Gastrointestinal effects of prebiotics

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The defining effect of prebiotics is to stimulate selectively the growth of bifidobacteria and lactobacilli in the gut and, thereby, increase the body’s natural resistance to invading pathogens. Prebiotic carbohydrates may also have additional, less specific, benefits because they are fermented in the large intestine. The prebiotic carbohydrates that have been evaluated in humans at the present time largely consist of fructans or galactans. There is consistent evidence from in vitro and in vivo studies that these are not digested by normal human enzymes, but are readily fermented by anaerobic bacteria in the large intestine. There are no reports of faecal recovery of measurable quantities of prebiotic carbohydrates. Through fermentation in the large intestine, prebiotic carbohydrates yield short-chain fatty acids, stimulate the growth of many bacterial species in addition to the selective effects on lactobacilli and bifidobacteria, they can also produce gas. Along with other fermented carbohydrates, prebiotics have mild laxative effects, although this has proved difficult to demonstrate in human studies because the magnitude of laxation is small. Potentially, the most important effect of prebiotic carbohydrates is to strengthen the body’s resistance to invading pathogens and, thereby, prevent episodes of diarrhoea. At the present time, this effect has not been convincingly demonstrated in either adults or children, although there have been attempts to ameliorate the diarrhoea associated with antibiotics and travel, but without success. However, prebiotic carbohydrates clearly have significant and distinctive physiological effects in the human large intestine, and on the basis of this it is likely that they will ultimately be shown to be beneficial to health.

Prebiotics: Fermentation: Biofilm: Travellers’ diarrhoea

Introduction

Prebiotics are food ingredients that stimulate selectively the growth and activity of bifidobacteria and lactobacilli in the gut and thereby benefit health. At the present time, all prebiotics described are short-chain carbohydrates with a degree of polymerisation of between two and about sixty, and are thought to be non-digestible by human, or animal digestive enzymes. However, the defining property of prebiotics is their effect on the microflora of the large bowel, so neither a specific chain length nor non-digestibility are essential to the definition, although such properties may be essential to their effect on health. Prebiotic proteins or lipids are unlikely to exist because of the nature of the metabolism of bifidobacteria and lactobacilli.

Prebiotics are an exciting new concept in human nutrition and digestive function for which, as is often the case with a new idea, many physiological and health claims have already been made. Table 1 lists these claims. Central to all claims is the effect on the microflora, which in turn should lead to strengthening of colonisation resistance to pathogen invasion in the large bowel, and a reduction in diarrhoeal diseases. As yet, however, no clinical benefit in diarrhoea has been shown. Other important gastrointestinal effects include the general benefits of fermentation, which prebiotics share with non-starch polysaccharides and resistant starch, effects on mineral absorption, especially calcium, and possibly protection against tumour growth, as demonstrated in animal models. Any of these claims, if proven, will justify the present interest and research into prebiotics.

Digestion

Non-digestibility in the small bowel is assumed for prebiotics, but in fact, this has been established in vivo for few of these carbohydrates. Measuring digestion of any substance in the stomach and small bowel in vivo is difficult. One useful model is the ileostomy patient, with an alternative approach being the aspiration of residual digesta from the ileum using intubation. Table 2 shows that for inulin and

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oligofructose, both techniques indicate that at least 88 % of these ingested prebiotics reach the caecum.

Other evidence of non-digestibility is more circumstantial. Oligofructose (from sucrose, essentially GF₂ and GF₃) have been incubated in vivo with either human saliva or rat pancreatic homogenate and reported to be ‘hardly digested’ (Hidaka et al. 1986). No change in blood glucose or insulin was seen when 25 g of the same product was given to healthy subjects, nor when inulin extracted from Jerusalem artichokes (30 % GF₇ or greater) at doses of 5, 10 or 20 g, were taken either alone or with other carbohydrates (Hidaka et al. 1986; Rumessen et al. 1990). Nilsson et al. (1988) incubated various cereal inulins in fresh human gastric juice for 1 h and showed that at pH 1.05, 10–15 % was hydrolysed, but above pH 1.8 less than 1 % was degraded. When incubated with homogenised rat intestinal mucosa the rate of hydrolysis of inulin was less than 1 % that of sucrose. In the same study, inulin disappearance from the intubated rat small bowel in vivo was virtually nil. Earlier, McCance & Lawrence (1929) had shown inulin to be labile in gastric juice. A number of other studies have found that after intake of prebiotics, breath hydrogen excretion increases. While this is evidence of their fermentability, it does not provide information on the true extent of their non-digestion (see later).

**Fermentability**

Having reached the caecum, prebiotic carbohydrates are highly likely to be fermented, since they are water soluble and relatively simple molecules. So completely are these carbohydrates fermented that feeding studies in humans of inulin and oligofructose have consistently failed to recover any of these materials in faeces (Table 3).

In vitro, prebiotic carbohydrates can be shown to support intestinal bacterial growth and produce various fermentation-derived end products. Two early studies (Hidaka et al. 1986; Mitsuoka et al. 1987) both showed that a range of bifidobacteria could utilise oligofructose (from sucrose) although other enteric bacteria were able to grow on a range of prebiotics, especially *Bacteroides* species. Utilisation of oligofructose by lactobacilli, *Escherichia coli* and *Clostridium perfringens* was poor. Using gas and short-chain fatty acid production as endpoints, Wang & Gibson (1993) showed that human faecal slurry fermented oligofructose, along with a wide range of other carbohydrates, but that inulin and oligofructose selectively stimulated the growth of bifidobacteria. In pure culture experiments, eight different bifidobacteria, including *B. bifidum*, grew well on oligofructose, as also did *E. coli* and *C. perfringens*, which was in direct contrast to the earlier results of Hidaka & Mitsuoka. However, these latter two organisms showed somewhat better growth rates on glucose, whereas of the bifidobacteria, only *B. longum* did. In competition experiments, Gibson & Wang (1994) showed that in pH controlled co-culture of *B. infantis*, *E. coli* and *C. perfringens* with oligofructose as sole carbohydrate substrate, the bifidobacteria grew well and exerted an inhibitory effect on the growth of *E. coli* and *C. perfringens*. These findings were subsequently confirmed in vivo in human feeding studies (Gibson et al. 1995).

The prebiotic properties of inulin and oligofructose are now well documented, but few groups have looked at the role of these carbohydrates in determining the composition of the mucosa-associated flora. When growing on surfaces, intestinal bacteria form biofilms (Macfarlane et al. 1999) and behave differently from those existing in a planktonic environment.
or free form. The biofilm communities of the gut epithelium may be more important in determining mucosal function, interacting with the gut associated immune system and in the catabolism of mucus. Using a novel design, (Horan & Cummings, 1999) glass fermentation chambers have been adapted to suspend several mucin-covered glass slides within a culture vessel. These are run at constant temperatures and pH and used to assess the effect of inulin and oligofructose on the planktonic and biofilm populations of bacteria. Faecal inocula from six healthy volunteers were used. After 12 h, the effect of the prebiotic mixture was to increase counts of bifidobacteria in the planktonic phase by $0.45 \log_{10}$ CFU/ml ($P=0.06$) and the biofilm count by $0.77 \log_{10}$ CFU/slide ($P<0.001$). Counts of clostridia fell and lactobacilli showed a small increase. As a follow-up to the in vitro work, Langlands et al. (2000) carried out a human feeding study to investigate this effect in vivo. Fifteen healthy subjects were selected from a colonoscopy waiting list and supplemented their usual diet with 15 g/day of an inulin + oligofructose mixture for 2 weeks before their colonoscopy. During this procedure, biopsy specimens of mucosa were removed for culture, and bacteria were identified according to their cellular fatty acid profiles (MIDI system). A group of age and sex matched healthy subjects attending for colonoscopy were used as controls. The effect on the mucosal flora was to increase significantly both bifidobacterial and lactobacilli counts on the epithelium. This was by one log CFU/g mucosa and 0.5 log CFU/g mucosa respectively, whilst counts of bacteroides, clostridia and enterobacteria were unchanged. This small feeding study has shown that the prebiotic effects of inulin and oligofructose may also be seen at the critical interface between the mucosa and surface-associated bacteria.

Whether the nature of the carbohydrate determines its fermentability is a question that has barely been addressed. Van Laere et al. (1997) produced a range of different short-chain carbohydrates with widely different sugar compositions and sizes, and tested their breakdown by several strains of bifidobacteria, clostridia, bacteroides, lactobacilli, etc. Fermentability differed with oligosaccharide structure. The fructo-oligosaccharides were extensively fermented, except by the clostridia, while few species were able to breakdown arabinoxylan in the conditions of the experiment. Xylo-oligosaccharides were well fermented. Linear oligosaccharides were catabolised to a greater degree than those with branched structures while bifidobacteria utilised low degree of polymerisation (DP) carbohydrate first, and bacteroides those with a high DP. Metabolic collaboration amongst species was evident in carbohydrate breakdown. Both the structure of the carbohydrate and the bacterial species present in the ecosystem are probably important factors in controlling fermentation of prebiotic carbohydrates.

The major products of prebiotic metabolism are short-chain fatty acids (SCFA), the gases H$_2$ and CO$_2$ and bacterial cell mass. Much has been written about SCFA production in the hindgut and of the differing metabolic significance of the individual acids (Cummings et al. 1995). Whilst prebiotics have been shown to be a source of SCFA both in vitro and in vivo, no particular distinguishing feature of the pattern of SCFA production has emerged as yet from in vivo studies in humans (Gibson et al. 1995; Luo et al. 1996; Alles et al. 1996; Kleesen et al. 1997).

The gases CO$_2$ and H$_2$ are inevitable products of fermentation but also provide the major clinical disincentive to consumption of prebiotics. Unwanted symptoms relating to gas production in the gut are widely reported in human prebiotic feeding studies. In Stone-Dorshow & Levitt’s study (1987) twelve subjects took 15 g oligofructose (from sucrose) daily for 12 days. When compared with a group of five subjects taking sucrose, symptoms of abdominal pain, eructation, flatulence and bloating were all significantly more severe in the oligofructose group. There was no adaptation over the 12-day period but symptoms were all reported as no more than mild. Other studies of oligofructose at doses of 5 and 20 g/d have shown dose-related increases in breath H$_2$ and mild flatulence and borborygmi in general with isolated individuals experiencing somewhat more discomfort (Ito et al. 1990; Kawaguchi et al. 1993; Luo et al. 1996; Pedersen et al. 1997). Paradoxically eight healthy subjects taking 10 g/d transgalacto-oligosaccharides (TOS) reported no digestive symptoms and a decrease in breath H$_2$ excretion (Bouhnik et al. 1997). Inulin at a dose of 14 g/d led to highly significant increases in flatulence, rumbling, stomach and gut cramps, together with bloating in a group of 64 women in a double-blind crossover study over 4-week periods. Twelve per cent of the volunteers considered the flatulence severe and unacceptable. No adaptation in symptoms occurred over time (Pedersen et al. 1997).

An explanation of these various and idiosyncratic effects of prebiotics on symptomatology and H$_2$ metabolism is difficult to find. Wide individual variation is known to occur in response to fermentation of prebiotics, and the stoichiometry of fermentation differs from carbohydrates of varying chain length and monosaccharide composition (Christl et al. 1992). Using breath H$_2$ excretion, it has been shown

### Table 3. Faecal recovery of inulin and oligofructose in humans

<table>
<thead>
<tr>
<th>Literature</th>
<th>Source g/day</th>
<th>Recovery (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulz (1874)</td>
<td>Inulin 50–120 g</td>
<td>0</td>
</tr>
<tr>
<td>Persia (1905)</td>
<td>Inulin ‘large doses’</td>
<td>0</td>
</tr>
<tr>
<td>Neubauer (1905)</td>
<td>Inulin 80 g</td>
<td>0</td>
</tr>
<tr>
<td>Lewis (1912)</td>
<td>Inulin 40–60 g</td>
<td>‘no increase in faecal CHO’</td>
</tr>
<tr>
<td>Molis et al. (1996)</td>
<td>Oligofructose 20.1 g</td>
<td>0%</td>
</tr>
<tr>
<td>Alles et al. (1996)</td>
<td>Oligofructose 5 and 15 g</td>
<td>0</td>
</tr>
</tbody>
</table>
that lactitol, isomaltose and polydextrose each increase breath H₂ by 112, 73 and 11% respectively, when given in equal doses to healthy subjects (Livesey et al. 1993). These findings were broadly reflected by in vitro fermentation studies and suggest that in general, molecules with longer chain length are fermented more slowly and with less net H₂ excretion. A similar result was obtained by Brighenti et al. (1995) when comparing lactulose, inulin and resistant starch (RS) in healthy subjects. Breath H₂ was only 4·7 ppm/h per g fed after RS compared with 19·1 for inulin and 26·6 for lactulose at a similar dose. In the studies of Christl (1992), who measured absolute H₂ excretion rates using a human calorimeter, total H₂ excretion for starch was only 40% of that from an equivalent dose of lactulose.

Prebiotics are clearly a major source of H₂ generation in the gut, and for some people the rapid formation of gas, and its volume, is a hindrance to consumption. Experiments to produce prebiotics of different chain lengths, degree of branching and DP might lead to less flatulent substrates – but this may alter their abilities to selectively influence the microflora.

Bowel habit

All carbohydrates that reach the large intestine have a laxative effect on bowel habit. Table 4 summarises those studies where bowel habit has been measured. The clearest demonstration of a laxative effect of prebiotics is in the controlled diet study of Gibson et al. (1995), which showed that 15 g of oligofructose increased stool output significantly from 136 to 154 g/d (n = 8) and in a smaller group of subjects 15 g of inulin was also laxative; 92 g/d control, 123 g/d inulin (n = 4). Three other human experiments have not shown an increase in stool output (Table 4) but in none was diet controlled, which would tend to mask a small effect. In the study of Alles et al. (1996), subjects started with unusually high faecal weights on the control diet, 272 ± 26 g/d. In that of Bouhnik et al. (1997) volunteers were given 10 g transgalacto-oligosaccharides daily for 21 days without effect on bowel habits. Ito et al. (1990) who fed 4·8–19·2 g/d oligomate (52% galacto-oligosaccharides) to twelve healthy subjects were also unable to demonstrate a change in bowel habit, despite showing bifidogenicity and the subjects reporting an increase in abdominal symptoms. In studies reporting only qualitative data, either oligofructose or inulin ‘improved’ constipation in small groups of hospitalised subjects (Sanno, 1987; Hidaka & Hirayama, 1991; Kleesen et al. 1997).

Inulin and oligofructose are probably laxative, but because the effect is small it is difficult to detect except in carefully controlled studies. The increase in faecal output is likely to be due to an increase in biomass. Alongside the increase in dry matter excretion is a significant increase in nitrogen (Table 5). In the study of Gibson et al. (1995), the additional excretion of 0·32 g/d nitrogen when oligofructose was added to the diet is equivalent to 5 g of bacterial solids which, at the moisture content of stool, is equivalent to 20–25 g of wet stool. This was exactly the change in stool output seen in the study.

### Table 4. Effects of prebiotics on bowel habit

<table>
<thead>
<tr>
<th>Source</th>
<th>Dose (g/d)</th>
<th>n</th>
<th>Faecal weight g/d</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Prebiotic</td>
</tr>
<tr>
<td>Oligofructose</td>
<td>15</td>
<td>8</td>
<td>134</td>
<td>154*</td>
</tr>
<tr>
<td>Inulin</td>
<td>15</td>
<td>4</td>
<td>92</td>
<td>123</td>
</tr>
<tr>
<td>Oligomate (52 % GOS)</td>
<td>4·8</td>
<td>12</td>
<td>151</td>
<td>134</td>
</tr>
<tr>
<td></td>
<td>9·6</td>
<td>12</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19·2</td>
<td>12</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>TOS</td>
<td>10</td>
<td>8</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>Oligofructose</td>
<td>5</td>
<td>24</td>
<td>272</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td></td>
<td>264</td>
<td></td>
</tr>
</tbody>
</table>

* P< 0·05 GOS=galacto-oligosaccharides; TOS=transgalacto-oligosaccharides.

### Table 5. Faecal nitrogen (g/d ± SEM) and energy excretion (kJ/day ± SEM) from subjects fed 15 g inulin or oligofructose daily compared to a sucrose control period

<table>
<thead>
<tr>
<th>n = 8</th>
<th>Sucrose</th>
<th>Oligofructose</th>
<th>Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen</td>
<td>1·51 (0·12)</td>
<td>1·83 (0·17)*</td>
<td>1·55 (0·19)</td>
</tr>
<tr>
<td>Energy</td>
<td>597 (56)</td>
<td>696 (78)</td>
<td>640 (83)</td>
</tr>
<tr>
<td>n = 4</td>
<td>Sucrose</td>
<td>Inulin</td>
<td></td>
</tr>
<tr>
<td>Nitrogen</td>
<td>1·31 (0·16)</td>
<td>1·56 (0·14)*</td>
<td></td>
</tr>
<tr>
<td>Energy</td>
<td>466 (42)</td>
<td>565 (64)</td>
<td></td>
</tr>
</tbody>
</table>

* Significantly different from sucrose.
From Gibson et al. (1995).

**Travellers’ diarrhoea**

Demonstrating a direct clinical or health benefit of prebiotics is proving difficult. Small changes in lipid metabolism, calcium absorption or immune function may not give rise to evident improvements in health for many years. However, resistance to pathogen invasion through increased colonisation resistance of the gut flora, brought about by stimulation of bifidobacteria and lactobacilli, should in principle be easier to show in vivo. Oligofructose has been reported to protect hamsters against C. difficile infection (Wolf et al. 1997) but studies in humans have so far been unsuccessful (Lewis & Cohen, 2000). However, most C. difficile infection is associated with antibiotic use and it would be surprising if prebiotic carbohydrates...
were able to protect the resident gut bacterial from the effect of antibiotics.

An alternative clinical situation in which to test prebiotics is that of travellers’ diarrhoea. Travellers’ diarrhoea remains a common problem for those journeying overseas for either business or holidays. It is particularly frequent in visitors to Central America, the Far East, India and parts of Africa. Current estimates are that 60 million travellers from the West visit high-risk areas annually, and of these, 30–50 % have episodes of diarrhoea. The infecting organisms are very much the same as those that cause acute diarrhoea in both developed and developing countries, e.g. salmonella, shigella, campylobacter, enterotoxigenic and other E. coli, protozoa such as Giardia lamblia and Entamoeba histolytica, and viruses, especially rotavirus. Part of the defence against invading organisms is the indigenous flora of the hindgut such as bifidobacteria and lactobacilli, both of which colonise adhesion sites and secrete bacteriostatic peptides, which are part of the process whereby invading pathogens are repelled. A preventive and therapeutic strategy that has been tried in the past is to supplement those at risk of diarrhoea, or suffering an acute attack, with oral doses of probiotic organisms, such as lactobacilli. These bacteria have been shown to survive gastric acid and adhere to small intestinal mucosa. Through this mechanism they are thought to prevent the adhesion of pathogenic bacteria and thus protect against diarrhoea or reduce the severity of attacks. However, in published studies where probiotic bacteria have been tried in travellers’ diarrhoea, the degree of protection has been relatively small at around 10 % (Lewis & Freedman, 1998; Gismondo et al. 1999; de Roos & Katan, 2000). Nevertheless, altering the environment in the hindgut towards a flora in which bifidobacteria are the predominant species using oral fructo-oligosaccharides, may provide a simple way of reducing morbidity in travellers to endemic regions of diarrhoea.

A study was therefore undertaken (Cummings et al. 2001a) in 244 healthy subjects, travelling to high and medium risk destinations for travellers’ diarrhoea. The protocol was a randomised, double-blind, placebo-controlled study, comprising a preliminary week for recording bowel habit by diary, a 2-week pre-holiday period with the diary and consumption of 10 g of oligofructose or placebo daily, followed by a 2-week holiday with continuation of treatment and diary. A post-study questionnaire (PSQ) was completed by all subjects on their return to the UK. Consumption of oligofructose led to a small, 6 % (P<0·02) increase in stool frequency in the pre-holiday period, while some subjects reported more flatulence. There were non-significant decreases in episodes of diarrhoea (Table 6) with 20 % on placebo and 11 % on oligofructose recording episodes in the PSQ (P=0·08) and 46 % placebo, 38 % FOS in the diary (P>0·1). No change in bowel frequency, consistency or stool size was recorded (Table 6).

In this study, oligofructose failed to prevent diarrhoea, but did give subjects an increased sense of well-being while on holiday. However, 42 % of subjects experienced diarrhoea whilst on holiday, which is a striking reminder of the prevalence of the problem in travellers.

A likely reason for the failure of oligofructose to prevent travellers’ diarrhoea may lie in its mechanism of action and in the aetiology of diarrhoea in travellers. Oligofructose primarily affects the large intestinal microflora and may well improve colonisation resistance. However, there are multiple causes of diarrhoea in travellers, other than those that target the large intestine. Many pathogens affect the small bowel, for example, aeromonas, enteropathogenic and enterotoxigenic E.coli, campylobacter, giardia, salmonella and vibrios. In order to prevent the effect of these and similar organisms a preventive strategy aimed at the small intestine would be required. Furthermore, in all reported studies where the aetiologic agent of diarrhoea has been sought in travellers, in at least 20 % no organism has been identified. Whilst this failure to identify an incriminating pathogen has often been ascribed to inadequacy of microbiological methods, sampling problems etc, it is equally likely that subjects experience episodes of diarrhoea for reasons other than simple infection. Many people travelling abroad eat unusual foods to which they may never have been exposed, and which may cause food intolerance and diarrhoea. Equally, people on holiday may take far more alcohol than usual and again this is known to upset bowel habit. Overall, therefore, the multiple causes of diarrhoea in travellers make it unlikely that a single preventive strategy will be effective.

**Conclusion**

Prebiotics are an exciting and challenging new concept in

### Table 6. Effect of oligofructose on diarrhoea in subjects travelling to high and medium risk areas

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Oligofructose</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of stools (14-day holiday period)</td>
<td>20·3 (6·1)</td>
<td>21·3 (8·2)</td>
<td>0·3</td>
</tr>
<tr>
<td>Frequency (%) of symptoms from post study questionnaire</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bloating</td>
<td>7·8</td>
<td>11·2</td>
<td>0·5</td>
</tr>
<tr>
<td>flatulence</td>
<td>18·8</td>
<td>34·5</td>
<td>0·03</td>
</tr>
<tr>
<td>diarrhoea</td>
<td>19·5</td>
<td>11·2</td>
<td>0·08</td>
</tr>
<tr>
<td>constipation</td>
<td>10·2</td>
<td>10·3</td>
<td>0·99</td>
</tr>
<tr>
<td>less irritable bowel symptoms</td>
<td>3·9</td>
<td>7·8</td>
<td>0·3</td>
</tr>
<tr>
<td>feeling well</td>
<td>4·7</td>
<td>12·9</td>
<td>0·04</td>
</tr>
</tbody>
</table>

From Cummings et al. (2001a).
nutrition and digestive function. They are normal constituents of the diet, selectively stimulate the growth of beneficial bacteria in the large bowel, are safe and potentially of benefit to health. Any prudent diet should contain quantities of prebiotics. While the mechanism of their effect in gut bacteria is slowly being discovered, their effects on health are much more difficult to demonstrate. Nevertheless, this is an important new area for food and nutrition science.

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