Prebiotics to manage the microbial control of energy homeostasis

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Abstract

The prevalence of obesity is continuously growing and has reached epidemic proportions. It is clear that current methods to combat obesity are not effective enough to reduce the problem. Therefore, further investigation is needed to develop new strategies. Recent research pointed out a potential role of the microbial community associated to the human host in controlling and influencing the energy homeostasis. According to the concept of Gastrointestinal Resource Management, this microbiota and its metabolic potential can be steered with the aim of improving host health. This review therefore focuses on the modulation of the intestinal microbiota through prebiotics with the aim to control of several aspects of metabolic homeostasis. In a first part, the importance of host-microbe cross-talk at the intestinal epithelium is discussed. Yet, energy metabolism, which includes both lipid and glucose metabolism, is also regulated by several key organs including the adipose tissue, brain, liver, muscles, pancreas and gut. Therefore, in a second part, we will discuss the microbial factors that are involved in the communication between these different tissues, and their potential management. Finally, we will give some future prospects of the use of prebiotics in an individualized treatment of metabolic disorders.

Introduction

Humans and microbes co-evolved for several thousands of years. Such an interaction is so bounding that - according to the hologenome theory of evolution - the host organism and its microbiota can be considered as a holobiont, a unit of selection in evolution (Rosenberg and Zilber-Rosenberg, 2011). This complex microbiota can be seen, in economic terms, both as an asset and liability with the capability of influencing the fitness of the host (Possemiers *et al.*, 2009).

In 2004-2005, the first reports about the effect of gut microbiota on the development of obesity and energy metabolism were published by the group of Jeffrey Gordon (Bäckhed *et al.*, 2004; Ley *et al.*, 2005). Since then, the microbial impact on several aspects of metabolic homeostasis was investigated (Burcelin *et al.*, 2009; Cani and Delzenne, 2007; Maurer *et al.*, 2009), such as the effect on lipid metabolism and atherosclerosis (reviewed by Caesar *et al.* (2010)), on metabolic syndrome (reviewed by Cani and Delzenne (2009); Sanz *et al.* (2010); Tilg (2010); Wellen and Hotamisligil (2005)) and insulin resistance and diabetes (reviewed by Delzenne and Cani (2010); Musso *et al.* (2011)). Although the mechanisms of action and the triggering factors are not fully understood, it is commonly accepted that the final health effect is the result of a complex interplay between various bacteria, which interact through various mechanisms with the host.

The capacity and the possibility to interfere in these complex interactions has been defined in the intuitive concept of Gastrointestinal Resource Management (GRM), i.e. the management of the complex gut microbiota and its metabolism with the aim of improving the health of the host (Possemiers *et al.*, 2009).

The use of prebiotics is a possible example of how to try to bring to practice the GRM concept. A prebiotic action is defined as the selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host (Roberfroid *et al.*, 2010).

The focus of this work will be to review the available knowledge on the effect of prebiotics on several aspects of metabolic homeostasis. In a first part, the importance of host-microbe cross-talk at the intestinal surface level is discussed. In a second part, we will discuss the microbial factors that are involved in the cross-talk between different organs of the host, and their potential management. Finally, we will give some future prospects on the use of prebiotics in an individualized approach to control metabolic disorders.

Part 1. The intestinal surface as site of host-microbe crosstalk and its barrier function

Host-microbiota cross-talk at the intestinal surface along the intestinal tract

Around 10^{14} microbes colonize the human gut with a coding capacity exceeding that of the host by a factor 100 (Egert *et al.*, 2006). Throughout evolution, humans co-evolved with this abundant microbiota and an intimate interaction came to existence (Zaneveld *et al.*, 2008). Van den Abbeele *et al.* (2011) recently reviewed the cross-talk at the host-microbial interface, which was crucial during this co-evolution. In addition, this cross-talk is relevant for the disturbances of the host-microbiota association, which can lead to disease states such as allergies (Bjorksten *et al.*, 1999), inflammatory bowel diseases (Garrett *et al.*, 2007) and obesity (Turnbaugh *et al.*, 2006). It should be noted that the latter diseases are currently in the rise (Blaser, 2006). Key in the host-microbe cross-talk mostly is that the host continuously detects microbial signals through strategically localized host receptors (Medzhitov and Janeway, 2002). These microbial signals are referred to as microbe-associated molecular patterns (MAMPs). While fungi and viruses are often recognized through their β-glucans and

nucleic acids, respectively, bacteria are often detected through lipopolysaccharides (LPS), peptidoglycans and teichoic acids (reviewed by Van den Abbeele *et al.* (2011). The host receptors that detect these MAMPs are called pathogen recognition receptors (PRRs) and include a diverse set of transmembrane (e.g. Toll-like receptors) (Takeda *et al.*, 2003), cytosolic (e.g. NOD-like receptors) (Ting *et al.*, 2008) and secreted receptors (e.g. collectins) (Gupta and Surolia, 2007). This allows the host to characterize the nature of the microbial signal and respond appropriately. The resulting host response includes production of antimicrobial peptides (Medzhitov and Janeway, 1997), activation of adaptive immune cells and production of resulting effector molecules including e.g. Immunoglobulin A (IgA) (Macpherson and Uhr, 2004). As a result of the continuous detection of microbes, host defence molecules are continuously secreted and trapped in the overlaying mucus layer, which allows the host to particularly control the composition and abundance of the mucosa-associated microbiota (Figure 1). Specific microbial characteristics such as capacity to adhere to the mucus layer, oxygen tolerance, the ability to degrade host-derived glycans further determine the unique composition of the mucosal microbiota (Van den Abbeele *et al.*, 2011). While mucosal microbes would be crucial for priming the immune system or increasing the bioavailability of beneficial microbial metabolites at the intestinal surface, the luminal microbiota have an important metabolic function.

Given the fact that humans closely interact with their co-evolved luminal and mucosal intestinal microbiota, there is great interest in dietary interventions with e.g. prebiotic compounds that are able to modulate both the luminal and mucosal microbial composition and activity (Langlands *et al.*, 2004; Van den Abbeele *et al.*, 2011). In that way, prebiotics may beneficially steer the host-microbe interactions.

Importance of a proper mucosal barrier and risks in case of increased permeability

Over the last few years, the research group of Nathalie Delzenne produced several groundbreaking papers regarding the onset of obesity and its related metabolic disorders. In several studies, one investigated, the impact of a high-fat diet on the intestinal microbiota and rodent hosts (Cani *et al.*, 2007a; Cani *et al.*, 2008; Cani *et al.*, 2006; Cani *et al.*, 2007d; Cani *et al.*, 2009b; Neyrinck *et al.*, 2011). Rodents fed a high-fat diet suffered from impaired gut barrier function. This barrier function is crucial since it forms the basis of the strategic localization of PRRs and subsequent detection of MAMPs. This can be illustrated by the detection of lipopolysaccharides (LPS), a MAMP, trough Toll like receptor 4 (TLR-4) (Cario and Podolsky, 2000) and nucleotide-binding oligomerisation domain-1 (NOD-1) (Girardin *et al.*, 2003) (Figure 1). TLR-4 is only in low levels expressed on the apical side of the epithelium while NOD-1 is expressed inside the cell. In this way, LPS is not detected on the apical side where it merely derives from the commensal mucosa-associated microbes but on locations where its presence may derive from potentially dangerous microbes. The increased permeability which is caused by the high-fat diet leads to LPS leakage trough the gut wall ultimately leading to increased LPS levels in the blood (endotoxemia). At that point, LPS of commensals is overly detected by the PRRs of the host resulting in inflammatory responses and symptoms of metabolic disorder (Cani *et al.*, 2007a; Cani *et al.*, 2008).

It has been shown that the detrimental effect corresponding to metabolic disorders can be partially reversed by reinforcing the gut barrier function. This can be obtained through modulation of the gut microbiota with (potential) prebiotic compounds such as fructans (Cani *et al.*, 2006; Cani *et al.*, 2007d; Cani *et al.*, 2009b) and long-chain arabinoxylans (Neyrinck *et al.*, 2011). The exact nature of the microbial modulations throughout these experiments remains to be elucidated although strong indications exist that specific microbial groups may play a major role. Firstly, as bifidobacteria decreased during fat feeding (Cani *et al.*, 2007d),

while their abundance increased during supplementation of the (potential) prebiotic compounds (Cani *et al.*, 2006; Cani *et al.*, 2009b; Neyrinck *et al.*, 2011), this genus may have an important protective role towards barrier integrity (Khailova *et al.*, 2009). Also other studies indicate that increased bifidobacteria levels are correlated with normal weight in children (Lundell *et al.*, 2007) and women (Collado *et al.*, 2008), while overweight in these studies corresponded to lower bifidobacteria abundances. Improved gut barrier function has also been attributed to specific *Lactobacillus* spp. through protection of the epithelial tight junctions during external stress (Montalto *et al.*, 2004; Seth *et al.*, 2008).

Besides reinforcing tight junctions between epithelial cells, restricted permeability of the gut wall may also be achieved through elevated secretion of mucin. A future focus may thus be to analyze the mucin composition of the mucus layer, which overlies the epithelium upon prebiotic treatment. This mucus layer normally consists of a double protective layer: a very dense, firmly attached and quite sterile inner mucus layer and a less dense, loosely attached, more strongly colonized outer mucus layer (Johansson *et al.*, 2010; Schreiber, 2010). Prebiotics are typically shown to increase mucin-levels by decreasing the pH (Barcelo *et al.*, 2000; Shimotoyodome *et al.*, 2000), increasing the mechanical stimulation by increased intestinal content and tissue weight (Schmidt-Wittig *et al.*, 1996) or increasing the butyrate production (Barcelo *et al.*, 2000), especially by species residing in the mucosal environment (Van den Abbeele *et al.*, 2011). In contrast, the type of mucin that is produced upon administration of a prebiotic compound is something which has often been neglected. This may be important as specific muc-types, such as the membrane-bound Muc17 (mouse homolog Muc3), have shown to promote epithelial barrier integrity (Resta-Lenert *et al.*, 2011). Further, it has been shown that a mix of *Lactobacillus reuteri* strains is able to reach the epithelium and prevent inflammation and translocation in DSS-treated mice. It was proposed that this might be due to an increased expression of membrane-bound Muc3 (Schreiber, 2010).

In conclusion, the loss of gut barrier integrity leading to increased infiltration of microbial signals may be an important factor at the onset of obesity and its related metabolic disorders, Moreover, prebiotics may be protective by avoiding this loss of barrier integrity.

Part 2. Microbial regulation of host signals involved in lipid metabolism

Energy metabolism is regulated by several key organs including the adipose tissue, brain, liver, muscle, pancreas and the gastrointestinal tract (GIT). The diverse host parameters that are involved in these processes are listed in Table 1. This part of the review will focus on the microbial factors that are involved in the communication between the different tissues, and their potential management with prebiotics.

Impact of prebiotics on gut peptides involved in fat storage

Prebiotics may possibly have an effect on gut peptides that are involved in fat storage. The fasting induced adipose factor (FIAF), also known as angiopoietin-like protein 4 (ANGPTL4), has been thoroughly investigated as a multifunctional signal protein produced by many tissues such as the liver (Kim *et al.*, 2010), adipose tissue (Dutton and Trayhurn, 2008), intestine (Bäckhed *et al.*, 2004) and hypothalamus (Kim *et al.*, 2010). Once secreted in the blood, FIAF inhibits the activity of lipoprotein lipase, an enzyme responsible for the conversion of triglycerides to monoglycerides and fatty acids from circulating lipoproteins (Mandard *et al.*, 2006; Yoshida *et al.*, 2002). As a consequence, these triglycerides cannot be stored in the fat tissue, resulting in a lower body weight (Bäckhed *et al.*, 2004).

A particular feature of the intestinal FIAF gene is that its expression is strongly regulated by the presence of an intestinal microbial community (Bäckhed *et al.*, 2004; Fleissner *et al.*, 2010). Intestinal FIAF expression is significantly repressed in mice with a normal intestinal microbial community compared to germ-free mice. Further, conventionalization of these germ-free animals with intestinal bacteria significantly decreased FIAF levels, resulting in an enhanced fat storage and weight gain (Bäckhed *et al.*, 2004). Moreover, elevated FIAF levels may protect germ-free mice against certain types of high-fat diet-induced obesity through induction of the peroxisome proliferator-activated receptor-γ coactivator-1α (Pgc-1α), thereby regulating genes involved in energy metabolism (Bäckhed *et al.*, 2007; Fleissner *et al.*, 2010). Fleissner *et al.* (2010) reported that, despite the intestinal FIAF repression in conventionalized mice, their plasma FIAF levels were not decreased as compared to germfree mice. In contrast, in conventionalized mice, a higher concentration of cleaved FIAF was observed whereas the native FIAF concentration was unchanged. These results suggest that the microbial community increases (cleaved) FIAF in sites of the body other than the intestine. Therefore, the impact of the microbial community on FIAF regulated processes should be further explored, not only in the intestine, but also in other parts of the human body.
To the best of our knowledge, only one substrate with impact on FIAF expression was reported. In obese mice fed a high fat diet, it was observed that chitosan from mushrooms significantly decreased FIAF expression in visceral adipose tissue (Neyrinck *et al.*, 2009). It was however not investigated whether this was due to shifts in either microbial fermentation products or in composition of the microbial community.
Grootaert *et al.* (2011) showed that SCFAs such as butyrate and propionate, but not acetate, stimulate FIAF transcription in several colorectal and hepatic cancer cell lines. When investigating the effect of specific intestinal monocultures, differential effects on FIAF expression were identified. An *in vivo* mouse study from Bäckhed *et al.* (2007) demonstrated that FIAF production was more repressed when inoculating germ-free mice with a combination of *Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*, than with each of them separately. Incubation of HCT-116 cells with *E. coli* resulted in decreased FIAF secretion (Grootaert *et al.*, 2011). In contrast, *in vitro* incubations of intestinal HT-29 and Caco-2 cells with *Enterococcus faecalis* increased FIAF production after a few hours (Are *et al.*, 2008; Grootaert *et al.*, 2011). Similarly, it was shown that *Lactobacillus paracasei* ssp paracasei F19, *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* BB12, and not *Bacteroides thetaiotaomicron*, were able to stimulate FIAF expression in several colonic cell lines including HCT-116, HT-29, LoVo and SW-480 cells (Aronsson *et al.*, 2010). In the case of *Lactobacillus* F19, the FIAF stimulatory effect was attributed to a secreted microbial factor, which was however not identified in the study. In addition, conventionalization of mice with *Lactobacillus* F19 increased native FIAF levels in blood plasma, and resulted in decreased fat storage and increased blood VLDL levels.
Summarized, although FIAF is an interesting molecule to focus on for prebiotic treatment, its functionality largely depends on the site of production, isoform appearance and final target organs. Until now, the most dominating effect of microbial FIAF modulation is not identified yet and needs further investigation with relevant models.

Prebiotics that alter energy intake through satiety signals

Prebiotics may also be used to decrease appetite by modulation of specific hormones involved in appetite and satiety. Leptin is a hormone mainly produced by adipose tissues and inhibits food intake. Prebiotic substrates such as chitosan decrease the production of leptin in adipocytes in high fat diet-induced obese mice (Neyrinck *et al.*, 2009), although the exact mode-of-action is not known. In addition, leptin was also decreased in rats weaned with

inulin-containing high fiber diets (Maurer *et al.*, 2009). Xiong *et al.* (2004) demonstrated that SCFA belonging to C2-C6 fatty acids stimulate leptin in murine adipocyte cell lines and primary adipocyte cell culture. In case of propionate, significantly increased leptin production was attributed to increased GPR41 activation. Leptin stimulation through G-coupled protein receptors was also shown in human adipose tissue (Lahham *et al.*, 2008).

Glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) are satiety stimulating hormones, released in response to nutrient ingestion by L-cells in mainly ileum and colon. GLP-1 promotes insulin secretion and pancreatic β-cell proliferation and controls glycogen synthesis in muscle cells (Delzenne *et al.*, 2007), whereas PYY slows down gastric emptying. In contrast, ghrelin stimulates appetite and is mainly produced by P/D1 cells in the stomach and ε-cells of the pancreas (Inui *et al.*, 2004).

Non-digestible carbohydrates, such as oligofructose (Cani *et al.*, 2007b; Maurer *et al.*, 2009; Piche *et al.*, 2003), lactitol (Gee and Johnson, 2005) and resistant starch (Zhou *et al.*, 2008) are effective to induce satiety by modulating the production of the gut peptides GLP-1, PYY and ghrelin through a mechanism that also involves modulation of the intestinal microbial community (Cani *et al.*, 2007b). For instance, rats fed a oligofructose-enriched diet showed a significantly increased GLP-1 and decreased ghrelin production, and doubled the number of GLP-1-expressing cells in the proximal colon (Cani *et al.*, 2004; Cani *et al.*, 2007c). In addition, also human studies showed higher plasma GLP-1, PYY and/or ghrelin levels after intake of oligofructose (Cani *et al.*, 2009a; Parnell and Reimer, 2009; Piche *et al.*, 2003), which may explain the increased satiety feeling and decreased energy intake behaviour of the subjects. Finally, lactitol mainly increased PYY production both in rats and humans (Gee and Johnson, 2005), whereas resistant starch significantly increased both PYY and GLP-1 production (Zhou *et al.*, 2008). The bacterial regulation of gut peptides is mediated by SCFA produced from these indigestible substrates. Physiological concentrations of acetate, propionate and butyrate, but also a pH decrease from 7.5 to 6, significantly increased proglucagon and PYY in the entero-endocrine colon cell line STC-1 (Zhou *et al.*, 2008). In addition, the presence of glucose in the intestine also enhances the GLP-1 production in the L-cells (Egan and Margolskee, 2008). These mechanisms may explain why gut peptide modulation is only observed with highly fermentable fibers (Massimino *et al.*, 1998).

Recently, also FIAF was identified as a potential signal protein with effect on hypothalamic control of appetite. Bacteria by means of LPS are able to induce a low-grade inflammation, as already discussed (Cani *et al.*, 2007a). Brown *et al.* (2009) showed that when mice were treated with LPS, body weight was significantly decreased and increased levels of FIAF were observed in the hypothalamic, pituitary, cortical and adipose tissues. Similar effects on FIAF levels were observed when N-1 neuronal and 3T3-L1 adipocyte cells were treated with LPS (Brown *et al.*, 2009). Therefore, FIAF is considered as one of the mediators of hypothalamic control of appetite and energy metabolism through LPS. In fact, LPS-induced endotoxemia was also associated to an anorectic response via hypothalamic-dependent mechanisms (Huang *et al.*, 1999; Rummel *et al.*, 2008). Yet, it is not desirable to steer this FIAF response by addition of LPS to the host, as LPS stimulates inflammatory responses in other tissues.

In summary, we conclude that the influence of microbiota on satiety hormones is a promising issue for prebiotic treatment, especially for substrates that enhance SCFA production. Indeed, a large part of the SCFAs are transported into the blood stream, thereby targeting several tissues, such as the adipose tissue, which may be induced to produce hormones involved in appetite and satiety.

Prebiotic modulation of cholesterol and lipid metabolism

Several pro- and prebiotics may have a possible effect on serum cholesterol and lipid levels, thereby not only affecting fat storage, but also the development of cardiovascular diseases (reviewed by Ooi and Liong (2010) and Williams (1997)). Several mechanisms have been proposed, including enzymatic deconjugation of bile acids (Bongaerts *et al.*, 2000), assimilation of cholesterol (reviewed by St-Onge *et al.* (2000)), co-precipitation of cholesterol with deconjugated bile, cholesterol binding to bacterial cell walls, incorporation of cholesterol into microbial cell membranes, conversion of cholesterol into coprostanol and production of short-chain fatty acids upon fermentation (reviewed by Ooi and Liong (2010)). Examples of probiotic bacteria influencing cholesterol and lipid metabolism are *Lactococcus lactis* (Nakajima *et al.*, 1992), *Streptococcus thermophilus* (Pulusani and Rao, 1983; Richelsen *et al.*, 1996), *Lactobacillus acidophilus* (Gilliland *et al.*, 1985), *E. faecium* (Richelsen *et al.*, 1996), *Bifidobacterium bifidum* (Beena and Prasad, 1997; Mohan *et al.*, 1996) and *B. longum* (Xiao *et al.*, 2003).

Several human and rodent *in vivo* studies also mention the cholesterol and lipid lowering effects of oligofructose (de Luis *et al.*, 2010; Delzenne *et al.*, 1993; Fiordaliso *et al.*, 1995; Trautwein *et al.*, 1998; Williams and Jackson, 2002), xylo-oligosaccharides (Hsu *et al.*, 2004), chito-oligosaccharides (Li *et al.*, 2007), soybean oligosaccharides (Chen *et al.*, 2010) and resistant starch (Cheng and Lai, 2000; Venter *et al.*, 1990). These effects may be linked to the production of propionate, which inhibits hepatic cholesterol synthesis from acetate (Berggren *et al.*, 1996; Lin *et al.*, 1995; Todesco *et al.*, 1991). Yet, the concentration of propionate that is needed to induce the cholesterol and lipid lowering effect is 10 to 100 fold higher for human than for rat hepatocytes (Lin *et al.*, 1995).

Hepatic lipogenesis is not only regulated by short chain fatty acids, but also by serum glucose and insulin levels (Towle, 2001). Enhanced sugar uptake has been observed in presence of gut bacteria compared to germ-free conditions, which can be explained by several mechanisms. First of all, the presence of an intestinal microbial community leads towards an increase in the amount of capillaries that underlie the small intestinal epithelium (Hooper *et al.*, 2002). Secondly, host monosaccharide transporters are induced by the polysaccharide-processing activity of the microbiota, as was demonstrated by studies with germ-free mice colonized with *B. thetaiotaomicron* (Hooper *et al.*, 2001). The monomers generated from indigestible polysaccharides are delivered as substrates for lipid production in the liver. Besides, they may also activate the lipogenic enzymes in the liver by ChREBP- and SREBP-1- mediated mechanisms (Bäckhed *et al.*, 2004). Hence, the polysaccharide-degrading potential of an intestinal microbial community may be an important determinant for hepatic lipid production. In obese *ob/ob* mice, the intestinal microbial community is enriched for genes that are able to harvest calories from complex plant-derived polysaccharides compared to lean mice. These genes encode for enzymes involved in sugar degradation, sugar transport and acetate and butyrate production (Turnbaugh *et al.*, 2006).

We conclude that the potential influence of intestinal microbiota and prebiotics on lipid and cholesterol production in the host is a complicated process which involves several nutrients, target organs and signalling pathways. More investigation is warranted to identify the dominating mechanism by which prebiotic modulation of the intestinal microbial community may contribute to lipid and cholesterol lowering effects.

Part 3: Prebiotic modulation of glucose and insulin metabolism

As mentioned before, intestinal bacteria can impact food intake and lipid metabolism, but may also be involved in carbohydrate maintenance and disturbances thereof, such as insulin resistance. Insulin resistance is the fundamental defect in type 2 diabetes, a disease that afflicts 6% of adult Americans, up from 3% in the early 1970s (Taubes, 2009). A role of

dietary fibers in general and prebiotics in particular has been shown in regulating glucose maintenance in numerous studies and will therefore also be used in this part to illustrate the role of intestinal bacteria.

Indeed, consumption of whole grains dietary fibers has been shown to improve blood glucose and insulin responses (reviewed by Gemen *et al.* (2011)). It is now believed that the underlying mechanism is of a multifactorial nature with different activity profiles throughout the gastrointestinal tract (Figure 2). Firstly, inclusion of dietary fiber in dietary products may replace part of the available carbohydrates in the food product, leading to lower glycemic response. For instance, resistant starch lowers the glycemic index, by being indigestible in the upper intestine, as opposed to digestible starch. The resistance to digestion of resistant starch is mainly attributed to particular physical structures, such as the amylose / amylopectin ratio. A higher ratio leads to a more branched polymer structure, which is less susceptible to enzymatic digestion in the small intestine (Brouns *et al.*, 2002; Fassler *et al.*, 2006; Storey *et al.*, 2007; Venter *et al.*, 1990).

Secondly, depending on their structure, dietary fibers such as arabinoxylans and beta-glucans, form a viscous solution in the stomach, thereby delaying gastric emptying and physically trapping nutrients, such as glucose and thereby reducing their absorption. In addition, the passage of digestive enzymes through the viscous food bolus is limited, which reduces the hydrolysis by digestive enzymes (Mohlig *et al.*, 2005; Regand *et al.*, 2009; Wood *et al.*, 2000). The combination of these processes will again lower the glycemic response. Reduced serum glucose concentrations decrease the amount of insulin needed to clear the glucose load. Upon repeated consumption of such fiber, the reduced ambient insulin concentrations may result in an up-regulation of cell surface insulin receptors, thereby increasing insulin sensitivity (Song *et al.*, 2000).

As mentioned before, changes in the intestinal bacterial community are involved in obesity, but also in insulin resistance. Interesting work has recently been published on the use of mice genetically deficient in Toll-like receptor 5 (TLR5). These mice spontaneously develop symptoms of the metabolic syndrome, among which insulin resistance (Vijay-Kumar *et al.*, 2010). Transfer of the intestinal microbiota of these mice into germ-free wild-type mice allowed transferring the metabolic phenotype into the wild-type mice, including insulin resistance. As this shows that specific microbial community composition may be implicated in insulin resistance, alterations of the community through dietary interventions may also affect glucose and insulin metabolism. A third mode of action of dietary fibers may therefore be related to the modulation of the intestinal microbiota.

Dietary fibers are typically non-digestible and therefore reach the colon, where they can be metabolized into SCFA by the intestinal bacteria. There is evidence that hepatocytes may, when exposed to an increase in short-chain fatty acids, increase glucose oxidation, decrease fatty acid release, and increase insulin clearance - an environment conductive to enhanced insulin sensitivity (Frayn *et al.*, 1996; Thorburn *et al.*, 1993; Venter *et al.*, 1990). This would be related with specific interactions with G-protein-coupled receptors GPR41 and GPR43 (Delzenne and Cani, 2011; Dewulf *et al.*, 2010). Whereas acetate is typically considered to act as substrate for lipogenesis in the liver, propionate would inhibit *de novo* lipogenesis and gluconeogenesis from lactate, decrease inflammation and improve insulin sensitivity (Al-Lahham *et al.*, 2010; Berggren *et al.*, 1996; Lin *et al.*, 1995). Finally, butyrate has also been linked with improved insulin sensitivity (Gao *et al.*, 2009).

As described in the section on the role of the intestinal barrier and low-grade inflammation in obesity and metabolic disorders, specific changes induced in microbial community composition upon (prebiotic) fiber intake may also be involved in improvements of glucose maintenance, through altered host-bacteria interactions, involving improvement of gut barrier function and reduction of LPS leakage (Cani and Delzenne, 2009; Neyrinck *et al.*, 2010;

Neyrinck *et al.*, 2011). In addition, dietary fibers such as beta-glucans, may directly interact with the mucosal immune system and influence insulin sensitivity through immune-modulation (King *et al.*, 2007; Vos *et al.*, 2007).

Delzenne and Cani (2011) recently summarized the current evidence on the relation between specific microbial community composition and diabetes. Changes in community composition seem to involve reduced presence of Firmicutes as opposed to Bacteroidetes (Larsen *et al.*, 2010). Other researchers showed lower representation of the genus *Bifidobacterium* and *Bacteroides vulgatus* (Wu *et al.*, 2010) or the abundance of *Faecalibacterium prausnitzii* (Furet *et al.*, 2010) in microbiota from diabetic individuals and a lower presence of microbiota-related metabolites in the blood and urine of diabetic individuals (Lucio *et al.*, 2010; Zhao *et al.*, 2010).

The interaction between dietary fibers, intestinal microbiota and gut peptide hormones has been described extensively in relation to weight management and lipid metabolism (Cani *et al.*, 2005; Delzenne and Cani, 2011; Delzenne *et al.*, 2007). Interaction of these peptide hormones with glucose metabolism and insulin sensitivity was also shown in numerous animal studies (Delzenne and Cani, 2010) For instance, dietary fiber such as oligofructose can increase the number of endocrine L-cells in the proximal colon of rats (Cani *et al.*, 2007c) and increase the production of GLP-1 and GLP-2, the former being involved in the regulation of insulin sensitivity (Maurer and Reimer, 2011) and the latter in barrier function control (Cani *et al.*, 2009b). Another example is the potential role of adiponectin (Weickert and Pfeiffer, 2008). In a cross-sectional analysis, high intakes of cereal dietary fiber were positively associated with plasma adiponectin after adjusting for lifestyle factors and dietary glycemic load (Qi *et al.*, 2005). Adiponectin may act as a peripheral starvation signal promoting the storage of triglycerides preferentially in adipose tissue (Kim *et al.*, 2007). As a consequence, reduced triglyceride accumulation in the liver and in the skeletal muscle might convey improved systemic insulin sensitivity (Weickert and Pfeiffer, 2006).

Summarized, the positive effects of (prebiotic) dietary fibers on postprandial glucose and insulin response are becoming more and more clear. Recently, Gemen *et al.* (2011) provided a clear overview of the existing scientific literature, in which 39 publications were referred to. Although further research is needed to differentiate the variety of existing fiber sources in their efficacy and specific mode of action, the basic principles of the underlying mechanisms and the intriguing role of the gut microbiota become unravelled.

Future perspectives

The studies described in this review - although they have been conducted on animals - suggest that a successful prebiotic intervention with respect to obesity and its related metabolic disorders could be possible (Cani *et al.*, 2006; Cani *et al.*, 2007d; Cani *et al.*, 2009b; Neyrinck *et al.*, 2011). However, new metagenomic technologies have also pointed out that the interindividual variability of our holobiont is a key factor for the success of a given strategy. For instance, Walker *et al.* (2011) recently showed a strong variation in terms of microbial modulation among human subjects in response to prebiotic supplementation. As a consequence, the management of the intestinal microbiota with the aim of improving human health will optimally require a prior characterization of the microbiota, i.e. the concept of personalized health-care. In this respect, several options may be available. When the necessary genes/species/strains are present, one may target them through specific prebiotics. If not present, the so-called synbiotic approach could be a valuable solution: addition of specific bacteria with a metabolic capability of interest (e.g. probiotics but also microbes beyond the current definition such as butyrate producing species – *Eubacterium rectale, Faecalibacterium prausnitsii, Anaerostipes caccae, Roseburia intestinalis*). A final option

could be the transfer of entire communities (or part of the microbial population) through faecal transplantation (Khoruts *et al.*, 2010), as an extension of the concept of synbiotics. This implies that studies demonstrating the beneficial effect of prebiotics are useful but need a better characterization of the exact modulation of the intestinal microbiota (both luminal and mucosal microbiota) in order to mechanistically explain the beneficial host effect. As an alternative to the individual specific approach, it may be possible that individuals may be grouped and subsequently treated with specific prebiotics based on an enterotype-like classification as proposed by (Arumugam *et al.*, 2011).

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Figure legends

Figure 1. Intestinal section with focus on the effect of a fat diet and a prebiotic treatment on LPS detection, trough TLR-4 and NOD-1. An increased permeability which is caused by the high-fat diet leads to LPS leakage trough the gut wall, PRRs' detection, thus resulting in an inflammatory response.

Figure 2. Schematic overview of the impact of dietary fiber on several parameters involved in energy metabolism**. The mechanism of increased viscosity, decreased absorption of nutrients and replacement of available carbohydrates is relevant for the whole gastrointestinal tract.**

Table 1. Overview of *in vivo* and *in vitro* experiments in which the effect of prebiotics on several parameters involved in fat and sugar metabolism is confirmed. n.r. = not reported.

Signal molecule	Produced by	Function	Bacteria/bacteria-related mode of action	Prebiotics	Experimental design	References
GLP-1	L-cells in ileum/colon	Promotes insulin secretion, pancreatic e-cell proliferation and muscle oxidation	Acetate, propionate and butyrate	Oligofructose, lactitol, resistant starch	Rat and human studies, STC cell line	(Gee and Johnson, 2005; Cani *et al.*, 2007b; Cani *et al.*, 2009a; Piche *et al.*, 2003; Zhou *et al.*, 2008)
GLP-2	L-cells in ileum/colon	Intestinal barrier	n.r.	Oligofructose	Mice studies	(Cani *et al.*, 2009b)
PYY	L-cells in ileum/colon	Slows down gastric emptying	Acetate, propionate and butyrate	Oligofructose, lactitol, resistant starch	Rat and human studies, STC cell line	(Cani *et al.*, 2009a; Gee and Johnson, 2005; Parnell and Reimer, 2009; Zhou *et al.*, 2008)
Ghrelin	P/D1 cells in the stomach and e-cells of the pancreas	Stimulates appetite	n.r.	Oligofructose, resistant starch	Rat and human studies	(Cani *et al.*, 2007b; Parnell and Reimer, 2009; Zhou *et al.*, 2008)
FIAF	Liver, adipose tissue, intestine, brain, thyroid, heart, kidney, skeletal muscles, spleen, pituitary gland, hypothalamus, placenta	Hypothalamic appetite control, fat storage in adipocytes	LPS	n.r.	N1-neuronal cells, 3T3-L1 cell line	(Brown *et al.*, 2009)
			Propionate, butyrate	n.r.	HT-29, Caco-2, HCT-116, HepG2 cell lines	(Grootaert *et al.*, 2011)
			Lactobacillus, *Bifidobacterium*, *Bacteroides*,	n.r.	HT-29, Caco-2, HCT-116, LoVo, SW-480 and HepG2	(Are *et al.*, 2008; Aronsson *et al.*, 2010; Bäckhed *et al.*, 2004; Bäckhed *et al.*, 2007; Grootaert *et al.*, 2011)

			Methanobrevibacter, Enterococcus, Escherichia coli		cell lines, mice studies	
			CLA	PUFA	COS cells	(Tien *et al.*, 2004)
			n.r.	Chitosan	High fat diet induced mice	(Neyrinck *et al.*, 2009)
Leptin	Adipocytes	Stimulates food intake	n.r.	Chitosan	High fat diet induced obese mice	(Neyrinck *et al.*, 2009)
			C2-C6 SCFA	n.r.	Murine primary adipocytes	(Xiong *et al.*, 2004)
			Propionate	n.r.	Human adipose tissue, transfected murine adipocyte cell lines	(Lahham *et al.*, 2008; Xiong *et al.*, 2004)
Adiponectin	Adipose tissue	Triglyceride storage, insulin sensitivity	n.r.	Cereal fiber	Human study	(Qi *et al.*, 2005)
Cholesterol	Liver/bile	Lipid transport in GIT and blood	SCFA, mainly propionate	Xylo-oligosaccharides, chito-oligosaccharides, soybean oligosaccharides, resistant starch	Rat, hamster, human, chicken	(Chen *et al.*, 2010; Cheng and Lai, 2000; de Luis *et al.*, 2010; Delzenne *et al.*, 1993; Fiordaliso *et al.*, 1995; Hsu *et al.*, 2004; Li *et al.*, 2007; Trautwein *et al.*, 1998; Venter *et al.*, 1990; Williams and Jackson, 2002)