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Review

Nutritional modulation of gut microbiota in the context of obesity and insulin resistance: Potential interest of prebiotics

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A B S T R A C T

Obesity in humans leads to changes in the composition of gut microbiota, some of those changes being reversed upon dieting and changes in dietary habits. The studies devoted to understand how gut microbes control host energy homeostasis are of interest, in order to estimate how specific nutrients that induce changes in gut microbiota composition and/or activity – such as prebiotics – could be relevant in the management of obesity and related disorders. This review presents the potential molecular mechanisms allowing the gut microbiota to control host energy homeostasis, and presents the potential mechanisms evoked in the improvement of obesity by colonic nutrients that target the gut microbiota. It also discusses the relevance of this new area of research in human nutrition and health.

Contents

1. Changes in gut microbiota composition occur upon obesity and related metabolic disorders

Obesity is associated with a cluster of metabolic disorders including glucose intolerance, insulin resistance, type 2 diabetes, hypertension, dyslipidemia, fibrinolysis disorders, epithelial dysfunction, atherosclerosis, cardiovascular diseases, non-alcoholic fatty liver diseases (NAFLD) and non-alcoholic steatohepatitis (NASH) (Eckel, Grundy, & Zimmet, 2005; Ogden, Yanovski, Carroll, & Flegal, 2007). The adverse health consequences of weight gain and obesity are especially prominent following prolonged periods of positive energy balance and is mostly associated with a high-fat diet ingestion in our Western countries.

Results obtained both in rodents and humans, suggest that obesity is associated with an altered composition of gut microbiota (for review see Ley, 2009). Obesity is characterized by a reduced level of gut microbes phylogenic diversity (Turnbaugh et al., 2009), and by a division wide shifts of the two major phyla: more *Firmicutes* characterize obese versus lean individuals; some authors show a drop in Bacteroidetes upon obesity, whereas other authors show no change or even an increase of Bacteroidetes in overweight (Collado, Isolauri, Laitinen, & Salminen, 2008; Duncan et al., 2008; Ley, Turnbaugh, Klein, & Gordon, 2006; Turnbaugh et al., 2006). The level of fecal *Bifidobacterium* spp. was shown to be higher in children remaining normal weight at the age of seven, whereas it was not the case in overweight children. In addition, the authors observed that the *Staphylococcus aureus* count was lower in children who maintain a normal weight than in overweight (Kalliomaki, Collado, Salminen, & Isolauri, 2008). For that reason, it has been proposed that changes in specific bacteria could play a role in the development of obesity.

A question remains open: are the changes in gut microbiota in overweight or obese individuals due to the obesity per se, or due to changes in nutritional habits in obese people?

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Interestingly, the first studies have shown that dieting – whatever are the nutritional changes (low carbohydrates or low fat diet) – was able per se to reverse the shift in Firmicutes/Bacteroidetes (Ley et al., 2006). Other studies have correlated changes in gut microbiota with carbohydrate intake (for review see Ley, 2009). Data obtained in animals suggest that a high-fat diet – and not the obese state per se – can modulate microbiota composition towards an increase in Firmicutes and a proportional decrease in Bacteroidetes (Hilderbrandt, Hoffman, & Sherrill-Mix, 2009)

2. Gut microbiota participates to the regulation of host energy homeostasis

Evidence on the role of the gut microbiota on energy harvesting from the diet came from studies performed in germ-free mice (Bäckhed et al., 2004; Ley, 2009). Bäckhed et al. (2004) found that conventionally raised mice contained 40% more total body fat and 47% higher gonadal fat content than germ-free mice. Several pathways are proposed to explain that the presence of the gut microbiota drives the increase in fat mass – shown both in animals fed a standard carbohydrate-rich or a fat-rich diet (Cani & Delzenne, 2009a, 2009b; Ley, 2009; Musso, Gambino, & Cassader, 2009). The gut microbiota might promote intestinal monosaccharide absorption, energy extraction from non-digestible food components (via short chain fatty acids (SCFA) production through the fermentation), hepatic de novo lipogenesis, and adipocyte fatty acid storage; this latter effect is driven through lipoprotein lipase regulation (LPL) via the suppression of intestinal expression of an LPL inhibitor (FIAF, fasting-induced adipose factor). The second pathway, further explored the underlying mechanisms related to the fact that germ-free mice are protected against high-fat diet-induced obesity and associated metabolic disorders, independent on energy harvesting (Bäckhed, Manchester, Semenkovich, & Gordon, 2007). The authors have shown that proposed form their data that the presence of the gut microbiota suppresses the liver and skeletal muscle AMP-activated protein kinase (AMPK) -dependent fatty acid oxidation, thereby lessening an important catabolic pathway. A third pathway, involving the gut microbiota fermentation end-products, namely the short chain fatty acids (SCFA), has been recently proposed. SCFA act not only as energy substrates for the host, but also as signalling molecules. They are ligands for at least two G protein-coupled receptors, GPR41 and GPR43. Samuel et al. (2008) have demonstrated that GPR41$^{-/-}$ mice colonized with a model of fermentative microbial community (*Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*) did not gain fat mass at the same extent as wild-type littermates did. The authors proposed that in the absence of GPR41 signalling, the reduced plasma PYY levels promotes gut motility and reduces energy harvest from the diet. However, this last hypothesis – based on the fact that modulation of PYY level influences intestinal transit, is not in accordance with the fact that the modulation of gut microbiota by prebiotics (discussed later in this paper) increased SCFA concentration in the caecum but also increased plasma PYY levels, a mechanism probably contributing to the reduction of food intake and fat mass development upon prebiotic treatment (Cani & Delzenne, 2009a; Delzenne, Cani, & Neyrinck, 2007).

Metabolic diseases are commonly linked to inflammatory processes and the gut microbiota can also play a role in this process. In fact, animal and human data indicate that an increased level of circulating lipopolysaccharides (LPS) – called endotoxemia – is observed upon high-fat feeding, and is linked to disturbed glucose homeostasis (Cani, et al., 2007a). The first study examining the kinetics of baseline endotoxemia concentrations in healthy human subjects has been published by Erridge, Attina, Spickett, and Webb (2007). In this study, the authors found that a high-fat meal induces a metabolic endotoxemia leading to LPS concentrations that may be sufficient to induce some degree of cellular activation of monocytes *in vitro*. In addition, endotoxemia correlates with fasting insulin in non-diabetes patients, and is two-fold higher in type 2 diabetes patients group than in the non-diabetic subjects (Creely et al., 2007). A positive correlation has also been demonstrated between plasma endotoxin levels and energy/or fat intake in humans (Amar et al., 2008).

Experimental data previously suggested that LPS, derived from gram negative bacteria present in the gut, plays a key role in driving fat mass development, insulin resistance and systemic inflammation, since all those metabolic alterations do no occur in CD14-receptor knock out animals (CD14 being a key receptor component allowing LPS cellular response) (Cani, et al., 2007a), and are avoided in obese animals treated with large spectrum antibiotics, a treatment blunting intestinal LPS content (Cani et al., 2008). LPS is transported from the intestine towards target tissues by a mechanism facilitated by lipoproteins, notably chylomicrons freshly synthesized from epithelial intestinal cells in response to fat feeding (Ghoshal et al., 2009). Other mechanisms are also involved in the increased endotoxemia upon obesity, such as an increase in gut permeability linked to the decrease in expression and of the adequate repartition of tight junction proteins (Zonula occludens 1 and Occludin) (Cani et al., 2008; Cani et al., 2009b).

The link between gut microbiota, LPS translocation upon obesity and the development of adiposity could involve serum amyloid (SAA) protein. The level of this protein is increased in obese individuals and in mice fed a high-fat diet. Results comparing conventionally raised and germ-free mice have shown that in the presence of gut microbes, SAA3 is elevated in the adipose tissue of mice, and this increase requires an LPS-mediated mechanism (Reigstad, Lundén, Felin, & Bäckhed, 2009).

Form this section, one could think that, finally, the presence of the gut microbiota could be "harmful" when considering obesity and related disorders, as illustrated by the numerous processes by which, globally, gut microbes drive energy sparing and fat mass development. However, most of these data have been obtained through the comparison of germ-free versus conventional mice, two "extreme" situations, which cannot be reproduced through a nutritional approach. Moreover, as shown before, qualitative changes of the gut microbiota occur upon obesity, and it is well known that specific genders, species, or even strains of bacteria can exert drastically different effects related to host physiology. Therefore, we will show in the next sections, how "targeted" modification of gut microbiota is able to counteract obesity and associated disorders

3. Food components that modulate the gut microbiota have an impact on obesity and related disorders: the potential interest of prebiotics

In a series of experiments in mice fed a high-fat/carbohydrate free diet, we showed that such a dietary manipulation, leading to obesity and diabetes, changes bacterial populations in the intestinal microbiota, with a strong reduction in *Bifidobacterium* spp. numbers, a reduced *Bacteroides*-related bacteria, *Eubacterium rectale–Clostridium coccoides* group content (Cani, et al., 2007a, 2007c). In those studies, we found that among the different gut bacteria analyzed, metabolic endotoxemia correlated negatively with the bifidobacteria count (Cani, et al., 2007c). The administration of *Bifidobacterium* spp. as a probiotic has been shown to reduce the intestinal endotoxin levels and to improve mucosal barrier function (Griffiths et al., 2004; Wang et al., 2006, 2004). Another possibility to selectively modulate the gut microbiota is the prebiotic approach. The prebiotic concept refers to non-digestible dietary

ingredients that are selectively fermented by certain bacteria in the gastro-intestinal tract, thereby modifying the composition and/or activity of the gut microbiota with beneficial effects for host health (Gibson & Roberfroid, 1995; Roberfroid, 2007; Saulnier, Spinler, Gibson, & Versalovic, 2009). Prebiotics can be given orally (Tuohy, Rouzaud, Bruck, & Gibson, 2005) to specifically increase the gut bifidobacteria content of high-fat diet treated mice. Some prebiotics, such as fructans are also able to promote other interesting bacteria such as *Faecalibacterium prausnitzii*, for example (Ramirez-Farias et al., 2009). Since the first modulating effect on gut microbiota was established with bifidobacteria, the relation with the health effects has mostly been associated with the changes in this genus. We found that in prebiotic treated mice, *Bifidobacterium* spp. significantly and positively correlated with improved glucose homeostasis markers and normalized inflammatory tone (decreased metabolic endotoxemia, plasma and adipose tissue proinflammatory cytokines) (Cani, et al., 2007c).

Several mechanisms have been proposed in order to explain the positive effect of the prebiotic approach in obesity models. Among those hypotheses, the modulation of endocrine function occurs in prebiotic-fed animals is a phenomenon that contributes to the improvement of obesity and associated disorders (Cani & Delzenne, 2009a, 2009b; Cani, et al., 2006b). Endocrine L cells are present all along the gastro-intestinal tract. The expression of proglucagon gene in those cells leads to the secretion of different peptides, including glucagon-like peptides (GLP) 1 and 2, which play a role in host gut function and physiology. The ingestion of prebiotics has been shown to increase the number of L cells in the proximal colon of rats (Cani, Hoste, Guiot, & Delzenne, 2007b). The resulting increase in portal GLP-1 allows this peptide to regulate food intake and glucose homeostasis (Cani, et al., 2006b; Maurer, Chen, McPherson, & Reimer, 2009; Urias-Silvas et al., 2008). On the other hand, the increase in GLP-2 contributes to the improvement of gut barrier function and to the decrease in endotoxemia in obese mice (Cani, et al., 2009b).

The relevance of gut peptide modulation by prebiotics in humans is only poorly studied until now, but data obtained in humans have recently linked the increase in post-prandial gut peptide serum levels and the increase in satiety (Cani, et al., 2009a) and a decrease in fat mass development (Parnell & Reimer, 2009).

In addition to the role of LPS in the development of obesity, portal endotoxemia has been suggested to be a major risk in inducing hepatic inflammation in alcoholic liver diseases and NAFLD (Brun et al., 2007; Cani & Delzenne, 2009a, 2009b). Targeted modulation of gut microbiota by prebiotics can also contribute to the regulation of hepatic disorders associated with obesity. The use of prebiotics significantly reduces the hepatic triglyceride accumulation (steatosis) but also modifies hepatic inflammatory processes in the liver of different animal models of obesity (for review, Delzenne, Cani, & Neyrinck, 2008). Ma, Hua, and Li (2008) have pointed out a mechanism that could implicate an increase in specific hepatic immune cells that play a role in the maintenance of the equilibrium between pro-and anti-inflammatory cytokine production (NKT cells) in the probiotics-related improvement of glucose and lipid metabolism, but also hepatic disorders induced by a high-fat diet in mice. Similarly, the prebiotic approach is able to increase the phagocytic activity of hepatic fixed macrophages (Kupffer cells), thereby counteracting LPS-induced hepatotoxicity (Neyrinck, Alexiou, & Delzenne, 2004). The modulation of hepatic immune cell responsiveness by prebiotics in obese animals remains to be clarified.

Concerning human studies, only one paper has reported an improvement of hepatic alterations upon prebiotic treatment in non-alcoholic steatohepatitis patients (Daubioul, Horsmans, Lambert, Danse, & Delzenne, 2005).

4. Probiotics and prebiotics approach in the management of obesity and associated diseases in human

Even if the amount of relevant intervention studies remain scare in this field, namely due to the novelty of this concept, there are some data supporting the fact that both probiotic and prebiotic approaches could be interesting in the management of metabolic diseases associated with obesity. Interestingly, several physiological effects previously described in animals are also true when assessed upon mid term treatment with prebiotics in humans. A decrease in appetite and an increase in satiety, leading to a decrease in total energy intake, as well as a decrease in hepatic de novo lipogenesis, have been demonstrated in human volunteers fed with inulin-type prebiotics (16 g per day for several weeks) as compared to maltodextrin as a placebo (Cani, Joly, Horsmans, & Delzenne, 2006; Cani, Lecourt, et al., 2009; Letexier, Diraison, & Beylot, 2003). Prebiotics are however unable to drive an acute (48 h) change in food intake and appetite, thereby suggesting that the adaptation of the gut microbiota is required to have a physiological relevance in the control of food intake. A decrease in body mass index, linked to a modulation of gut peptides and appetite, have been shown upon long term treatment of overweight and obese patients (Abrams, Griffin, Hawthorne, & Ellis, 2007; Parnell & Reimer, 2009). An improvement of hepatic alterations has been reported in NASH patients receiving inulin-prebiotics versus placebo (maltodextrin) during 4–8 weeks (Daubioul et al., 2005).

5. Conclusion

The presence of saccharolytic gut bacteria in the gastro-intestinal tract is generally described to provide energy for the host, namely through the fermentation of the non-digestible carbohydrate and by promoting nutrients storage. However, targeted changes in the gut microbiota provided through the prebiotic approach can improve several metabolic disturbances occurring upon obesity. Most of the data obtained to date have been obtained in experimental animal studies, but promising effects are also shown in humans, thereby supporting the interest in the nutritional modulation of the gut microbiota in the management of metabolic diseases in overweight or obese patients. This concept could be applied to the prebiotic, but also to the probiotic approach; moreover, the metabolomic analysis will allow to select the potential new microbial targets related to obesity and related disorders in the future.

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