Eur J Nutr 38:107–117 (1999)

REVIEW

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Immunological aspects of the potential role of dietary carbohydrates and lectins in human health

Received: 15 December 1998
Accepted: 15 March 1999

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Summary *Background:* Little is known regarding the immunobiology of dietary carbohydrate intake and its relevance to human health, although foodstuffs contain many simple and complex carbohydrates.
Synopsis: Lectins, immunoglobulins, viruses, bacteria and host cells interact with each other forming a delicate equilibrium within the alimentary canal which may be perturbed by saccharide intake. The ways in which these components may interact at different sites within the alimentary canal are discussed, as are the possible influences on mucosal immunity and the induction of oral tolerance. The possible systemic influences of absorbed saccharides at loci remote from the gut are considered in terms of inhibition of dietary and endogenous lectins, inhibition of bacterial attachment, and alteration of leukocyte homing behaviour. Finally, possible means by which dietary carbohydrates might modify various specific diseases are considered.
Conclusions: It is probable that dietary carbohydrates can alter the equilibria between lectins, secretory IgA and micro-organisms in the alimentary canal, and this consideration could be exploited to promote health. The possible effects of dietary saccharides on allergy/oral tolerance or on recognition events at gut-remote sites warrant further investigation.

Key words Lectins – secretory IgA – bifidobacteria – gut associated lymphoid tissue – oral tolerance

Introduction

Little is known about the immunological aspects of dietary carbohydrate intake and the potential consequences for human health. Human foods of both plant and animal origin contain a variety of simple and complex carbohydrates as well as carbohydrate-binding proteins (lectins). Both saccharides and lectins have the capacity to interfere with bacterial and viral attachment to epithelial cell surfaces within the alimentary canal, as has the major mucosal immunoglobulin, secretory IgA. It is well known that the lectin from jack fruits, jacalin, can bind to serum IgA_1, but secretory IgA also possesses oligosaccharide receptors for bacterial lectins in fimbriae and can agglutinate *E. coli* by this antigen non-specific mechanism (92). Indeed, all of a small group of lectins tested were found by immunoblotting to bind to secretory IgA via the secretory component (M.A. Kerr, personal communication). Thus within the alimentary canal, IgA, lectins, bacteria, viruses and mucous membrane exist within a delicate equilibrium which potentially may be perturbed by dietary saccharides.

These interactions need not be confined to the lumen of the alimentary canal. They may be relevant to mucosal immune mechanisms within the gut wall, where antigens may provoke protective immunity or induce tolerance. Such interactions may also influence processes remote from the alimentary tract, by modulating effects on systemic metabolism. Various tissues throughout the body

contain endogenous lectins (38) some of which may be important for immune recognition, and the function of such molecules could be altered by inhibitory saccharides.

In this review, I will try to highlight areas in which normal processes may be altered by dietary consumption of carbohydrates, and suggest areas in which future research might help to identify means of tilting the balance towards health and away from pathological consequences.

Carbohydrates in the human diet

A high proportion of "dietary carbohydrate" may be starch and cellulose, but many different saccharides are present in, or are derived from, a normal diet. Dietary monosaccharides are represented by glucose and fructose. The commonest disaccharides are sucrose and lactose, but maltose and trehalose may also be present. Indeed, there is current commercial interest in expanding the application of trehalose as a food additive and freshener (37). Higher oligosaccharides like raffinose, stachyose and verbascose occur in plant food sources. Dietary polysaccharides include the glucose and fructose polymers, glycogen and inulin, homopolymers of mannose, galactose, arabinose and xylose as well as heteropolysaccharides like hyaluronic acid, chondroitin and heparin. In addition, a vast variety of glycoconjugates, glycoproteins and glycolipids occur in food stuffs, providing complex arrangements of fucose, galactose, mannose, N-acetylglucosamine, N-acetylgalactosamine, sialic acids, etc.

Milk carbohydrates have attracted particular interest as one of the protective factors responsible for the benefit of breast feeding in relation to infectious diseases (43, 91). Quantitatively, human milk contains around 5 g/l of complex oligosaccharides compared to only about 0.05 g/l in bovine milk. The most abundant free components are lacto-N-tetraose, lacto-N-fucopentaoses and sialyllactoses. Milk (bovine and human) also contains a high concentration of lactose at 40–70 g/l.

Lectins in the human diet

Plant and animal materials used as foodstuffs contain lectins as well as carbohydrates (52, 66, 72). Some of these are usually denatured by cooking, and indeed that might be necessary to avoid severe toxicity. That still leaves many other lectins which are present in foodstuffs that typically are eaten uncooked while other lectins are still active after cooking or processing (52, 66, 72). These lectin sources include fruit juices, edible fruits like tomatoes or raspberries, and salad components like mung bean or soybean sprouts, all of which might be consumed in relatively large amounts.

As a generalisation, lectins appear to be refractory to hydrolysis by digestive enzymes. There is evidence that lectins as phylogenetically distinct as those from wheat germ (11) and tomato fruits (41) can travel from the human mouth to the colon with a substantial proportion of the molecule remaining in an intact form. This is not surprising, given that a similar resistance to the digestive process has been found for various lectins introduced into the stomachs of rodents (63).

It seems likely, therefore, that dietary lectins may be biologically active throughout the human alimentary tract and any activities they may possess therein could be modified by inhibitory sugars in the diet. Lectins may also be neutralised by provoking an IgA response; certainly salivary IgA could interact with dietary peanut agglutinin, pea lectin and wheat germ agglutinin (27).

Atypical dietary lectins are the cytokines, tumour necrosis factor and interleukin 1, which are present in human milk (69, 91). Although the concept of cytokines as lectins has been questioned (discussed elsewhere: (38)), TNF is certainly a genuine lectin since its lytic activity towards *Trypanosoma brucei* can be inhibited by chitobiose and was independent of the classical TNF receptor (47). It is conceivable these cytokine lectins influence the development of the infant's immune system; a concentration of 620±183 pg TNF/ml of milk is high enough to be biologically significant (69). Transforming growth factor-β, at around 1 μg/ml, is the most abundant human milk cytokine (91); its relevance to oral tolerance will be discussed later.

In rodent models, lectins present in experimental diets induce pathological changes after binding to the lumen of the gut, and these effects may ultimately prove fatal. The best studied lectin in this regard is PHA. Yet the same PHA preparations are much less toxic when administered in the same way to rats maintained under sterile conditions (63). The reason for this is not known, but two considerations may be relevant. First, it points to the importance of the balance between lectin activity and bacterial growth in the intestine. Second, it may be significant that germ-free animals are immunologically underdeveloped.

Bacteria in the human alimentary canal

Several hundred species of bacteria are said to reside in the alimentary canal, most of which appear to be harmless or positively beneficial. The mouth is a rich source of bacteria including Viridans streptococci, *Bacteroides* and *Neisseria*, while in the throat particularly, pneumococci and *Haemophilus* species may be encountered. These buccal bacteria may survive passage through the oesophagus but are sensitive to the acidic environment of the stomach. Bacterial density increases slowly again during passage through the small intestine, then increases dramatically (perhaps a million-fold) within the colon, where

bacteroides and fusobacteria are common as well as *E. coli*, Clostridia, Peptostreptococci, *Proteus*, *Pseudomonas* and bifidobacteria.

As well as having a nutritional function (vitamin supplementation, etc.), normal gut flora possess a significant host defensive role. This function is achieved in several ways including the provision of competition against pathogens, ensuring the relative exclusion of the latter; the production of anti-microbial metabolites; and by priming the immune system, which may be particularly relevant when carried out during the period when protection is afforded by the passive transfer of maternal antibodies.

The nature of the normal flora is probably determined by a combination of many factors, including pH, relative resistance to bile/other natural anti-bacterial agents and complex inter-microbial interactions. Certainly, the characteristics of the normal flora can be altered by dietary manipulation; it would be reasonable to suppose that dietary saccharides could be relevant. Indeed, it has been shown that diets giving rise to oligosaccharides like oligofructose – a bacterial degradation product of inulin – stimulates the growth of bifidobacteria. The advantages of human breast milk over formula feeds can partly be attributed to the effects of its oligosaccharide content on bifidobacterial growth (8, 56). These bacteria are thought to be beneficial to adults as well as infants, and there is currently some interest in deliberately adding fructo-oligosaccharides to the diet (28). Such compounds are part of the fibre content of numerous plants; they resist the host digestive process and reach the colon in a largely intact state.

While some diets may promote the growth and colonisation of beneficial bacteria, conversely, foodstuffs may promote the growth and adverse consequences of pathogenic bacteria. The latter colonise epithelial surfaces via adherence factors, although disease may result from the subsequent secretion of toxins or from a host cytokine response to colonisation or toxin production (82). Adhesion factors are usually fimbriae which may be regarded as bacterial lectins. Type-1 (F1) fimbriae bind to mannose-containing structures. Mannose-resistant fimbriae, often associated with pathogenic strains, recognise other sugars like galactose, N-acetylglucosamine or sialic acids (6). P-fimbriae bind to saccharides on globosides associated with the blood group P antigen (40). Non-fimbrial adhesions may also be lectins (6); indeed, one of them is one of the very few blood group M specific lectins known (40). Bacterial toxins, too, may be sugar-binding molecules. In short, lectin-carbohydrate interactions between bacteria and host epithelia are critical to the balance of beneficial and harmful bacterial colonisation and hence to the balance between health and disease. The carbohydrate composition of dietary components might be expected to influence that balance. A list of known bacterial lectin-carbohydrate antigen receptor pairs is given in Table 1.

Table 1 Bacterial lectin – carbohydrate receptor pairs

Species	Receptor	Reference
E. coli		
(1) F1 type fimbriae	mannose structures	(6)
(2) P fimbriae	blood group P, P1 & p^k	(45)
(3) X-adhesin	Dr^a (Cromer)/ DAF	(45)
Haemophilus influenzae	An Wj (Anton); Le^a	(45)
Mycoplasma pneumoniae	Ii	(45)
Helicobacter pylori	Le^b; sialyllactose	(9, 77)
Staphylococcus aureus	Le^a	(18)
Neisseria meningitidis	Le^a	(18)
Haemophilus influenzae	Le^a	(18)

Interactions within the lumen of the alimentary canal

Mouth and throat

It is perhaps not universally appreciated that the human mouth is a rich reservoir of bacteria; ironically, it is also a rich source of anti-bacterial agents like lysozyme and IgA. Several high molecular weight glycopeptides in saliva can interact with bacteria and viruses (60). Some such compounds could be involved with the selective clearance of harmful microbes, but others have also been implicated in the formation and development of dental plaque. It is readily conceivable that competing dietary saccharides could influence the balance between healthy microflora and harmful microbes that promote caries and other oral diseases.

Dietary lectins might also interact with buccal epithelial cells and/or bacteria and viruses. Certainly for two lectins occurring in normal diets, peanut agglutinin and wheat germ agglutinin, binding to epithelial cells has been noted (26). These lectins also bound oral bacteria. Furthermore, WGA enhanced the uptake of *Streptococcus sanguis* onto epithelial cells. *Streptococcus mutans* can be agglutinated by lectins in carrots (12), avocado pears (80) and bananas (25). While the physiological significance of these observations is unclear, it is evident that dietary lectins have the potential to alter oral bacterial ecology and may be of relevance to periodontal diseases.

The mouth may also be the site of interactions the consequences of which occur elsewhere. The influence of sugars on lectins in the same meal, for example, could influence the nutritional significance of these lectins in the gut. Rea et al. (66) have related food lectin concentrations to glycemic responses and found a significant inverse correlation in both normal and diabetic individuals. Even

PHA in cooked kidney beans reduced the rate of starch digestion from white bread.

Streptococcus pneumoniae and *Haemophilus influenzae* are normal throat bacteria which can be pathogenic in the respiratory tract and sometimes in the meninges. Both colonise surfaces via fimbriae that recognise oligosaccharide receptors. This interaction can be inhibited by glycoconjugates in human milk (3). It is noteworthy that 62 % of *H. influenzae* strains tested had receptors for Lewis^a blood group antigen (18).

Stomach and duodenum

The acidic, enzyme-containing environment of the stomach appears to be inhospitable to most bacteria, although lectins and saccharides can survive it intact. Little consideration has been given to indigenous gastric flora, and gastric bacteria are often thought of only in the context of disease. In this respect, the recent literature has been dominated by work on *Helicobacter pylori* (21, 30). This bacterium has been identified as the causative agent of antral gastritis, and by implication gastric and duodenal ulcers. Associations have also been reported with adenocarcinomas and B cell lymphomas of the stomach. I am not aware of any reported benefits of inclusion or exclusion diets in preventing *H. pylori* infection – even eradication by antibiotics is difficult – but limitation of infection by lectins or saccharides is an area of future research that might prove fruitful. Indeed, Lewis^b antigen (9) and sialyllactose (77) mediate the attachment of *H. pylori* to human gastric mucosa and the latter administered orally to infected human subjects caused a significant reduction in the gastric load of *H. Pylori* (77). Moreover, colonisation and the resultant deleterious effects can be reduced by sucralfate and sulglycotide, anti-ulcer agents bearing sulphated sugar residues (78).

Intestines

The interaction of numerous lectins, but particularly PHA, with the rat small intestine has been intensively studied (63, 64). From these experiments, we can make the following generalisations: (1) To a significant extent, lectins reach the gut in a structurally intact and biologically active form; (2) lectins may bind to the gut wall and, if so, act as local growth promoters, but also as systemic toxins; (3) the toxic effects are not observed in germ-free animals, suggesting bacterial overgrowth and toxin production is crucial.

There is every reason to believe that such generalisations apply also to some of the dietary lectins. Certainly, severe enteritis can result from eating kidney beans insufficiently cooked to denature PHA (62). Pokeweed mitogen in pokeberries was toxic enough to be fatal (5). Concanavalin A deliberately ingested caused (fortunately less severe) enteric signs and symptoms (22). The lectins in normal diets do not seem to be harmful, but, if not, why not? At relatively high concentrations, wheat germ agglutinin is anti-nutritive in rats (65) and has been implicated in the pathogenesis of human Coeliac disease (42, 89). PNA in peanuts has also been implicated in human pathology (13). On the other hand, the majority of human lectins may reach the gut and interact with the gut wall in a harmless or even beneficial way.

While much work remains to be done on the effects of possibly harmful and possibly beneficial lectins, their interactions with the gut wall, and any competition between harmful and beneficial effects, these interactions are sure to be influenced by the nature and concentration of any saccharides present. Indeed, lactose, but not glucose or sucrose, was very effective in preventing enteric symptoms associated with soya bean infant formula (17). This corresponds with the sugar specificity of the soya bean lectin.

Although inhibition of specific dietary lectin activity by specific saccharide structures should be feasible, this circumstance alone is unlikely to account fully for any observed effects. The relative lack of lectin toxicity in animals raised under sterile conditions, and the widespread use of lectin-carbohydrate interactions by bacteria, implies that lectin-bacterial interactions also have to be considered. Furthermore, IgA may bind to both lectins and bacteria as an antibody or as a lectin receptor. Could the immunological immaturity of germ-free animals be relevant, damage being mediated by an inadequate or inappropriate immune response?

Dietary lectins can even survive into the colon, since they can be recovered from the faeces. The relevance of lectins in the lumen of the large intestine is not known, but at this site lectins and lectin-carbohydrate interactions could presumably affect bacterial growth and ecology.

On the basis of its mitogenic activity towards colonic cell lines and observations on human biopsy material, Rhodes and coworkers have suggested that peanut agglutinin may be carcinogenic (70, 71). Since wheat germ agglutinin and *Agaricus bisporus* lectin are non-mitogenic and antagonise the effect of peanut agglutinin on the same cell lines (96), foodstuffs containing these lectins – as well as appropriate saccharides, perhaps in fruits – might be expected to protect against colonic cancer. Is the potentially toxic action of wheat germ agglutinin on the small intestine trivial compared with the potential benefit of cancer prevention in the colon?

Certainly, reports that PHA is an anti-cancer agent in mice (61) are unlikely to lead to human clinical application. However, of more serious relevance is the anti-cancer action of the bacterial lectins PA-I and PA-II on murine tumour cells (29). These are hardly dietary lectins, but dietary considerations might influence the growth of *Pseudomonas* in the bowels. PA-I and PA-II can bind to the T and Tn blood group antigens, which are also

common human tumour-associated antigens. This may point to an unexpected mechanism by which specific enteric bacteria help to prevent tumour growth and might indicate a way diet could influence carcinogenesis indirectly via the composition of the normal microflora.

Mucosal immunity and tolerance

Non-specific and barrier protection

The mucosal barrier within the alimentary canal resembles the skin in defining a boundary with the external environment. Like the skin, the mucosal barrier must be of major importance in defence and indeed the numerous non-specific (in the immunological sense) factors in mucosal defence are probably more important than the gut associated lymphoid tissue. I am referring to such factors as peristalsis; secretion of lactoferrin, lysozyme, mucin and proteolytic enzymes; the negative charge on microvilli; tight junctions between epithelial cells; etc. These non-specific factors include a mixture of high molecular weight glycoproteins in saliva, functions proposed for which include selective clearance and adherance of bacteria and viruses (60). If so, interference with or augmentation of such a function by dietary lectins or saccharides might have harmful (lectin) or beneficial (saccharide) effects. Carbohydrates and lectins could also interfere with the presumed protective glycoconjugates in mucus.

Having acknowledged the importance of non-specific defence mechanisms, I will leave them to devote more space to the back-up system of specific or adaptive immunity.

Gut associated lymphoid tissue

The gut associated lymphoid tissue (GALT) is a major component of the mucosal associated lymphoid system and indeed, if viewed collectively, corresponds to a very substantial immune organ. It consists principally of three components: the Peyer's patches; the lymphocytes and plasma cells of the lamina propria; and the intraepithelial lymphocytes. The most obvious function of GALT is the massive production of IgA antibodies for secretion onto mucosal surfaces. It also performs one very clever trick: it discriminates between harmful antigens (like polio virus) against which a protective response is mounted, and harmless (e.g. food) antigens against which the potential immune response is suppressed.

The intraepithelial lymphocytes are a heterogeneous group without proven function(s). They are mainly granulated with a very low T4:T8 ratio and a relatively high proportion have T cell receptors with γ/δ subunits (83).

The Peyer's patches are lymphoid aggregates found on the antemesenteric side of the ileum and colon which extend through the lamina propria and submucosa. They differ from lymph nodes elsewhere in the body by lacking a capsule and in being without afferent lymphatics. The efferent lymphatics drain to the mesenteric lymph nodes. The Peyer's patches are probably a major site of both initiation and amplification of the local immune response and are certainly crucially involved in IgA production.

Lymphocytes first sensitised in the Peyer's patches migrate throughout the body to other mucosal sites. Some activated lymphocytes will home to the gut lamina propria to differentiate into plasma cells predominantly producing secretory IgA.

Circulating (plasma) IgA appears to have no function, while secretory IgA is widely believed to function by neutralising harmful toxins and viruses, regulating bacterial adherance to epithelia and preventing excessive uptake of food antigens (31). Yet, selective IgA deficiency is relatively common (affecting about 0.14 % of the population) and is not usually associated with clinical symptoms. There is some evidence, however, that lack of IgA may mildly predispose to sinopulmonary infections, allergic asthma, Coeliac disease and autoimmune connective tissue diseases (2). It may be that other components of the immune response can compensate for lack of IgA most, but not all, of the time; however, it must be considered a possibility that the properties of IgA are of little real significance to human health.

On the other hand, if IgA be irrelevant, why do microbes produce a proteolytic enzyme for IgA_1? Why do some pathogenic streptococci bind to IgA via Fcα receptors if not as an immune escape mechanism? Why do some streptococci produce glycosidases that remove the carbohydrate from IgA if not to circumvent the bacterial lectin-IgA receptor interaction? However, it is possible the carbohydrate is removed to provide a substrate for fermentation.

Another area of Peyer's patch physiology which might reward the attention of the carbohydrate biochemist concerns the interactions of M cells (10, 35, 54). These are specialised epithelial cells which make up about 10 % of the cells forming the one-cell covering of the Peyer's patch dome. M cells are so called because they differ from absorptive epithelial cells in having a few "*m*icrofolds" instead of many microvilli. Their principal function seems to be antigen sampling by transporting antigens from the gut lumen into the Peyer's patch. Typically, M cells are surrounded by several lymphocytes on the non-luminal side, and it is possible they act directly as antigen presenting cells, but perhaps more likely that they simply transport antigenic material through the epithelium for presentation by nearby macrophages or dendritic cells. Human M cells may express HLA-DR, as do absorptive epithelial cells, but that in itself does not mean either of them must present antigen. It is possible, however, that either cell type might act as an antigen presenter in inflammatory pathological conditions.

What is clear is that while M cells transport a wide variety of intestinal antigens and micro-organisms, they are selective and transport certain micro-organisms with high efficiency (75). Since bacterial lectin-carbohydrate receptor interactions are usually important in bacterial adhesion, it would not be surprising if that were also so for bacterium-M cell receptor coupling. If so, both dietary carbohydrates and lectins might be expected to interfere with this process, with unknown consequences for protective immunity or tolerance induction. Interestingly, lectins are among a diverse group of compounds with adjuvant activity for mucosal vaccines and differ from typical soluble proteins in provoking an active immune response rather than suppression when administered orally (15). Studies of uptake in the presence and absence of sugar hapten inhibitors would be greatly facilitated by the isolation and culture of M cells in vitro.

Oral tolerance

Oral tolerance, the Salzberger-Chase phenonomen, is the induction of systemic unresponsiveness to an antigen by its administration through the alimentary canal (51, 81, 86). This can be most readily demonstrated using soluble proteins; ovalbumin is a popular experimental choice. Cell mediated immunity is suppressed more than the humoral response, with the interesting exception of IgE. Viable organisms like viruses and bacteria do not induce tolerance, whereas food antigens usually do. Particulate antigens and carbohydrate antigens are less likely to be tolerogenic than soluble peptides or polypeptides. How the gut immune system knows how to make this extremely useful distinction is unknown – it can be conjectured, for example, that food antigens pass through adsorptive epithelia and induce tolerance, while viable organisms are taken up by M cells and provoke normal immunity – but, whatever the mechanism, the function appears to be the prevention of food hypersensitivity by preventing specific IgE and delayed-type hypersensitivity responses. Recent animal studies indicate a critical role for γδT cells in the regulation of oral tolerance (36).

Much interest in oral tolerance has arisen from its possible application to the immunotherapy of autoimmune diseases (87). Examples include suppression of diabetes in NOD mice by oral pig insulin (98), amelioration of adjuvant arthritis in rats by oral collagen (99) and prevention of experimental myasthenia gravis in rats by oral acetylcholine receptor (85). Experimental autoimmune encephalomyelitis, considered by some to be a rat model of human multiple sclerosis, has been particularly well studied. It is provoked by myelin basic protein and can be prevented by prior oral administration of the same antigen in several experimental animal model systems. This work provided the rationale for a double blind clinical trial of oral bovine myelin in multiple sclerosis. Only 40 % of the myelin-treated patients had a major disease exacerbation during the time of the trial compared to 80 % of patients receiving placebo, a difference reaching borderline statistical significance (88). Rather similar results have also been reported for oral collagen in human rheumatoid arthritis (84).

Two aspects relevant to the induction of oral tolerance deserve our particular consideration. First, the regulation of this important phenomenon may be influenced by the intestinal flora (51). The evidence for this belief includes the following: (1) food hypersensitivities are commonest in infants around the time of weaning; (2) food hypersensitivities sometimes develop subsequent to gut infections; (3) germ-free mice cannot be tolerized by feeding sheep red blood cells, unlike conventionally-reared mice. If the nature of the microflora can influence the immune response and is itself influenced by dietary carbohydrate, the latter might be expected to affect the regulation of oral tolerance.

Second, the suppression of experimental autoimmune encephalomyelitis by orally administered myelin basic protein in rats and mice is mediated by the secretion of transforming growth factor-β (TGFβ) (49, 74). TGFβ constitutes a family of immunoregulatory factors that generally down-regulate immune function (68). Notably, TGFβ in human milk inhibited anti-sheep red blood cell antibody production when ovine erythrocytes were given orally but had a stimulative effect with the same cells administered parenterally (32). Another transforming growth factor, termed $TGF\gamma_2$, is similar in amino acid sequence to 14kD S-type lectins (94). This surprising finding is nonetheless consistent with several observations linking S-type lectins with both growth promotion and suppression (39, 73, 90). Moreover, human placental S-type lectin can suppress experimental autoimmune encephalomyelitis (55) and electrolectin can suppress experimental myasthesia gravis (44).

If S-type lectins and transforming growth factors are similar or overlapping molecular families, this could have interesting implications for dietary manipulation. The growth modulatory function of S-type lectins is separate from carbohydrate-binding activity and my own suspicion is the lectin activity functions to direct the growth controlling activity to specific sites for a limited time-span. For example, it might be advantageous to have a growth factor present in a particular place attached via S-type lectin-laminin interactions during a specific phase of differentiation but only for that period. This would explain the frequently observed developmental regulation of S-type lectins and account for the sulphydryl-dependent lability of the lectin activity. Similarly, S-type lectins may influence the induction of an immune response, but might be harmful if they remained in an active form for more than a critical period. If these speculations have any substance, it follows that β-galactosides present in the diet could limit or abrogate certain gut immune responses indirectly by preventing their taking place at the required site.

A related group of S-type lectins have IgE binding activity (38). Various plant lectins have been shown to react with rodent intestinal mast cells, whether sensitised with IgE or not, with a spectrum of consequences ranging from anaphylaxis to suppression (63). It is possible that dietary lectins could also interact with human gut mast cells, and if so, any consequences would surely be amendable to modification by simultaneously present dietary carbohydrates with the ability to inhibit. Dietary carbohydrates might also influence bacteria-induced histamine release (33).

Finally, it should be noted that glycosylation has considerable influence on peptide immunogenicity (50). The mechanism(s) involved may include altering the peptide conformation in such a way as to influence binding of MHC-class II and hence antigen presentation. It is also noteworthy that immunisation with a non-glycosylated peptide can result in anti-carbohydrate antibodies (76). These studies may be an indication of unforeseen consequences for gut immunity arising from dietary carbohydrates.

Systemic effects of dietary carbohydrates

Effects on lectins

Carbohydrates which bind to the active site of dietary lectins in the lumen of the alimentary canal are presumably still bound and acting as lectin inhibitors after absorption into the circulation. (It is not known how much lectin absorption is dependent on a free carbohydrate binding site). This could have significant physiological consequences, as there is reason to believe dietary lectins exert metabolic effects at locations remote from the gut. Animal studies have clearly shown that some absorbed lectins influence distant target tissues in various ways, for example, promoting growth of the pancreas or atrophy of the thymus (63). Corresponding studies on humans have not been done, but some lectins survive the digestive process and are to some extent absorbed intact. It is likely the consequences of dietary lectin absorption – as well as the extent of lectin absorption – would be different depending on whether or not inhibitory saccharides were present as well.

It must also be considered that carbohydrates present in plasma as a result of absorption from food might also affect endogenous lectins. In this way, some inhibition of the activity of circulating mannan binding protein and/or membrane bound C-type lectins could take place. Inhibition of the lectin activity of cytokines is another theoretical possibility, and since the function of the carbohydrate binding ability of IL-2, etc. is unknown, there is no way of guessing what interference with this property might do. Finally, there is the possibility of interference with cellular recognition events such as lymphocyte homing which will be discussed later.

Influence on bacterial infections

Carbohydrates absorbed through the gut might inhibit microbial lectins at distant milieux and so prevent attachment and productive infection. Cranberry (*Vaccinium macrocarpon*) juice allegedly affords protection against urinary tract infections. The biochemical basis of this has been investigated by Zafriri et al. (97). The fructose content of the juice could be responsible for inhibiting the type 1 fimbrial-mediated adhesion of *E. coli* to various eukaryotic cells, but fructose was inactive towards P fimbriae, which are often expressed by pyelonephritogenic isolates of *E. coli*. However, the juice also contained a non-dialysable inhibitor(s) of P fimbriae, something not found in orange juice or pineapple juice.

Influence on homing mechanisms

The mechanisms involved in the homing of lymphocytes and other leukocytes to specific (e.g. mucosal) sites are not understood in detail in mice and far less is known about the human situation (57). However, it is known that lymphocytes exposed to antigen in the gut make their way through Peyer's patches and other routes to the mesenteric lymph nodes from which they enter the blood stream via the thoracic duct. In due course, they leave the blood stream and take up residence in mucosal sites, within and outwith the gut. By this means, primed lymphocytes come to be present within the Peyer's patches and as gut intraepithelial lymphocytes. It is also believed that some intraepithelial lymphocytes are derived from the bone marrow, but they too must home in a specific fashion from the blood stream to the gut lamina propria (57).

The homing mechanism appears to require a complex set of molecular interactions, involving adhesive molecules on both the lymphocyte cell surface and the surface membranes of vascular endothelial cells (14). The key step is the interaction of lymphocyte homing receptors with vascular addressins in high endothelial venules. The directed migration of other leukocytes (neutrophils, monocytes) to inflammatory loci is also controlled by interactions between members of the same molecular families. Some local regulation is achieved by cytokines released at sites of inflammation resulting in chemotaxis, cellular activation and up-regulation of specific adhesive molecules.

In general, the initial adherance event involving leukocytes is mediated by the selectin family, while subsequent firmer adhesion is mediated by the members of the integrin family, with the latter also transmitting signals via cytoskeletal proteins (14). Selectins (7, 38) are membrane-bound C-type lectins which share a common carbohyrate-binding domain while differing in the number of complement binding protein-like repeat sequences. L(leukocyte), E(endothelial) and P(platelet) selectins all recognise fucosylated saccharide structures

similar to and including sialyl-Lewis^x and it is therefore likely their natural ligands will possess similar structures. Most work in this area has been done on mice; for a summary of what is known of the structure and specificity of the selectins, the reader is referred to Lowe (46).

It may seem unlikely that dietary oligosaccharides taken up into the circulation could interfere with the normal migration of lymphocytes or the recruitment of neutrophils and monocytes to inflammatory loci. Nevertheless, sialyl-Lewis^x and related saccharides can alleviate neutrophil-mediated tissue injury in vivo in animal models, and the commercial target is now to synthesise a drug which is inexpensive to produce and different from natural compounds but similar in steric structure. This work raises the possibility that natural diets may also possess anti-inflammatory agents which are oligosaccharide in chemical structure.

Diseases possibly influenced by dietary carbohydrate

Although the main emphasis has been on possible positive influences of the diet on health, good health to a large extent is the absence of disease. There are many idiopathic disorders, some very serious, which might benefit from a new approach to their investigation and treatment. Some of these are listed below with reasons for speculating that dietary manipulation might be worth investigating.

Coeliac disease

Gluten-sensitive enteropathy (Coeliac disease) is an HLA-associated disease provoked by dietary gluten and characterised by villous atrophy and lymphocytic infiltration of the jejunal mucosa resulting in malabsorption. The role of cereal lectins in the disease process is controversial and unclear (63), but sufficient suspicion exists to warrant further studies to explore interactions with saccharides, competing lectins and the influence of the microbial composition. Dietary manipulation (avoidance of gluten) is an established treatment, but less drastic dietary options which might permit consumption of cereals would obviously be desirable and might provide new insights into the pathogenesis of Coeliac disease and dermatitis herpetiformis.

Inflammatory bowel diseases

The major inflammatory bowel diseases are Crohn's disease and ulcerative colitis. Crohn's disease may affect any part of the alimentary canal, although the small intestine is most typically affected, and is characterised by a discontinuous, granulomatous transmural inflammation. Ulcerative colitis predominantly affects the rectum and distal end of the colon and is characterised by a continuous, superficial inflammation of the mucosa.

Both diseases are of unknown cause, have only a weak, ill-defined familial tendency, and are associated with vague, non-specific immune abnormalities. Both appear to be commoner in industrialised countries which may be an indication of a dietary etiology. The increased risk of bowel carcinomas in association with inflammatory bowel diseases may also reflect a dietary influence. Certainly, diet can influence the course of Crohn's disease (67). In contrast to Coeliac disease, a miscellany of food intolerances can provoke disease exacerbations, with cereals, dairy produce and yeast-containing foods most commonly implicated. It is possible that Crohn's disease results from an abnormal mucosal immune response to food antigens, or, alternatively, arises from an infection associated with abnormal gut flora. Either way, dietary carbohydrate could be relevant and studies specifically addressing the role of particular saccharides might be helpful.

HIV enteropathy

Intestinal disease is a common manifestation of HIV disease worldwide, and may result from direct HIV infection as well as HIV associated secondary opportunistic infections (48). Intestinal epithelial cells can be infected with HIV in vitro, and galactosyl-ceramide has been implicated as an HIV receptor (93). M cells have also been found to bind and endocytose HIV (1). The infectivity of HIV depends on its envelope glycoprotein, although the role of the carbohydrate moiety is uncertain and controversial. Certainly several lectins can block HIV infection in vitro, of which mannose-specific lectins are the most potent (20). The human plasma lectin, mannan binding protein (MBP), is an example (19). It may be pertinent that MBP deficiency is more frequent in HIV infected subjects than in controls (23, 53).

If HIV can really cross the mucosal barrier of the alimentary tract, dietary lectins and/or carbohydrates might serve a protective function.

Insulin dependent diabetes mellitus

Diabetes mellitus Type 1 has a strong genetic component, but there is overwhelming evidence for an environmental etiological trigger. Early exposure to cow's milk (or limited breast feeding) in infancy is probably a risk factor for insulin-dependent diabetes (24). An attractive hypothesis advanced to explain this association is that autoimmunity is provoked via a cross-reaction between an epitope on bovine albumin and a β-cell surface antigen, p69 (34). However, the lack of demonstrable cell mediated immunity to BSA has cast considerable doubt on the validity of this hypothesis (4). An alternative explanation might be that oligosaccharides in breast milk offers better protection against diabetogenic viruses. Perhaps less likely, but with some experimental foundation (95), is the possibility that dietary oligosaccharides absorped into the

circulation could selectively block homing of autoreactive T lymphocytes to the pancreatic islets by inhibiting selectin function.

Multiple sclerosis

It has been suggested that breast feeding may protect against future development of multiple sclerosis (59). Another study failed to show any such association (79), but, if true, one explanation could be carbohydrate-mediated protection against a slow acting viral infection.

Metastatic cancer

The spread of tumour cells via blood vessels may depend partly on interactions involving selectins (16). S-type lectins have also been implicated in metastasis, and in a rat model dietary galactosides were found to be effective inhibitors (58). Although it may seem unlikely that saccharides absorbed from a normal diet would be able to prevent tumour cell migration without damaging normal cellular interactions, the importance of metastatic cancer may justify further investigations in this field.

Conclusions

It is likely that dietary carbohydrates can shift the balance that exists within the lumen of the alimentary canal between lectins, secretory IgA and bacteria. Changes in dietary saccharide composition would be expected to lead to changes in the indigenous flora. It is possible that optimal tissue protection from pathogenic bacteria and viruses could be achieved by an ideal diet providing sugars of the right composition and quantity to minimise harmful microbial attachment and colonisation of human tissues.

Although the influence of dietary carbohydrate on immune induction within the gut associated lymphoid tissue is unknown, the investigation of lectin-receptor interactions during antigen uptake and transport by M cells may be helpful in understanding the allergy/tolerance dichotomy.

Animal work with selectins indicates that specific saccharides can influence recognition events at gut-remote sites.

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