4000) polyethylene glycol has been found in patients with food allergy and atopic dermatitis, or atopic dermatitis alone. In these patients, possible histological abnormalities are not known as morphological studies had not been carried out. Finally, increased macromolecular absorption has also been demonstrated in severely malnourished children. From these aforementioned studies, it is clear that antigen absorption is a normal physiological phenomenon and that increased antigen absorption is a consequence of either intestinal immaturity or increased passive permeability of damaged enterocytes. Some children with food induced disorders such as cow's milk allergy (CMA) and cow's milk protein intolerance, a term preferred by the offending foods and would either spit out or vomit the food if forced to ingest them. Although such a "protective" behaviour might be beneficial, with consequent decreased antigen absorption, it might also contribute to serious nutritional consequences such as failure to thrive, impaired growth and malnutrition.

Table 2. Intestinal barrier for antigen absorption: specific mechanisms

| A. Secretory immunoglobulin A (sIgA) | B. Human milk IgA (Breast-fed infants) |
---|---|

Specific mechanisms which minimize antigen absorption

In addition to the non-specific intestinal mechanisms which militate against excessive entry of antigens into the epithelium and lamina propria discussed above, the gastrointestinal tract mounts a significant local immune response to dietary antigens through the gut associated lymphoid system. (GALT) T lymphocytes have been shown to migrate into human fetal intestine at about 12-14 weeks gestation, and their numbers increase gradually thereafter. By about 20 weeks of gestation these T-cells are capable of responding to luminal stimuli by the production of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-gamma). GALT is capable of responding to food antigens by production and secretion of secretory immunoglobulin A (sIgA) to the epithelial luminal surface. This response aids in diminishing antigen absorption by increasing the ability of brush border peptides to completely hydrolyze antigenic peptides into non-antigenic 

The sIgA response, however, is not developed in premature infants until about 35 weeks gestation. Maturation of the sIgA response occurs throughout infancy and early childhood. A recent study which measured salivary IgA in infants showed that sIgA increased rapidly in the first six months after birth in infants who were exclusively breast-fed than in those who were exclusively bottle-fed. Human milk contains soluble factors mitogenic to B-cells. These factors include, among others, the IL-6 and interleukin-6 (IL-6) cytokines. IL-6 has been shown to stimulate IgA synthesis by human appendix B-cells. Further, recent study by Ramsay et al in which targeted disruption of the gene that encodes IL-6 in mice resulted in greatly reduced numbers of IgA-producing cells at mucosa, the mucosal defect in IgA secretion as well as antigen-specific IgA antibody production could be restored by expression of IL-6. Immunological mechanisms through which IL-6 may be important in the genesis of adverse reactions to food is beyond the scope of this review. An excellent recent review of food allergy in children is provided by Stern. A list of common and some uncommon gastrointestinal manifestations of food protein-induced adverse reactions in children is shown in Table 3. Among the various features listed, bloody diarrhoea due to colitis in infants less than three months of age deserves special mention. It is particularly, though not exclusively, seen in entirely breast-failed infants and is a transient disorder with complete resolution in the absence of milk in the diet. Close clinical observations suggest an aetiologic role for food antigens from maternal diet which have been secreted into breast milk, the result of which is currently under investigation. The European Society for paediatric gastroenterology and nutrition has established a working group for the diagnostic criteria for food allergy. Recommendations of this expert group should be of further interest to those interested in food allergy.

Table 3. Gastrointestinal manifestations of adverse reactions to food antigens

<table>
<thead>
<tr>
<th>A. Acute</th>
<th>B. Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Diarrhoea associated with Colic</td>
<td>Haematemesis (rare)</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Anorexia, food aversion</td>
</tr>
<tr>
<td>Anaemia</td>
<td>Intestinal failure</td>
</tr>
<tr>
<td>Bloody diarrhoea due to colitis</td>
<td></td>
</tr>
</tbody>
</table>

Food specific enteropathy (FSE)

Small intestinal enteropathy (enteropathy) is now a well-recognized histopathological feature of gastrointestinal adverse reactions to food in children. While cow's milk protein (CMP) and soy protein have been known to cause enteropathy in the common antigen involved, FSE had been documented in relation to egg protein, rice, fish, gluten and others. With the exception of gluten-sensitive enteropathy (coeliac disease) FSE caused by other dietary proteins is usually a transient disorder affecting children in the first 2-3 years of life. The enteropathy resolves completely when offending antigens are excluded from the child's diet but it recurs if the antigen is reintroduced into the diet within a few days or weeks. After prolonged periods of exclusion, however, usually 12 months or more, the enteropathy does not recur and the child remains tolerant to the food protein(s) thereafter. In contrast, critical importance to gluten-induced enteropathy is its permanent and lifelong phenomenon. The immunological mechanisms that result in failure of development of tolerance or, less commonly, breakdown in established tolerance to food protein and FSE are poorly understood. Immunogenicity of the antigens, structural integrity of the gut epithelium, luminal factors such as microbial flora and breast milk, as well as genetic factors, are all important factors in gastrointestinal immune reactivity during critical, particularly vulnerable periods of life, such as infancy and during recovery from acute viral gastroenteritis have all been considered to be important. The intestine of young infants seems to be particularly vulnerable to disturbances of regulatory mechanisms which normally prevent immunopathologic damage due to antigen entry into the mucosa. The histological and immunopathologic lesions of the mucosa in FSE have all the hallmarks of damage caused by abnormal activation of T-lymphocytes. The remarkable similarities in immunopathologic lesions seen in the mucosa of human foetal intestinal explants which have been exposed in vitro to various luminal mitogens to that seen in human infants in vivo and in patients with gluten sensitive enteropathy in FSE lend strong support to this hypothesis. Recent studies which employed sophisticated molecular genetic techniques to selectively inactivate IL-10 gene and create conditional knockout mice have shown that the IL-10 promoter region and secretion have thrown further light on immunological mechanisms which may be relevant to FSE. This in IL-10 "knock-out" mouse model, the small bowel of these mice shows lesions resulting in impaired growth and anemia consequent to malabsorption bear remarkable similarity to FSE in infants. A role for luminal antigenic stimuli in the immunopathology of the small intestinal lesions in this mouse model became apparent when it was observed that the lesions attenuated when the mutants were cared for in a specific-pathogen-free environment. Uncontrolled antigenic activation in IL-10-deficient mice may have been responsible for enhanced stimulation and activation of T-helper cell subset 1 (Th-1). IL-10 is known to suppress the macrophage-dependent activation of Th-1 cells and natural killer cells (NK). Enhanced production of cytokines by Th-1 cells and NK, and the specific effects of these cytokines on enterocytes such as aberrant expression of MHC class II molecules in their surface, may contribute to the failure of normal development of B-lymphocytes into antibody producing plasma cells under the influence of Th-2 cells and luminal antigens entering the mucosa, and the disease model. The chain of events starting with antigen entry into the mucosa, followed by dysregulated and enhanced activation of T-cells which leads to local and systemic immune tolerance, and culminating in a clinical syndrome of FSE with chronic diarrhoea, malabsorption, failure to thrive.
Antigen absorption: food, fire or fuel?

KR Ramath

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?

Antigen absorption: food, fire or fuel?
with growth and nutritional deficit can therefore be justifiably described as "fire" caused by antigen absorption.

Causative effect of antigenically unrelated food proteins in potentiating mucosal lesions in FSE

In common with many other forms of intestinal mucosal insults, the mucosal damage in FSE is not always accompanied by clinical manifestations. After exclusion of the offending antigen from the diet, however, both the mucosal damage and symptoms resolve. This suggests that the mucosal damage is initiated and maintained by continued antigen entry in the phase of perturbed and heightened immunoreactivity to the antigens. Some infants whose FSE is caused by CMP are often found to be intolerant to other antigenically unrelated proteins such as SP. This phenomenon is particularly common if SP is introduced into the diet when the mucosal damage caused by CMP has not yet resolved. In this scenario, there is progressive damage to the small bowel mucosa, suggesting the possibility that the mucosal damage induced by one protein increases permeability of the mucosa to other antigens, consequently leading to more severe mucosal response to the second food protein antigens.

In a substantial proportion of infants with FSE caused by CMP, it has been observed that if the mucosal damage caused by CMP is subclinical, then complete resolution of the lesion may yet occur despite continued ingestion of CMP, suggesting that tolerance develops despite increased permeability of the epithelium to antigens in some infants. In some similar cases of FSE due to SP, we have observed worsening of mucosal damage and overt clinical symptoms due to SP if the infant was taken off SP, placed on CMP for 12 to 24 hours and was then re-fed SP. It is probable that interposition of CMP had injured the mucosa further and made it vulnerable to SP challenge in these infants. This phenomenon, where a second food protein taken later prevents the development of tolerance to the first protein taken earlier underscores the complex and changing inter-relationship between abnormal antigenal response, mucosal reactivity and food antigens. Perhaps some antigens "fuel" the "fire" caused by other antigens.

The transient nature of FSE in infants is now well known. The exact immunohistological mechanisms resulting in the development of tolerance to food antigens, however, remain poorly understood. Limited observations in Finnish children showed that the development of tolerance was associated with altered intestinal local immune response to food antigens. The intestine of infants who developed tolerance showed significant rise in food antigen-specific antibody-secreting cells of IgA isotype. Clinical tolerance seems to coincide with the ability of the mucosa to mount a local immune response to food antigens, particularly of the IgA isotype. As cytokines such as IL-4 and IL-6 and growth factors such as transforming growth factor beta 1 (TGF-β1) influence the development of mucosal IgA production, it is conceivable that tolerance is primarily associated with maturation of T cell subsets capable of influencing gut mucosal B-cells with these cytokines and growth factors.

Alternatively, the possibility that the primary event associated with clinical tolerance is restoration of epithelial integrity due to a combination of maturational events and prolonged period of antigen exclusions, and that the normal local humoral immune response coinciding with clinical tolerance is a secondary event cannot be excluded. Indeed, these two alternative mechanisms are not mutually exclusive, especially in the light of recent observations that enterocytes and intracellular lymphocytes (IEL) influence each other's function in a complementary, physiologically meaningful fashion.[24,25] In their recent elegant studies, Cepak et al[25] showed that E-cadherin expressed on the basolateral plasma membrane of enterocytes were the counter-receptors for E-cadherin immunoreceptors expressed on the plasma membrane of IEL. The unique heterophilic interaction between these two classes of counterpart-receptors would therefore explain the tissue-specific compartmentalisation of IEL. Equally important is the observation by Boivin and Havan that IEL of the γδ T subset produce keratinocyte growth factor which promotes growth of cultured epithelial cells[24] This suggests that γδ IEL have a physiological role in surveillance and repair of damaged enterocytes. In this context the observation that T cells bearing the γδ TcR represent less than 1% of CD3 + cells in the lamina propria while they constitute about 10% of IEL is highly relevant[4]. Further clinical and experimental studies to improve our understanding of the phenomenon of tolerance and sensitivity of the intestine to food antigens should be of immense value in the appropriate management and prevention of food-protein-sensitive disorders.

Acknowledgement: Miss CA Frazer for preparation of the manuscript.

References