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Recent developments in prebiotics to selectively impact beneficial microbes and promote intestinal health

Robert A Rastall and Glenn R Gibson

Prebiotics are non-digestible food ingredients that have a specific stimulatory effect upon selected populations of gut bacteria. The usual target microorganisms for prebiotic approaches are bifidobacteria. Numerous human feeding studies have shown the prebiotic influences that galactans and fructans can exert. Other candidate prebiotics are under investigation. The field is now moving towards identifying the health aspect associated with their use. Many avenues of gut related health are being researched, including reduction of diarrhoea, immune stimulation, and improved mineral bioavailability. Most current emphasis appears to be towards various parameters associated with metabolic syndrome. These include markers of insulin resistance, appetite, satiety, blood lipids and inflammatory status.

Addresses
Department of Food and Nutritional Sciences, The University of Reading, Whiteknights, Reading RG6 6AP, UK

Corresponding author: Rastall, Robert A (r.a.rastall@reading.ac.uk)

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Introduction

Since introduction of the concept in 1995 [1], interest in prebiotic carbohydrates has grown steadily. They have recently been defined as '*a selectively fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health*' [2]. Prebiotics can bring about large (specific) shifts in the populations of bacterial groups in the gut ecosystem and direct carbon flux from carbohydrate substrates to metabolic end products like organic acids. Accumulation of organic acids in the gut is thought to improve local and systemic health. For example, acetate is used to generate ATP in muscle tissue, propionate is thought to regulate liver cholesterol synthesis and butyrate is an important fuel for colonocyte function [2]. In general terms therefore, a saccharolytic gut microbial fermentation is said to be positive for health. In addition to direct microbe–host interactions, these metabolic end products are absorbed and, it is becoming increasingly apparent, have a systemic effect on the host [3,4•]. The consequences to health are being studies in several disease states. In the last few years, most health aspects have been directed towards obesity and inflammation. As such, this represents the main focus for this overview article. Other health parameters are covered by Sanders *et al.* [5] and Brownawell *et al.* [6]. These include effects on pathogens with potential to reduce infections including *Clostridium difficile* [7], stimulation of absorption of minerals such as calcium [8•], reduced Traveller's diarrhoea [9,10], repression of allergic symptoms [11], immune regulation [12], influences on Irritable Bowel Syndrome [13,14] and Inflammatory Bowel Diseases [15]. Because of the potential of prebiotics to impact on health, there is much in developing novel candidate prebiotics [16] and waste biomass is a promising resource in this regard.

Prebiotics, obesity and inflammation

Early studies in mice suggested that the gut microbiome may play a role in obesity [17] although this has not been fully borne out in human studies [18]. Agreement in studies to date in humans is not strong but there may be a decrease in levels of bifidobacteria, a decrease in Firmicutes and a reduction in *Methanobrevibacter* [19,20]. An increase in capacity to produce short chain fatty acids (SCFA) may also be a characteristic of the obese microbiome [21] and this has been reversed by a prebiotic approach [22]. Prebiotics have been shown to increase levels of bifidobacteria in obese women [23] using HitChip and qPCR analyses. This study of 44 obese women showed non-significant reductions in BMI, fat mass, waist:hip ratio and fat mass:lean mass ratio. Whilst it is not clear at the present time that manipulating the bifidobacterial populations in the gut will have an impact on obesity, there is promising evidence suggesting that prebiotics might have an impact on appetite, thus indirectly impacting upon weight gain. Verhoef *et al.* [24] fed the prebiotic oligofructose (OF) to 28 healthy adults for 13 days and studied appetite profiles, energy intake and expression of the gut hormones PYY and GLP-1. They found that although oligofructose consumption did not suppress appetite, energy consumption was reduced by 11% on day 13 when consuming 16 g OF per day. Expression of both gut hormones was increased. The authors suggest that this might be due to production of elevated levels of SCFA by fermentation of OF. In this regard, Frost [25] showed that in mice, colonic acetate can

cross the blood brain barrier and produce appetite suppression, at the level of the hypothalamus, in the absence of increased levels of PYY and GLP-1. A recent systematic review has been conducted of the effect of OF and inulin on appetite regulation, energy intake and weight loss in children and adults [26]. Studies amplifying this have been published by Cani *et al.* [27,28] who showed that fructan prebiotics could influence satiety in humans. Similarly, Parnell and Reimer [29] demonstrated that the same type of prebiotics could influence hormonal regulation and therefore appetite in overweight humans. The conclusion is that OF and inulin may have a contribution to make to reducing energy intake and weight loss.

Obesity is associated with chronic low-grade inflammation [30•] and there is evidence that prebiotics may act to reduce this state. The hypothesis is that SCFA resulting from prebiotic fermentation in the gut can reduce intestinal permeability with concomitant reduction in levels of circulating inflammatory mediators, notably bacterial lipopolysaccharides (LPS) [30•]. Consumption of inulin-enriched pasta reduced intestinal permeability as determined by the lactulose-mannitol excretion assay [31] and this was correlated with lower zonulin but higher GLP-2 expression. These peptides regulate tight junction integrity and have been shown to be modulated by prebiotic fermentation in animal models [30•]. The Dewulf study [23] also measured serum LPS and the inflammatory marker, C-reactive protein (CRP) and found that both were reduced on consumption of OF. A mixture of OF and inulin has shown positive effects in a study of women with type-2 diabetes [32] where 52 women with type-2 diabetes were fed 10 g OF + inulin per day or a maltodextrin placebo. Plasma LPS was significantly decreased and a non-significant effect was seen with CRP. Volunteers on the fructans also exhibited lower plasma glucose levels and lower glycosylated haemoglobin levels. Significant reductions were found in IL-6 and TNFα and a non-significant decrease in interferon-γ and increase in IL-10 were also seen.

Similar effects have been seen with galacto-oligosaccharide (GOS) prebiotics [20]. Consumption of 5.5 g GOS per day by 45 overweight women for 12 weeks in a placebo controlled crossover study reduced their inflammatory state as determined by faecal calprotectin and plasma CRP. This correlated with increased expression of secretory IgA. By the end of the study, significant decreases were also seen in total cholesterol, HDL-cholesterol, total cholesterol:HDL-cholesterol ratio and triglycerides. Plasma glucose levels were not changed but insulin levels were reduced at the end of the study period relative to the placebo. GOS has a good track record of manipulating the microbiota in human studies [33–36] and in this study, an increase in bifidobacteria and decreases in bacteroides and the *Clostridium histolyticum* group were seen [20].

Overall, a picture is emerging of prebiotic fermentation modulating the immune system towards an anti-inflammatory state and reducing systemic inflammation via effects on intestinal permeability.

Novel candidate prebiotics

The weight of evidence behind the health effects of prebiotics is generally behind the inulin-derived fructans (fructooligosaccharides, FOS: inulin and oligofructose) and GOS with less data supporting sucrose-derived oligofructose and lactulose [16,33]. There is, however, potential for generation of other candidate prebiotic oligosaccharides either by synthesis or polysaccharide hydrolysis [16]. This may include waste stream bioprocessing.

Prebiotics from simple sugars

GOS is conventionally manufactured from lactose, a waste product of the dairy industry, by enzymatic synthesis reactions catalysed by β-galactosidase enzymes [33]. Potentially prebiotic GOS has been synthesised using lactulose as a substrate [37]. The resulting oligosaccharides displayed similar fermentation profiles to conventional GOS using *in vitro* testing with faecal batch cultures. These preparations did not contain residual lactose but residual lactulose, itself a prebiotic. These preparations may prove to be more potent per gram than conventional GOS products.

There has been some interest recently in the prebiotic potential of gluco-oligosaccharides (GlOS). These are α-linked oligosaccharides of glucose containing 1→6, 1→3 and 1→2 linkages. They can also be branched in structure. Commercial GlOS products have been shown to be selective for bifidobacteria and bacteroides with a decrease in *Faecalibacterium prausnitzii* using *in vitro* faecal batch cultures [38] and bacterial counting using group-specific fluorescent gene probes. Whilst an increase in bifidobacteria would be considered as a health-positive change, a decrease in *F. prausnitzii* might not be desirable as this species is attracting interest as an anti-inflammatory component of the gut microbiota [39•]. This study was carried out using faecal inocula from lean and obese individuals and no differences were seen between these two groups.

Prebiotics from waste

A very promising source of novel candidate prebiotics is waste biomass from agricultural and food processing [40]. Traditionally, enzymes have been used for the generation of oligosaccharides from plant polysaccharides, but recently there has been interest in the use of autohydrolysis processes [41,42]. This involves treating polysaccharide-containing material at elevated temperature and pressure.

Autohydrolysis has been coupled with membrane processing to manufacture oligosaccharides from wood mannan

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