CHAPTER 1

Prebiotics for the Improvement of Human Health

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The human gut is the natural habitat for a large and dynamic bacterial community, which has been referred to as the "intestinal microflora" in the past. The term "microflora" literally means "small plants". However, bacteria, viruses, yeasts and protozoa are taxonomically markedly different from plants and consequently the use of the alternative term 'microbiota' (small life) has been recommended (Tannock, 1995). Most bacteria are benign; however, certain gut species are pathogenic and may be involved in the onset of acute and chronic disorders. Bifidobacteria and lactobacilli are thought to be beneficial (Manning and Gibson, 2004). The microbiota in the human large intestine comprises about 95% of the total cells in the body, representing 10^{12} cells/g dry weight contents. Through the activities of the resident microbiota, the colon plays a major role in host nutrition and welfare (Manning and Gibson, 2004).

There is much interest in increasing the numbers and activities of beneficial bacteria in the large gut, preferably at the expense of more harmful bacteria. A way in which this can be achieved is by consumption of live microbial supplements, such as fermented dairy products or freeze-dried cultures. However, because the viability of live bacteria (probiotics) in food products and during transit through the gastrointestinal (GI) tract may be variable, the prebiotic concept has been developed. Here, the selective growth of indigenous gut bacteria is required. Prebiotics are indigestible food ingredients that beneficially affect the host by selectively stimulating growth and/or activity of one or a number of health-promoting colon bacteria (Gibson and Roberfroid, 1995).

A prebiotic effect has been attributed to many food components, sometimes without due consideration to the criteria required. In particular, many oligosaccharides and polysaccharides have been claimed to have prebiotic activity, but not all dietary carbohydrates are prebiotics. There are three criteria that need to be fulfilled for a food ingredient to be designated a prebiotic (Gibson et al., 2004). First, the ingredient must be nondigestible by host enzymes. For humans, the best way to demonstrate nondigestibility is with ileostomised volunteers (Ellegaard et al., 1997). Second, the ingredient must be fermented in the GI tract. This can best be shown by means of fermentation test *in vitro.* Third, there must be selectivity in the stimulation of intestinal bacteria and of metabolic activity (Van Loo, 2004). This criterion is of utmost importance. By definition, a prebiotic substrate is not available to all bacterial species that inhabit the GI tract. It must be particularly readily available to some groups of bacteria (of which lactobacilli and bifidobacteria are considered indicator organisms) that are beneficial for the health of the intestine but less available to potentially pathogenic bacteria such as toxin-producing clostridia, proteolytic bacteroides and toxogenic *Escherichia coli* (Manning and Gibson, 2004). In this manner, a "healthier" microbiota composition is obtained whereby the bifidobacteria and/or lactobacilli become predominant in the intestine and exert possible health-promoting effects.

Any dietary component that reaches the colon intact is a potential prebiotic; however, the prebiotic property has been demonstrated adequately for only a few food ingredients. According to Gibson et al. (2004), to date only the inulin-type fructans, galactooligosaccharides and lactulose are proved prebiotics. The latter, however, is considered a therapeutic ingredient rather than a food ingredient. Fructan is a linear ß-D-linked polymer of fructose containing a terminal glucose unit. Naturally occurring fructans exist with a spectrum of degree of polymerisation (DP) from 2 to 60, with an average DP of 10. Fructooligosaccharides (FOS) and oligofructose are considered to be synonymous names for the mixture of small inulin oligomers with a maximum DP of less than ten (Roberfroid, 2002).

There are currently no tables of oligosaccharide content of foods and few data giving oligosaccharide consumption of any populations in the world (Van Loo et al., 1995). Inulin occurs naturally in foods such as chicory (from which inulin is extracted), and to a lesser extent in onion, garlic, banana, asparagus, leek and Jerusalem artichoke. For cereal grains, wheat is the best source, providing about 2.5g FOS as well as 2.5g inulin (fructopolysaccharide) per 100g raw bran and baked flour (Van Loo et al., 1995). Wheat is the major food source of naturally occurring inulin and FOS, providing about 70% of these compounds in American diets (Moshfegh et al.,

1999). The daily per capita intake of inulin and FOS in the USA varies between 1 and 4g and in Europe between 2 and 12g (Van Loo et al., 1995). These levels are probably too low to elevate bifidobacteria significantly (about one log^{10} value) in the human gut. Fructooligosaccharides have been found to be effective in humans at doses of 5g/day. Hence, there exists much interest in the approach of fortification of commonly ingested foodstuffs with prebiotics (Manning and Gibson, 2004), extracted from chicory or commercially produced through hydrolysis of polysaccharides (e.g. dietary fibres, starch) or through enzymatic generation.

As prebiotics exploit the use of non-viable dietary components to improve gut health, the range of foods into which they can be added is much wider than that for probiotics, where culture viability needs to be maintained. This has the advantage that heat stability or exposure to oxygen is not an issue. As such, virtually all carbohydrate containing food can be supplemented. Potential applications for prebiotics as food ingredients to improve the gastrointestinal health of the consumer include beverages, bakery products, table spreads, sauces, infant formulae and weaning foods, cereals, confectionary, snack bars, soups, salad dressings and dairy products (Franck, 2002).

NUTRITIONAL PROPERTIES OF PREBIOTICS

The nutritional properties of prebiotics are related directly to the physiologic changes that they induce in the host. Bacterial metabolites are probably the main effectors of most observed effects. The most important metabolites are the short-chain fatty acids (SCFA) acetate, propionate and butyrate (Cummings et al., 2001). Prebiotic consumption can double the pool of SCFA in the GI tract.

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 colonization resistance of the gut microbiota, brought about by stimulation of bifidobacteria and lactobacilli, should in principle be easier to show *in vivo* (Cummings and MacFarlane, 2002).

A number of benefits has been ascribed to prebiotic intake (Gibson et al., 2000). However, some areas of interest are described below.

BOWEL HABIT

All carbohydrates that reach the large intestine have a laxative effect on bowel habit. The mechanism works via stimulation of microbial growth, increase in bacterial cell mass and thus stimulation of peristalsis by the increased bowel content (Cummings, 1994). It can be predicted, therefore, that prebiotics will be laxative. In carefully controlled studies it has indeed been shown that prebiotics that are fermented completely increase bowel frequency (Den Hond et al., 2000), bringing relief from constipation in chronically constipated subjects, and induce a faecal bulking effect of 1.5 to 2g of faeces/g prebiotic consumed (Gibson et al., 1995). However, this is less than seen with non-starch polysaccharide sources such as wheat bran (5.4g) or fruit and vegetables (4.7g), but similar to that produced by more rapidly fermented polysaccharides such as pectin (1.2g) (Cummings, 1993).

INCREASED MINERAL ABSORPTION

There has been increased interest in recent years in the possibility of increasing mineral (particularly calcium) absorption through the consumption of prebiotics. Although the small intestine is the principal site of calcium absorption in humans, significant amounts may be absorbed throughout the length of the gut, consequently, maximizing of colonic effects is desirable. Numerous animal studies have indicated that prebiotics increase calcium absorption from the colon (Delzenne et al., 1995; Younes et al, 2001; Coudray et al., 2003), resulting in increased bone density and bone trabecular structure (Ohta et al., 2002; Scholz Ahrens et al., 2002).

The absorption results have been evaluated in human dietary intervention trials. In one study, the consumption of 40g inulin/day for 28 days by nine healthy subjects resulted in a significant increase in calcium absorption (Coudray et al., 1997). A lower dose, 15g inulin, fructo-oligosaccharide (FOS) or galacto-oligosaccharide (GOS)/day, when fed to 12 healthy volunteers for 21 days, resulted in no effect on absorption of calcium or iron (Van den Heuvel et al., 1998). In a later study, 12 adolescent boys (aged 14-16) consumed 15g FOS/day for 9 days in a placebo-controlled study (Van den Heuvel et al., 1999). An increase (10.8%) in calcium balance was found with no significant effect on urinary excretion. Griffen et al. (2002) reported an increase in calcium

absorption when inulin plus a FOS mixture were fed to 59 healthy girls (aged 11-13.9), but not with FOS alone. Other researches also found that not all prebiotics promote mineral absorption to the same extent, and that the effects were more pronounced when long-chain fructans were present (Coudray et al., 1997). These observations have led to the hypothesis that short-chain fructans (DP 2-8)(which are very soluble and are fermented quickly) are able to modify the composition of the intestinal microbiota in the proximal part of the colon and that the long-chain fructans (DP 12-65) (which are fermented slowly) keep the improved microbiota metabolically active for a prolonged period of time and hence in the more distal parts of the intestine (Van Loo, 2004).

Several mechanisms have been proposed to explain the effect on mineral absorption. The intake of prebiotics acidifies the intestinal contents, which aids the solubilization of minerals (Coudray et al., 2003). The increased presence of butyrate, the SCFA which is a source of energy for intestinal epithelial cells, improves the absorptive capacity of the mucosa (Buddington et al., 1999). Other researchers have observed an increased capacity of calcium transporters (calbindin) in the colon (Ohta et al., 1998).

ANTICARCINOGENIC EFFECTS

It is known that several species of bacteria commonly found in the colon produce carcinogens and tumour promoters from the metabolism of food components. There have been several studies on anti-carcinogenic effects of dietary prebiotics in various experimental animal models. Inulin, for instance has been shown to inhibit the formation of aberrant crypt foci (ACF), a biomarker colon cancer, in rats (Reddy et al., 1997). Again, the more pronounced reduction of ACF by the long chains (sustained activity of the saccharolytic fraction of the intestinal microbiota), especially in the more distal parts of the colon, was demonstrated clearly (Van Loo, 2004). However, very few human studies have been carried out to date. Human studies tend to focus on faecal markers of carcinogenesis rather than being epidemiological in nature. Fructooligosaccharides and GOS have been investigated in this regard. Fructooligosaccharides have been found to reduce genotoxic enzymes concomitant with increasing bifidobacteria (Bouhnik et al., 1996). However, a more recent study on GOS found no significant changes in bifidobacteria or in markers of carcinogenesis (Alles et al., 1999). The lack of effect may be explained by the rather high starting bifidobacteria populations in the volunteers. It has been noted previously (Rycroft et al., 2001) that the magnitude of the response to prebiotics by bifidobacteria depends on the starting levels.

At least two mechanisms have been proposed to explain the effect of prebiotics on the development of cancer:

(i) Production of protective metabolites. Butyrate is a common fermentation end product and is known to stimulate apoptosis in colonic cancer cell lines and it is also the preferred fuel for healthy colonocytes (Prasad, 1980).

(ii) Shift of colonic metabolism away from protein and lipid metabolism towards more benign end products (saccharolysis, Manning and Gibson, 2004).

It is thought that lactic acid bacteria have inhibitory effects on several bacteria that produce carcinogenic enzymes and are themselves non-producers. Moreover, prebiotics may indirectly modify the activities of enzymes produced by the lactic acid bacteria that are involved in carcinogenesis (Reddy, 1998).

IMMUNOLOGICAL EFFECTS

Research with prebiotics in this field of interest is very recent and mostly from experimental models. It has been observed that consumption of inulin-type fructans increases the phagocytic capacity of macrophages (Kelly-Quangliana et al., 2003). There is increasing evidence from animal studies that the addition of fermentable fibre to the diet can modulate the type and function of cells from different regions of the gut-associated lymphoid tissue (GALT) (Schley and Field, 2002), increase the number of Peyer's patches (Pierre et al., 1997) and alter leucocyte and lymphocyte numbers in the intestinal mucosa (Gaskins et al., 1996).

Human studies have only recently begun. A study in healthy children, supplemented with FOS, demonstrated an impact on the occurrence of febrile illness, either associated with diarrhoea or upper respiratory illness (Saavedra and Tschernia, 2002).

The proposed mechanisms underlying the immunomodulating effects may include the following (Schley and Field, 2002):

- direct contact of lactic acid bacteria or bacterial products with immune cells in the intestine;
- production of SCFA from fermentation, and
- modulation of mucin production.

Although further work is needed to better define

the changes, the mechanisms for immunomodulation and the ultimate impact on health, there is convincing preliminary data to suggest that the consumption of fermentable fibres can modulate immune parameters in GALT, secondary lymphoid tissues and peripheral circulation (Gibson et al., 2004; Swanson, 2002).

EFFECTS ON LIPID METABOLISM

There is interest in the food industry in developing functional foods to modulate blood lipids such as cholesterol and triglycerides. However, human studies done on lipid metabolism have failed to show a uniform outcome. In some studies no effect on lipid metabolism were noticed (Pederson et al., 1997; Kruse et al., 1999; Van Dokkum et al., 1999) while in some studies TC and LDL-C decreased in comparison with placebo (Davidson et al., 1998) and in some studies prebiotics decreased fasting triglyceride levels (Jackson et al., 1999). According to Van Loo (2004), this variety of results can be attributed to the complexity of the biochemistry of lipid metabolism. There is evidence that FOS decrease the *de novo* synthesis of triglycerides by the liver. The means by which this occurs is not fully understood but the effect appears to be exerted at transcriptional level (Delzenne and Kok, 1999).

DISCUSSION

The purpose of this review is to show that carbohydrate prebiotics interact with physiological processes such as bowel habit, mineral absorption, cancer, immunology and lipid metabolism. This was observed by monitoring biomarkers of these physiological processes. The way in which prebiotics modify these physiologic processes may result in a reduced risk for disease or an improved health status. Because the physiologic effect is dependent on the type of intestinal fermentation induced by a specific prebiotic, it can be concluded that all other physiologic processes are a consequence of these fermentation processes, either directly from the bacteria or indirectly from the metabolites that they produce.

With respect to the prebiotic effect itself, the selectivity of the prebiotic cannot be described in terms of the names of bacterial species that increase in numbers and the species that decrease in numbers (Van Loo, 2004). The problem is that more than 80% of the bacterial species present in the intestine are unknown (cannot be grown *in vitro*, therefore cannot be classified taxonomically). The selectivity is recognized in terms of groups of bacteria (e.g. saccharolytic *vs* proteolytic), each with representative marker organisms (e.g. *Bifidobacteria* and *Clostridia*) (Van Loo, 2004).

Prebiotics can be used in a wide variety of foodstuffs such as dairy, bakery, meat products, drinks, spreads and confectionary (Franck, 2002). They are legally classified as food or food ingredients (not as additives) in many countries of which most of them have agreed that inulin and FOS may be labelled as 'dietary fibres' (Coussement, 1999). However, the classical methods for analysis of dietary of fibre (AOAC and Englyst methods) do not analyse them (because they are either too soluble in ethanol or degraded in the acid hydrolysis steps). Recently the AOAC International has adopted the 'Fructan method' (method number 997.08) that allows specifically the accurate quantitative determination of inulin and FOS in foods (Hoebregs, 1997).

Inulin and oligofructose can be used for either their nutrition advantages or technological properties (Franck, 2002), but they are often applied to offer a dual benefit: an improved organoleptic quality and a better-balanced composition.

In conclusion, the microbiota of the gastro-intestinal tract is key for nutrition and health of the host. Modulation of the microbiota can occur through diets that contain prebiotics. The approach of using diet to induce microbial change offers a very straight forward approach towards improved health. In terms of new developments, it is important that the definite health bonuses associated with prebiotic intake be determined.

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ABSTRACT The prebiotics concept was launched in 1995, defined as non-digestible food ingredients that affect host health beneficially by selectively stimulating the growth and/or activity of one or a limited number of bacterial species in the colon. In this review the prebiotics concept is revisited and the physiologic consequences of prebiotic consumption are evaluated. The review focuses primarily on randomised controlled trials in humans. Most of the research has been done with the ß(2-1) fructans. Therefore, they are used as an example of prebiotics. The results are relevant to the fields of gut function, mineral absorption, immunology, lipid metabolism and cancer. Thus it can be concluded that modification of intestinal microbiota by selectively fermented prebiotics is central in determining their nutritional properties and are thought to improve health status by reducing markers of disease risk.

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