Gut microbiota and metabolic disorders: how prebiotic can work?

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Abstract
Experimental data in animals, but also observational studies in obese patients, suggest that the composition of the gut microbiota differs in obese v. lean individuals, in diabetic v. non-diabetic patients or in patients presenting other diseases associated with obesity or nutritional dysbalance, such as non-alcoholic steatohepatitis. In the present review, we will describe how changes in the gut microbiota composition and/or activity by dietary fibres with prebiotic properties, can modulate host gene expression and metabolism. We will evaluate their potential relevance in the management of obesity and related metabolic disturbances, in view of the experimental data and intervention studies published up to date.

Key words: Gut microbiota; Obesity; Prebiotics; Inflammation; Gut peptides

The worldwide epidemic of obesity is a crucial problem of public health, as it is associated with a cluster of metabolic disorders such as insulin resistance, type 2 diabetes and fatty liver disease(1). The cause of obesity is basically linked to ‘nutritional disequilibrium’ in an individual who consumes an excess of fat and calories v. energy expenditure, over a relatively long period of time. In addition, overfeeding is often associated with inadequate nutrition, leading namely to a low intake of n-3 PUFA and of dietary fibres. In that respect, some dietary habits related to an increase in bioactive food components present in whole grain cereals could be helpful in prevention of chronic diseases(2). Novel culture-independent technologies based on the analysis of the bacterial gene 16SrRNA (e.g., pyrosequencing) allowed significant progress in the knowledge of our microbial partners(3,4). Even if most of the function of the microbial genes remains unknown until now, and if we are conditioned at birth with a ‘personal’ profile of gut microbes, several recent papers and reviews support the idea that ‘dysbiosis’ (inadequate change of gut microbiota composition and/or activity related to host disease) characterises obese or overweight individuals(7–11).

The first studies reporting changes in gut microbiota composition in obese individuals have focused on changes in phyla proportion (decreased Bacteroides:Firmicutes ratio). Recently, Arumugam et al.(12) have identified, in individuals from different countries and continents, three robust clusters of gut microbial communities defined as ‘enterotypes’ by the authors. They found that these enterotypes were identified by the variation at the level of one of the three following genera: Bacteroides, Prevotella and Ruminococcus. Wu et al.(10) have shown that enterotypes were strongly associated with long-term diet, namely protein and animal fat (associated with Bacteroides) v. carbohydrates (Prevotella). Experiments performed in a model of mice colonised with the human gut microbiota reveals that changes in the diet composition (from high carbohydrates to western diet) allows a rapid switch of the microbial community, which can be transferred to germ-free mice(13). Interestingly, the transfer of this modified gut microbiota to germ-free mice also transfers the obese phenotype(13). Those data suggest that the gut microbiota composition/activity associated with nutritional imbalance might contribute to obesity and related disorders(8,14–17). If dysbiosis exists, is there a means to favourably change the microbial environment, and thereby to improve host health? This idea fits with the concept of prebiotic, originally described in the 90s, referring to dietary compounds that modulate the composition and activity of the gastrointestinal microbiota to improve health and wellbeing(18–20). The main purpose of the present paper is to report how nutrients with potential prebiotic properties are interacting with host metabolism in the context of obesity.

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Abbreviation: LPS, lipopolysaccharides.
We will refer to both mechanistic approaches in animals and to the lower number of intervention studies performed with prebiotics in human subjects.

Selection of nutrients with prebiotic properties: the bifidogenic effect as a starting point

Wu et al.\(^{(10)}\) have shown that microbiome composition may change 24 h after initiating a high-fat/low-fibre or a high-fibre/low-fat diet, but that enterotype identity remained stable during a 10 d nutritional intervention. They suggest that nutrients like dietary fibres, which are not digested by host enzymes, could modulate the gut microbiome in a relatively short period of time, independent of the effect of changes in transit time. Would it be possible to link the properties of dietary fibres, which specifically modulate the gut microbiota, with host functions related to obesity and overfeeding? Fermentable carbohydrates have initially been recognised as prebiotics, because they were preferentially fermented by specific types of bacteria, generally recognised as beneficial for host. Indeed, *Bifidobacterium* spp. represent an important and complex group of bacteria whose presence is often associated with interesting health effects\(^{(21–23)}\). In the context of obesity, several studies reported that a low number of *Bifidobacterium* spp. correlated with the development of obesity and/or diabetes\(^{(24–26)}\). We have previously demonstrated that diet-induced obesity (high-fat–low-carbohydrate diet) in mice markedly affects the gut microbial community, where the levels of *Bifidobacterium* spp. were significantly reduced, in accordance with the observation in human subjects\(^{(27,28)}\). Several fermentable carbohydrates (glucans, galactans, fructans, etc.) are easily and widely fermented by Bifidobacteria. Several data have shown the bifidogenic effect of dietary fructans or arabinoxylans added in the diet of obese mice or rats\(^{(27,29–35)}\).

In fact, promoting Bifidobacteria is not the sole consequence of the prebiotic treatment. By pyrosequencing and microarray analysis of the caecal 16SrDNA of ob/ob mice treated or not with prebiotics, we were able to point out a complex modulation of the gut microbial ecology also occurs upon prebiotic treatment in obese individuals\(^{(28,50,51)}\). The serum level of SCFA...
lipopolysaccharides (LPS), the main component of the Gram-negative bacteria, is approximately doubled in obese, diabetic or high-fat diet-fed individuals, a phenomenon that contributes to proinflammatory processes. The increase in LPS may occur by processes involving an increase in chylomicron formation (upon high-fat diet feeding), a decrease in gut barrier integrity and/or a decrease in alkaline phosphatase activity, which is the enzyme responsible for the cleavage of LPS in the intestine (for review see Cani & Delzenne(15) and Cani et al.(52)). Several prebiotics (glucans, fructans) are able to counteract the increase in LPS level in animal models of obesity(27,31,32,55). The decrease in LPS absorption occurs in prebiotic-treated animals through an improvement of the expression and activity of proteins involved in gut barrier function, including glucagon-like peptide 2, which is co-secreted with glucagon-like peptide 1 by endocrine L cells. In addition, a drop in endocannabinoid system activation in the intestinal cells also participates in the gut barrier function by prebiotics in obese animals(27,32,39,46,54–58). Further mechanistic studies are needed in order to better understand how prebiotic nutrients may interact with the host immune response in the context of obesity and related disorders. Moreover, the relevance of those effects remains to be studied in human subjects.

**Effect on glucose and lipid metabolism**

In the majority of studies, the administration of prebiotics lead to an improvement of fasting and/or post-oral glucose load glycaemia (for review see Roberfroid et al.(39)). The mechanisms could involve the secretion of gut peptides with incretin function, such as glucagon-like peptide 1, which participates in the improvement of hepatic insulin resistance(57). Several studies in human subjects also show an improvement in postprandial glycaemia (for review see Roberfroid et al.(19)). The mechanisms could involve the secretion of gut peptides with incretin function, such as glucagon-like peptide 1, which participates in the improvement of hepatic insulin resistance(57). Several studies in human subjects also show an improvement in glycemia upon prebiotic treatment, which appear much wider than the single increase in Bifidobacteria initially described, can be related to an improvement of gut bacterial functions implicated in the regulation of host energy homoeostasis. The promotion of gut hormones’ release, changes in the gut barrier integrity and/or the release of bacterial-derived metabolites could contribute to counteract metabolic alterations linked to obesity, including hyperglycaemia, inflammation and hepatic steatosis, at least in animal models (Fig. 1). The mechanistic studies suggest that the changes in the gut microbiota occurring upon prebiotic treatment, which appear much wider than the single increase in Bifidobacteria initially described, can be related to an improvement of gut bacterial functions implicated in the regulation of host energy homoeostasis. The promotion of gut hormones’ release, changes in the gut barrier integrity and/or the release of bacterial-derived metabolites such as LPS or aminotransferases, without referring to the modulation of the gut microbiota(61,62).

**Conclusion and perspectives**

Highly fermentable carbohydrates, such as prebiotics, are able to counteract several metabolic alterations linked to obesity, including hyperglycaemia, inflammation and hepatic steatosis, at least in animal models (Fig. 1). The mechanistic studies suggest that the changes in the gut microbiota occurring upon prebiotic treatment, which appear much wider than the single increase in Bifidobacteria initially described, can be related to an improvement of gut bacterial functions implicated in the regulation of host energy homoeostasis. The promotion of gut hormones’ release, changes in the gut barrier integrity and/or the release of bacterial-derived metabolites such as LPS or aminotransferases, without referring to the modulation of the gut microbiota(61,62).
could all participate in the improvement of host health in the particular context of overfeeding and obesity. Appropriate human intervention studies with ‘colonic’ nutrients (dietary fibres, prebiotics and others) able to selectively promote beneficial bacteria, or with food containing colonic nutrients, are essential to confirm the relevance of those nutrients in the nutritional management of overweight and obesity.

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