Therapeutic Microbiology: Probiotics and Related Strategies
Edited by J. Versalovic and M. Wilson

Nathalie M. Delzenne
Patrice D. Cani
Audrey M. Neyrinck

14

Prebiotics and Lipid Metabolism

EFFECT OF PREBIOTICS ON FATTY ACID METABOLISM

Triacylglycerols (TAG) have important physiological roles, and abnormalities in their metabolism are implicated in major pathologies such as obesity, insulin resistance, type 2 diabetes, dyslipidemia, and atherosclerosis. The main sites of endogenous TAG synthesis from glycerol-3-phosphate and fatty acids are the liver and adipose tissue. Most of the fatty acids used for this synthesis are provided by breaking down other TAG, whereas de novo lipogenesis, the synthesis of new molecules of fatty acids from nonlipid substrates, is a minor pathway. In rats fed a lipid-rich diet containing 10% fructans, a decrease in triglyceridemia occurs without any protective effect on hepatic TAG accumulation and lipogenesis, suggesting a possible peripheral mode of action (Roberfroid and Delzenne, 1998). In contrast, in obese Zucker rats, dietary supplementation with fructans reduces hepatic steatosis, with no effect on postprandial triglyceridemia. This effect is likely to result mainly from a lower availability of nonesterified fatty acids coming from adipose tissue, since fat mass and body weight are decreased by the treatment (Daubioul et al., 2000).

A decrease in hepatic and serum TAG is observed when inulin-type fructans (Delzenne and Kok, 2001), fermented resistant rice starch (Cheng and Lai, 2000), or raw potato or high-amylose corn starch (Lopez et al., 2001) is added for several weeks to the standard diet of rats or hamsters—which is rich in carbohydrates. The doses required to obtain such an effect are relatively high (3 to 20% [wt/wt] in the diet), and depending on the model, the effect appears to be dose dependent (Tokunaga et al., 1986; Hokfelt et al., 1999). The TAG-lowering effect is also found in beagle dogs receiving 5% of a short-chain inulin-type fructan associated with 10% sugar beet fiber (Diez et al., 1997). The TAG-lowering effect of inulin type fructans has also been shown in apolipoprotein E (apo-E)-deficient mice. In this model, the inhibition of plaque formation was more pronounced with long-chain inulin than with shorter ones (Rault-Nania et al., 2006). A decrease in serum TAG is even more pronounced in animal models in which the diet is enriched with dietary fructose (Kok et al., 1996; Busserolles et al., 2003).

Short-chain fructo-oligosaccharides also decrease hepatic TAG accumulation (steatosis) in models in which

Nathalie M. Delzenne, Patrice D. Cani, and Audrey M. Neyrinck, Université Catholique de Louvain, School of Pharmacy, MD/FARM/PMNT 7369 UCL, 73 Avenue Mounier, B-1200 Brussels, Belgium.

TAG synthesis in the liver is promoted, either induced by a fructose-rich diet in rats or due to leptin receptor defect (Delzenne and Kok, 1998; Daubioul et al., 2000, 2002; Busserolles et al., 2003). They also protect rats fed a high-sucrose/high-fat diet against hepatic steatosis, and in this model, they decrease susceptibility to the hepatotoxic effect of phenobarbital treatment (Sugatani et al., 2006).

In most studies involving animals (rats and mice), the decrease in triglyceridemia and/or in hepatic TAG level due to feeding of fructans is accompanied by a decrease in fat mass development, observed after 2 to 4 weeks of treatment in mice or rats (depending on the model), and a lower body weight after a prolonged treatment (more than 4 weeks in rats). Subcutaneous and visceral fat mass are both decreased by prebiotics.

It has been reported that chronic resistant starch (RS) feeding in rats causes a decrease in adipocyte cell size, a decrease in fatty acid synthase expression, and reduced whole-body weight gain relative to digestible starch feeding (Lerer-Metzger et al., 1996). On a whole-body level, this attenuation of fat deposition in white adipose tissue in response to an RS diet could be significant for the prevention of weight gain in the long term (Higgins et al., 2006). The decrease in fat mass development is clearly linked to a decrease in energy intake. Besides this effect on fat mass development, no effect on serum nonesterified fatty acids is observed in the animals receiving prebiotics.

The decrease in serum TAG due to prebiotics such as fructans results mainly from a decrease in very low density lipoproteins as shown in rats or hamsters (Fiordaliso et al., 1995; Trautwein et al., 1998). In animals, the reduced triglyceridemia observed after fructans feeding is often linked to a decrease in de novo lipogenesis in the liver, but not in adipose tissue (Delzenne and Kok, 2001). The activities and mRNA levels of key enzymes involved in fatty acid synthesis (acetyl coenzyme A carboxylase [ACC], glucose-6-phosphate dehydrogenase, ATP citrate lyase, and fatty acid synthase [FAS]) are lower in animals fed fructans, suggesting that a lower lipogenic gene expression is involved in the decreased lipogenic capacity after supplementation with fructans (Kok et al., 1996). This effect on hepatic de novo lipogenesis was also shown in rats fed RS (Takase et al., 1994). Moreover, following an overnight fast, male Wistar rats ingesting a meal with an RS content of 2 or 30% of total carbohydrate exhibited a lower rate of lipogenesis in white adipose tissue (Higgins et al., 2006).

The decrease in glycemia and/or insulinemia observed in animals fed synthetic (from saccharose) or chicory root-derived inulin has been proposed as a mechanism explaining the lower de novo lipogenesis (Delzenne and Williams, 2002; Sugatani et al., 2006). In fact, glucose and insulin promote lipogenesis through the activation of several key peptides or nuclear factor (activation of sterol response element binding protein [SREBP-1C] and phosphorylation of AMP kinase) (Ferre and Foufelle, 2007). No data have been published to date to support a relationship between a lower SREBP-1C or AMP kinase in the antilipogenic effect of inulin-type fructans and other nondigestible carbohydrates.

Levan from *Zymomonas mobilis*, which is largely fermented in the cecocolon by bifidobacteria, also reduces the expression of genes coding FAS and ACC in the liver (but not in the adipose tissue) of rats fed a high-fat/high-sucrose diet; this phenomenon correlates with a decrease in the insulin level (Kang et al., 2006). The authors, in view of their experimental results, suggested that, in addition to the lower glucose-induced lipogenesis, prebiotics could also promote fatty acid oxidation via an activation of hepatic peroxisome prolierator-activated receptor alpha (PPARα). Some recent data obtained in our laboratory support a role for PPARα in oligofructose effects, since PPARα KO (−/−) mice treated with oligofructose had the same hepatic and serum TAG level as the one measured in the controls (P. D. Cani, E. Dewulf, A. Neyrinck, and N. Delzenne, personal communication, 2007).

EFFECT ON CHOLESTEROL HOMEOSTASIS

Cholesterol is an important constituent of cell membranes, where it is implicated in the control of important cellular functions. There are two sources of the compound at the whole-body level: dietary intake and endogenous synthesis, the latter being quantitatively the most important in humans. Type 2 (high-amylose) RS (200 g/kg of food) lowers the cholesterol content in total serum and triglyceride-rich lipoprotein in rats (Lopez et al., 2001). This fact is in accordance with the lower cholesterol absorption observed in rats fed with soluble corn bran arabinoxylans or fermentable starch (Lopez et al., 1999, 2001). Increased low-density lipoprotein (LDL) receptor mRNA content could also contribute to the decrease in serum total cholesterol occurring in rats receiving bean RS in their diet for 4 weeks (Fukushima et al., 2001). Other fermentable soluble dietary fibers, such as pectin, low-viscosity guar gum, and beta-glucan from oat bran, have been shown to lower serum cholesterol in rats (Delzenne and Williams, 1999; Slavin, 2005; Queenan et al., 2007).

Several studies have also reported a decrease in total serum cholesterol after dietary supplementation with inulin (10%) in mice or rats (Levrat et al., 1991; Fiordaliso

et al., 1995; Delzenne et al., 2002; Mortensen et al., 2002; Fava et al., 2006; Rault-Nania et al., 2006). Experiments with apo-E-deficient mice support the fact that dietary inulin (mainly long-chain inulin) significantly lowers the total cholesterol level by about one-third. This is accompanied by a significant decrease in the hepatic cholesterol content. The authors suggest that the decrease in serum cholesterol could reflect a decrease in TAG-rich lipoproteins, which are also rich in cholesterol in apo-E-deficient animals (Rault-Nania et al., 2006).

With regard to the hypocholesterolemic effect of prebiotics, several mechanisms have been proposed which are often related to a modulation of the intestinal metabolism of bile acids, but other properties (e.g., steroid-binding properties) may be involved, which are independent of the fermentation of the prebiotic in the lower intestinal tract (Trautwein et al., 1999; Delzenne and Williams, 1999; Adam et al., 2001; Lopez et al., 2001).

ROLE OF SHORT-CHAIN FATTY ACIDS IN THE MODULATION OF LIPID METABOLISM BY PREBIOTICS

Gut fermentation of prebiotics leads to the production of short-chain fatty acids, mostly acetate, propionate, and butyrate, which are almost completely absorbed along the digestive tract. Whereas butyrate is widely metabolized by enterocytes, propionate and acetate reach the liver through the portal vein (Demigne et al., 1999). When acetate enters the hepatocyte, it is activated mainly by the cytosolic acetyl coenzyme A synthetase 2 and then enters the cholesterogenesis and lipogenesis pathways. This effect has been proposed as a rationale for the hypercholesterolemic effect of those nondigestible carbohydrates such as lactulose whose fermentation in the colon results in enhanced acetate, but not propionate, production. Conversely, propionate is a competitive inhibitor of the protein controlling the entrance of acetate into liver cells (N. M. Delzenne, N. Kok, A. Neyrinck, and C. Daubioul, unpublished results), a phenomenon which contributes to a decrease in lipogenesis and cholesterogenesis, at least in vitro in rat hepatocytes. The production of a high concentration of propionate, through fermentation, has been proposed as a mechanism to explain the reduction in serum and hepatic cholesterol in rats fed RS or fructans (Levrat et al., 1994; Demigne et al., 1995; Jenkins et al., 1998; Cheng and Lai, 2000; Lopez et al., 2001; Delzenne and Kok, 2001). It thus appears that the pattern of fermentation of prebiotics, and mostly the ratio of acetate to propionate reaching the liver through the portal vein, is a putative intermediate marker that could be used to predict the potential lipid-lowering properties of prebiotics and other nondigestible fermentable carbohydrates. Oligofructose fermentation by human fecal bacteria can increase butyrate production in vitro (Morrison et al., 2006). However, oligofructose appears to be fermented by mainly acetate- and lactate-producing bacteria rather than butyrate-producing bacteria (Morrison et al., 2006). As bacterial acetate conversion to butyrate and lactate conversion to acetate, propionate, and butyrate were observed, carbohydrates with similar properties represent a refinement of the prebiotic definition, termed butyrogenic prebiotics, because of their additional functionality.

Interestingly, acetate, when supplied in the diet of diabetic mice at a dose of 0.5% for 8 weeks, activates AMP kinase in the liver, a phenomenon that is related to the inhibition of de novo lipogenesis (Sakakibara et al., 2006). The incubation of rat hepatocytes with acetate (0.2 mM) activates AMP kinase and decreases SREBP-1c expression, two factors clearly implicated in the regulation of lipogenesis. Therefore, the classical deleterious role attributed to acetate as a precursor of lipogenesis might be modulated, taking into account its regulatory effect on key molecular factors involved in fatty acid synthesis in the liver.

In humans, key experimental data are lacking, with regard to the quantitative contribution of acetate and propionate, produced in the colon through prebiotic fermentation, in the regulation of lipid synthesis in vivo.

IMPLICATION OF ENERGY INTAKE AND ENERGY EXPENDITURE IN THE FAT-REDUCING EFFECT OF PREBIOTICS

The analysis of food intake behavior reveals that feeding of fructans decreases the total energy intake by about 5 to 10% throughout the period of treatment (Delzenne et al., 2007). This effect explains the relevance of these prebiotics to the control of fat mass development in different animal models. The "satietogenic" effect of nondigestible carbohydrates results from the overproduction of anorexigenic gut peptides (GLP-1 and PYY) and a decrease in orexigenic peptides (ghrelin) (Cani et al., 2004). We have shown, in high-fat-fed mice, that the antiobesity effect of fructans is clearly dependent on the higher production of GLP-1 by L cells in the colon and requires a functional GLP-1 receptor (Cani et al., 2006; Delmée et al., 2006; Cani et al., 2007b). In mice exhibiting a functional GLP-1 receptor, the following beneficial effects of oligofructose were observed: (i) a decrease in food intake, fat mass, and body weight gain; (ii) an improved glucose tolerance during oral glucose tolerance testing; and (iii) an improved hepatic insulin resistance.

The disruption of GLP-1R function, by chronic infusion of exendin 9-39, prevented the majority of those beneficial effects observed following oligofructose treatment. The importance of GLP-1R-dependent pathways was confirmed using GLP-$1R^{-/-}$ mice fed a high-fat diet: no beneficial effects of oligofructose treatment were observed in GLP-$1R^{-/-}$ mice. Moreover, in some specific experimental models, oligofructose did not have any effect on body weight and glucose homeostasis: those models were also characterized by a lack of effect of oligofructose on GLP-1 production in the colon (Delmée et al., 2006) or were characterized by a lack of GLP-1.

Leptin is another peptide known to control food intake. The acute administration of propionate has been shown to increase circulating leptin in mice, through the interaction with the orphan G protein-coupled receptor GRP41 (Xiong et al., 2004). However, the administration of oligofructose in rats receiving a diet rich in fructose led to a decrease in serum leptin (Busserolles et al., 2003). The administration of levan, which is largely fermented by bifidobacteria in the colon, also decreases, in a dose-dependent manner, the level of serum leptin in rats fed a high-fat diet for 4 weeks (Kang et al., 2006). This decrease in leptin correlated with a decrease in serum insulin. Although few data are available, it would appear that feeding of prebiotics lowers serum leptin, probably as a consequence of the decrease in fat mass observed in prebiotic-fed animals. Leptin is thus not involved in the control of food intake by prebiotics; in accordance with this hypothesis, several studies with mice or rats lacking leptin (receptor) expression or functionality showed that these animals' intake of energy was less throughout the treatment with nondigestible prebiotic carbohydrates, such as fructans, than that of control animals receiving the corresponding control diet (Daubioul et al., 2002).

THE ROLE OF THE INTESTINAL MICROBIOTA IN THE CONTROL OF LIPID HOMEOSTASIS BY PREBIOTICS

The gut microbiota may affect hepatic lipid metabolism involved in energy homeostasis. Germfree mice colonized with the gut microbiota derived from conventionally reared mice have a higher expression of factors/enzymes promoting de novo lipogenesis in the liver (increase in SREBP-1c and carbohydrate response element binding protein, ACC, and FAS) (Backhed et al., 2004). These data suggest that the gut microbiota may affect the pathophysiology of obesity. In fact, recent data have been published showing that the composition of the gut microbiota is different in obese and nonobese individuals (Ley et al., 2006). In humans, the relative proportion of *Bacteroidetes* versus *Firmicutes* is decreased in obese people in comparison with lean people, and this proportion increases with weight loss on two types of low-calorie diet (low-carbohydrate or low-fat diet). In obese mice (leptin-deficient ob/ob mice), the proportion of *Bacteroidetes* is also decreased compared to their lean siblings (Ley et al., 2005). These changes in bacterial composition—observed both in obese humans and animals—were division-wide, whereas bacterial diversity remained constant over time; no blooms or extinctions of specific bacterial species were observed in obese versus lean individuals, or after dietary (low-calorie) intervention (Ley et al., 2006). The composition of the microbiota has an impact on calorie sparing from food and on fat mass development. The ingestion of the same quantity of food allows ob/ob mice to harvest more calories than the corresponding lean animals: the "energy sparing" phenomenon is transmissible to germfree recipients when they are colonized with an "obese microbiota," suggesting that the microbiota composition seems relevant to explain this difference. It is important to note that this colonization results also in a greater increase in total body fat than the colonization with a "lean microbiota" (Turnbaugh et al., 2006). In contrast to mice with a gut microbiota, germfree animals are protected against the obesity that develops after consuming a high-fat/high-sugar diet (Backhed et al., 2007). Therefore, the presence of the gut microbiota itself controls the metabolic response to energy-dense food. This protection against fat mass development in germfree mice is attributable to a higher level of fasting-induced adipocyte factor (FIAF), which both inhibits lipoprotein lipase (and therefore limits fat storage of dietary fatty acids) and promotes fatty acid oxidation in muscles by inducing peroxisomal proliferator-activated receptor coactivator (PGC-1α). FIAF expression may be modulated by specific microbial determinants: when germfree mice are colonized by saccharolytic and methanogenic species (*Bacteroides thetaiotaomicron* and *Methanobrevibacter smithii*), intestinal FIAF expression is suppressed and de novo lipogenesis and host adiposity increase (Backhed et al., 2004; Rawls et al., 2006). Moreover, germfree animals exhibit a higher AMP kinase activity in the liver and in muscles, which promotes fatty acid β-oxidation (carnitine palmitoyltransferase I activity) and favors the inhibition of anabolism via inhibition of key enzymes controlling fatty acid and glycogen synthesis; those events are independent of FIAF expression (Backhed et al., 2007).

We have recently shown that specific modulation of the gut microbiota by prebiotics influences fat mass development and lipid metabolic disorders associated

with obesity (Cani et al., 2007c). We reported that high-fat feeding was associated with a higher endotoxemia and a lower *Bifidobacterium* spp. cecal content in mice (Cani et al., 2007a). Therefore, we tested whether restoration of the number of cecal *Bifidobacterium* spp. could modulate metabolic endotoxemia, the inflammatory tone, and the development of diabetes. Since bifidobacteria have been reported to reduce intestinal endotoxin levels and improve mucosal-barrier function (Griffiths et al., 2004; Wang et al., 2004, 2006), we specifically increased the gut bifidobacterial content of high-fat-diet-fed mice through the use of a prebiotic (oligofructose). We demonstrated that high-fat feeding significantly reduced intestinal gram-negative and gram-positive bacteria including levels of bifidobacteria, a dominant member of the intestinal microbiota which is regarded as physiologically positive, compared to normal-chow-fed mice. As expected, in prebiotics-fed mice the numbers of bifidobacteria were completely restored. High-fat feeding significantly increased endotoxemia, which was normalized to normal-chow-fed mice in prebiotics-treated mice. Multiple-correlation analyses showed that endotoxemia significantly and negatively correlated with the number of *Bifidobacterium* spp. in prebiotics-treated mice; *Bifidobacterium* spp. significantly and positively correlated with improved glucose tolerance, glucose-induced insulin secretion, and normalized inflammatory tone (decreased endotoxemia and plasma and adipose-tissue proinflammatory cytokines). Together, these findings suggest that the gut microbiota contributes towards the pathophysiological regulation of endotoxemia and sets the tone of inflammation for the occurrence of diabetes/obesity. Thus, it would be useful to develop specific strategies for modifying the gut microbiota in favor of bifidobacteria to prevent the deleterious effect of high-fat-diet-induced metabolic diseases.

COULD AN EFFECT BE MEDIATED BY PROBIOTICS THEMSELVES THROUGH THE MODIFICATION OF THE INTESTINAL MICROBIOTA?

Most prebiotics promote lactic acid-producing bacteria. The possibility that modification of the intestinal microbiota may have beneficial effects on lipid metabolism is equivocally supported by studies using lactic acid-producing probiotics (live microbial feed supplements, e.g., fermented dairy products) (Taylor and Williams, 1998; St Onge et al., 2000; Whelan et al., 2001; Andersson et al., 2001; McNaught and MacFie, 2001). The influence of probiotics on TAG homeostasis is only poorly documented. An interesting review suggests a moderate cholesterol-lowering effect associated with the consumption of dairy products fermented with specific strains of *Lactobacillus* and/or *Bifidobacterium* (Fava et al., 2006). The regular consumption of both probiotic and conventional yogurt for 4 weeks exerted a positive effect on the lipid profile (increase in high-density lipoproteins [HDL]/LDL ratio) in the plasma of healthy women (Fabian and Elmadfa, 2006).

In animals, a cholesterol-lowering action of certain fermented dairy products indicates that the bacterial content, and more precisely the combination of different types of bacteria such as *Lactobacillus acidophilus, Lactobacillus casei*, and *Bifidobacterium bifidum*, is responsible for the cholesterol-lowering action of dairy products (Andersson et al., 2001). Bifidobacterial proliferation does not seem to play an exclusive role in the hypocholesterolemic effect of prebiotics, since levan β-2-6, which is not bifidogenic, decreases serum cholesterol in rats (Yamamoto et al., 1999). An enhanced bile acid deconjugation and the subsequent enhanced fecal bile acid excretion have been implicated in the cholesterol reduction associated with certain probiotics and prebiotics (St Onge et al., 2000). Another hypothesis is that cholesterol from the growth medium of the fermented product is incorporated into the bacterial cell membrane and thus escapes digestion (Fava et al., 2006). The intestinal colonization potency of the probiotics, which is strongly dependent on the strain, seems a crucial factor in determining a hypocholesterolemic effect (Usman and Hosono, 2000). This may explain why a combination of probiotics (lactobacillus) and prebiotics (fructans) promotes a decrease in cholesterolemia (−0.23 mol/liter) in healthy people (Schaafsma et al., 1998). The positive effects of an altered intestinal microbiota have also been reported in studies in which no probiotic addition is given: in a four-phase randomized crossover study in healthy people, a higher HDL cholesterol level and a lower LDL cholesterol level were correlated with lower fecal output of fusobacteria and bacteroides, due to RS treatment (Jenkins et al., 1999).

EFFECT OF PREBIOTICS ON LIPID METABOLISM IN HUMANS

A small number of well-designed human studies have reported some positive outcomes with regard to the effects of prebiotics on blood lipids (Delzenne and Williams, 1999; Daubioul et al., 2000; Williams and Jackson, 2002; Daubioul et al., 2005; Beylot, 2005; Fava et al., 2006). Relevant studies reported in the literature with inulin-type fructans are presented in Table 1; the authors have investigated the response of blood lipids

Table 1 Effects of inulin-type fructans on lipid metabolism in humans[a]

Reference	Prebiotic	Dose (g/day)	Duration (weeks)	Effect on blood lipids
Yamashita et al., 1984	OFS	8	2	↓ T-Chol, ↓ LDL-Chol
Hidaka et al., 1991	OFS	8	5	↓ T-Chol
Luo et al., 1996	OFS	20	4	NS
Pedersen et al., 1997	Inulin	14	4	NS
Davidson et al., 1998	Inulin	18	6	↓ LDL-Chol, ↓ T-Chol
Jackson et al., 1999	Inulin	10	8	↓ TAG
Brighenti et al., 1999	Inulin	9	4	↓ TAG, ↓ LDL-Chol
Alles et al., 1999	OFS	15	3	NS
Havenaar et al., 1999	Inulin, OFS	15	3	NS
Luo et al., 2000	OFS	20	4	NS
Causey et al., 2000	Inulin	20	3	↓ TAG
Balcazar-Munoz et al., 2003	Inulin	7	4	↓ TAG, ↓ T-Chol
Letexier et al., 2003	Inulin	10	3	↓ TAG
Giacco et al., 2004	OFS	10.6	8	NS
Daubioul et al., 2005	OFS	16	8	NS
Forcheron and Beylot, 2007	Inulin, OFS	10	24	NS

[a]OFS, oligofructose; T-Chol, total cholesterol; LDL-Chol, LDL cholesterol; NS, no significant effect; ↓, decrease.

(usually total and LDL cholesterol and TAG) to prebiotic supplementation in human volunteers.

Studies have been conducted with both normal and moderately hyperlipidemic subjects. Inulin-type fructans tended to decrease TAG and cholesterol levels. No clear conclusion can be drawn concerning the influence of the duration of the treatment and the efficacy of prebiotics to lower blood lipids (Delzenne and Williams, 1999, 2002). However, in human studies performed with inulin-type fructans, lower doses (from 7 to 10 g/day) seem more efficacious than higher doses (15 to 20 g) in decreasing blood lipids (Beylot, 2005).

Some studies have shown that dietary supplementation with 15 or 20 g of fructo-oligosaccharides per day for 4 weeks had no effect on serum cholesterol or triglycerides in type 2 diabetic patients (Alles et al., 1999; Luo et al., 2000), whereas positive outcomes have tended to be observed more frequently in those studies conducted with subjects with moderate hyperlipidemia. In men with hypercholesterolemia, daily intake of 20 g of inulin significantly reduces serum triglycerides by 40 mg/dl (Causey et al., 2000), as previously shown in moderate hyperlipidemic patients receiving 9 g of inulin per day (Jackson et al., 1999). Subjects with a serum cholesterol above 250 mg/dl tended to have the greatest reduction of cholesterol after inulin supplementation. The effect of fructan (long-chain inulin) supplementation on hepatic lipogenesis and cholesterogenesis has been analyzed (deuterated water incorporation into lipids) in healthy subjects in a double-blind, placebo-controlled crossover study (Letexier et al., 2003; Forcheron and Beylot, 2007). It confirms the experimental data obtained with animals, namely that hepatic de novo lipogenesis is reduced by feeding fructans at a moderate dose (10 g of inulin per day for 3 weeks). However, there is no significant modification of cholesterol synthesis (Letexier et al., 2003). The analysis of mRNA concentrations from genes coding key enzymes or proteins involved in the regulation of lipid synthesis (FAS, ACC, and SREBP1c) in the adipose tissue revealed no differences between the placebo and inulin groups. This supports the fact that, at least for inulin-type prebiotics, the hypolipidemic effect is linked to modulation of liver rather than adipose-tissue metabolism. Contrary to what was observed in short-term studies, no significant beneficial effect of a long-term (6-month) administration of inulin-type fructans on plasma lipids was observed in healthy human subjects (Forcheron and Beylot, 2007).

In a pilot study performed with patients presenting nonalcoholic steatohepatitis, 16 g of oligofructose per day for 8 weeks led to a decrease in serum aminotransferases, thus suggesting a hepatoprotective effect of prebiotic treatment in that context; a slight decrease in serum TAG was observed, but it was not significant (Daubioul et al., 2005).

Other nondigestible fermentable carbohydrates with prebiotic properties have been studied. Glucomannans are prone to decrease TAG and cholesterol (LDL cholesterol) levels; these effects could be linked to their influence on fecal steroid excretion (Gallaher et al., 2002).

The effect of RS on lipid homeostasis in humans is controversial. Certain classes of RS (called type 1 RS) have been associated in humans with reduced postprandial insulin and higher HDL cholesterol levels, but these effects are more related to the sustained release of carbohydrate within the small intestine, rather than to an effect linked to fermentation (Jenkins and Kendall, 2000). A lack of effect of low doses of β-glucan (3 g/day for 8 weeks) on total and LDL cholesterol and triglyceridemia in volunteers with mild-to-moderate hyperlipidemia was also recently reported—a negative result—which is in contrast to some other previous positive studies that have employed higher daily doses of β-glucan (Lovegrove et al., 2000). The fact that higher doses of β-glucan are required to induce an effect on lipidemia is supported by a recent single-blind crossover study showing a significant lowering of serum LDL cholesterol (reduced by 9%) in hyperlipidemic subjects consuming 7 g of oat β-glucans incorporated in various foods for 3 weeks (Pomeroy et al., 2001).

In humans, data show that a decrease in plasma glucose after a meal containing β-glucan is not related to a decrease in de novo lipogenesis (Battilana et al., 2001). Lactulose is also able to decrease serum TAG (Vogt et al., 2006). In overweight subjects, a short-term decrease in free fatty acids level and glycerol turnover after lactulose ingestion corresponded to a decrease of lipolysis which was closely related to an increase in acetate production (Ferchaud-Roucher et al., 2005).

CONCLUSION

Several oligosaccharides which strictly correspond to the definition of prebiotics exhibit interesting effects on lipid metabolism. The resulting changes in the intestinal microbiota composition or fermentation activity could be implicated in the modulation of fatty acid and cholesterol metabolism. There is not a single biochemical locus through which prebiotics modulate serum, hepatic, and whole-body lipid content in animals. The effects observed depend on the pathophysiological and nutritional conditions. This may help to explain why in humans, where such conditions cannot be so rigorously controlled (namely, in terms of nutrient intake), the reported effects of prebiotics on circulating blood lipids are much more variable.

Most of the data described to date have been obtained in animal studies; the relevance of such observations on obesity and cardiovascular disease risk in humans remains a key question also addressed in this chapter. Fundamental research devoted to understanding the biochemical and physiological events (on glucose and lipid homeostasis, on gut hormone secretion, on satiety, etc.), as well as clinical research focusing on the target population, is required to achieve progress in the new area of the nutritional management of metabolic syndromes, based on modulation of the gut microbiota and intestinal function by specific food components.

References

Adam, A., M. A. Levrat-Verny, H. W. Lopez, M. Leuillet, C. Demigne, and C. Remesy. 2001. Whole wheat and triticale flours with differing viscosities stimulate cecal fermentations and lower plasma and hepatic lipids in rats. *J. Nutr.* 131:1770–1776.

Alles, M. S., N. M. De Roos, J. C. Bakx, E. van de Lisdenk, P. L. Zock, and G. A. Hautvast. 1999. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. *Am. J. Clin. Nutr.* 69:64–69.

Andersson, H., N. G. Asp, and A. Bruce. 2001. Health effects of probiotics and prebiotics. A literature review on human studies. *Scand. J. Nutr.* 45:48–75.

Backhed, F., H. Ding, T. Wang, L. V. Hooper, G. Y. Koh, A. Nagy, C. F. Semenkovich, and J. I. Gordon. 2004. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl. Acad. Sci. USA* 101:15718–15723.

Backhed, F., J. F. Manchester, C. F. Semenkovich, and J. I. Gordon. 2007. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl. Acad. Sci. USA* 104:979–984.

Balcazar-Munoz, B. R., E. Martinez-Abundis, and M. Gonzalez-Ortiz. 2003. Effect of oral inulin administration on lipid profile and insulin sensitivity in dyslipidemic obese subjects. *Rev. Med. Chil.* 131:597–604.

Battilana, P., K. Ornstein, K. Minehira, J. M. Schwarz, K. Acheson, P. Schneiter, J. Burri, E. Jequier, and L. Tappy. 2001. Mechanisms of action of beta-glucan in postprandial glucose metabolism in healthy men. *Eur. J. Clin. Nutr.* 55:327–333.

Beylot, M. 2005. Effects of inulin-type fructans on lipid metabolism in man and in animal models. *Br. J. Nutr.* 93(Suppl. 1): S163–S168.

Brighenti, F., M. C. Casiraghi, E. Canzi, and A. Ferrari. 1999. Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers. *Eur. J. Clin. Nutr.* 53:726–733.

Busserolles, J., E. Gueux, E. Rock, C. Demigne, A. Mazur, and Y. Rayssiguier. 2003. Oligofructose protects against the hypertriglyceridemic and pro-oxidative effects of a high fructose diet in rats. *J. Nutr.* 133:1903–1908.

Cani, P. D., C. Dewever, and N. M. Delzenne. 2004. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *Br. J. Nutr.* 92:521–526.

Cani, P. D., C. Knauf, M. A. Iglesias, D. J. Drucker, N. M. Delzenne, and R. Burcelin. 2006. Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* 55:1484–1490.

Cani, P. D., J. Amar, M. A. Iglesias, M. Poggi, C. Knauf, D. Bastelica, A. M. Neyrinck, F. Fava, K. M. Tuohy, C. Chabo, A. Waget, E. Delmee, B. Cousin, T. Sulpice, B. Chamontin, J. Ferrieres, J. F. Tanti, G. R. Gibson, L. Casteilla, N. M. Delzenne, M. C. Alessi, and R. Burcelin. 2007a. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* 56:1761–1772.

Cani, P. D., S. Hoste, Y. Guiot, and N. M. Delzenne. 2007b. Dietary non-digestible carbohydrates promote L-cell differentiation in the proximal colon of rats. *Br. J. Nutr.* 98: 32–37.

Cani, P. D., A. M. Neyrinck, F. Fava, C. Knauf, R. G. Burcelin, K. M. Tuohy, F. K. Gibbons, and N. M. Delzenne. 2007c. Selective increases of bifidobacteria in gut microflora improve high-fat diet-induced diabetes in mice through a mechanism associated with endotoxaemia. *Diabetologia* 50:2374–2380.

Causey, J. L., J. M. Feirtag, D. D. Gallaher, B. C. Tungland, and J. L. Slavin. 2000. Effects of dietary inulin on serum lipids, blood glucose, and the gastrointestinal environment in hypercholesterolemic men. *Nutr. Res.* 20:191–201.

Cheng, H. H., and M. H. Lai. 2000. Fermentation of resistant rice starch produces propionate reducing serum and hepatic cholesterol in rats. *J. Nutr.* 130:1991–1995.

Daubioul, C., N. Rousseau, R. Demeure, B. Gallez, H. Taper, B. Declerck, and N. Delzenne. 2002. Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *J. Nutr.* 132:967–973.

Daubioul, C. A., Y. Horsmans, P. Lambert, E. Danse, and N. M. Delzenne. 2005. Effects of oligofructose on glucose and lipid metabolism in patients with nonalcoholic steatohepatitis: results of a pilot study. *Eur. J. Clin. Nutr.* 59:723–726.

Daubioul, C. A., H. S. Taper, L. D. De Wispelaere, and N. M. Delzenne. 2000. Dietary oligofructose lessens hepatic steatosis, but does not prevent hypertriglyceridemia in obese zucker rats. *J. Nutr.* 130:1314–1319.

Davidson, M. H., K. C. Maki, C. Synecki, S. A. Torri, and K. B. Drennan. 1998. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. *Nutr. Res.* 18:503–517.

Delmée, E., P. D. Cani, G. Gual, C. Knauf, R. Burcelin, N. Maton, and N. M. Delzenne. 2006. Relation between colonic proglucagon expression and metabolic response to oligofructose in high fat diet-fed mice. *Life Sci.* 79:1007–1013.

Delzenne, N. M., and N. Kok. 1998. Effect of non-digestible fermentable carbohydrates on hepatic fatty acid metabolism. *Biochem. Soc. Trans.* 26:228–230.

Delzenne, N. M., and C. Williams. 1999. Actions of non-digestible carbohydrates on blood lipids in humans and animals, p. 213–232. *In* G. Gibson, and M. Roberfroid (ed.), *Colonic Microbiota, Nutrition and Health*. Kluwer Academic Publisher, Dordrecht, The Netherlands.

Delzenne, N. M., and N. Kok. 2001. Effects of fructans-type prebiotics on lipid metabolism. *Am. J. Clin. Nutr.* 73:456S–458S.

Delzenne, N. M., and C. M. Williams. 2002. Prebiotics and lipid metabolism. *Curr. Opin. Lipidol.* 13:61–67.

Delzenne, N. M., C. Daubioul, A. Neyrinck, M. Lasa, and H. S. Taper. 2002. Inulin and oligofructose modulate lipid metabolism in animals: review of biochemical events and future prospects. *Br. J. Nutr.* 87(Suppl. 2):S255–S259.

Delzenne, N., and P. D. Cani. 2005. A place for dietary fibres in the management of metabolic syndrome. *Curr. Opin. Clin. Nutr. Metab. Care* 8:638–640.

Delzenne, N. M., P. D. Cani, and A. Neyrinck. 2007. Modulation of glucagon-like peptide 1 and energy metabolism by inulin and oligofructose: experimental data. *J. Nutr.* 137(11 Suppl.):2547S–2551S.

Demigne, C., C. Morand, M. A. Levrat, C. Besson, C. Moundras, and C. Remesy. 1995. Effect of propionate on fatty acid and cholesterol synthesis and on acetate metabolism in isolated rat hepatocytes. *Br. J. Nutr.* 74:209–219.

Demigne, C., C. Remesy, and C. Morand. 1999. Short chain fatty acids, p. 55–63. *In* G. Gibson and M. Roberfroid (ed.), *Colonic Microbiota, Nutrition and Health*. Kluwer Academic Publisher, Dordrecht, The Netherlands.

Diez, M., J. L. Hornick, P. Baldwin, and L. Istasse. 1997. Influence of a blend of fructo-oligosaccharides and sugar beet fiber on nutrient digestibility and plasma metabolite concentrations in healthy beagles. *Am. J. Vet. Res.* 58:1238–1242.

Fabian, E., and I. Elmadfa. 2006. Influence of daily consumption of probiotic and conventional yoghurt on the plasma lipid profile in young healthy women. *Ann. Nutr. Metab.* 50:387–393.

Fava, F., J. A. Lovegrove, R. Gitau, K. G. Jackson, and K. M. Tuohy. 2006. The gut microbiota and lipid metabolism: implications for human health and coronary heart disease. *Curr. Med. Chem.* 13:3005–3021.

Ferchaud-Roucher, V., E. Pouteau, H. Piloquet, Y. Zair, and M. Krempf. 2005. Colonic fermentation from lactulose inhibits lipolysis in overweight subjects. *Am. J. Physiol. Endocrinol. Metab.* 289:E716–E720.

Ferre, P., and F. Foufelle. 2007. SREBP-1c transcription factor and lipid homeostasis: clinical perspective. *Horm. Res.* 68:72–82.

Fiordaliso, M., N. Kok, J. P. Desager, F. Goethals, D. Deboyser, M. Roberfroid, and N. Delzenne. 1995. Dietary oligofructose lowers triglycerides, phospholipids and cholesterol in serum and very low density lipoproteins of rats. *Lipids* 30:163–167.

Forcheron, F., and M. Beylot. 2007. Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. *Metabolism* 56:1093–1098.

Fukushima, M., T. Ohashi, M. Kojima, K. Ohba, H. Shimizu, K. Sonoyama, and M. Nakano. 2001. Low density lipoprotein receptor mRNA in rat liver is affected by resistant starch of beans. *Lipids* 36:129–134.

Gallaher, D. D., C. M. Gallaher, G. J. Mahrt, T. P. Carr, C. H. Hollingshead, R. Hesslink, Jr., and J. Wise. 2002. A glucomannan and chitosan fiber supplement decreases plasma cholesterol and increases cholesterol excretion in overweight normocholesterolemic humans. *J. Am. Coll. Nutr.* 21:428–433.

Giacco, R., G. Clemente, D. Luongo, G. Lasorella, I. Fiume, F. Brouns, F. Bornet, L. Patti, P. Cipriano, A. A. Rivellese, and G. Riccardi. 2004. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. *Clin. Nutr.* 23:331–340.

Griffiths, E. A., L. C. Duffy, F. L. Schanbacher, H. Qiao, D. Dryja, A. Leavens, J. Rossman, G. Rich, D. Dirienzo, and P. L. Ogra. 2004. In vivo effects of bifidobacteria and lactoferrin on gut endotoxin concentration and mucosal immunity in Balb/c mice. *Dig. Dis. Sci.* 49:579–589.

Havenaar, R., S. Bonnin-Marol, W. Van Dokkum, S. Petitet, and G. Schaafsma. 1999. Inulin: fermentation and microbial ecology in the intestinal tract. *Food Rev. Int.* 15:109–120.

Hidaka, H., Y. Tashiro, and T. Eida. 1991. Proliferation of bifidobacteria by oligosaccharides and their useful effect on human health. *Bifidobacteria Microflora* 10:65–79.

Higgins, J. A., M. A. Brown, and L. H. Storlien. 2006. Consumption of resistant starch decreases postprandial lipogenesis in white adipose tissue of the rat. *Nutr. J.* 5:25.

Hokfelt, T., C. Broberger, M. Diez, Z. Q. Xu, T. Shi, J. Kopp, X. Zhang, K. Holmberg, M. Landry, and J. Koistinaho. 1999. Galanin and NPY, two peptides with multiple putative roles in the nervous system. *Horm. Metab. Res.* 31:330–334.

Jackson, K. G., G. R. J. Taylor, A. M. Clohessy, and C. M. Williams. 1999. The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. *Br. J. Nutr.* 82:23–30.

Jenkins, D. J., and C. W. Kendall. 2000. Resistant starches. *Curr. Opin. Gastroenterol.* 16:178–183.

Jenkins, D. J., V. Vuksan, C. W. Kendall, P. Wursch, R. Jeffcoat, S. Waring, C. C. Mehling, E. Vidgen, L. S. Augustin, and E. Wong. 1998. Physiological effects of resistant starches on fecal bulk, short chain fatty acids, blood lipids and glycemic index. *J. Am. Coll. Nutr.* 17:609–616.

Jenkins, D. J., V. Vuksan, A. V. Rao, E. Vidgen, C. W. Kendall, N. Tariq, P. Wursch, B. Koellreutter, N. Shiwnarain, and R. Jeffcoat. 1999. Colonic bacterial activity and serum lipid risk factors for cardiovascular disease. *Metabolism* 48:264–268.

Kang, S. A., K. Hong, K. H. Jang, Y. Y. Kim, R. Choue, and Y. Lim. 2006. Altered mRNA expression of hepatic lipogenic enzyme and PPARalpha in rats fed dietary levan from *Zymomonas mobilis*. *J. Nutr. Biochem.* 17:419–426.

Kok, N., M. Roberfroid, and N. Delzenne. 1996. Dietary oligofructose modifies the impact of fructose on hepatic triacylglycerol metabolism. *Metabolism* 45:1547–1550.

Lerer-Metzger, M., S. W. Rizkalla, J. Luo, M. Champ, M. Kabir, F. Bruzzo, F. Bornet, and G. Slama. 1996. Effects of long-term low-glycaemic index starchy food on plasma glucose and lipid concentrations and adipose tissue cellularity in normal and diabetic rats. *Br. J. Nutr.* 75: 723–732.

Letexier, D., F. Diraison, and M. Beylot. 2003. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. *Am. J. Clin. Nutr.* 77:559–564.

Levrat, M. A., M. L. Favier, C. Moundras, C. Remesy, C. Demigne, and C. Morand. 1994. Role of dietary propionic acid and bile acid excretion in the hypocholesterolemic effects of oligosaccharides in rats. *J. Nutr.* 124:531–538.

Levrat, M. A., C. Remesy, and C. Demigne. 1991. High propionic acid fermentations and mineral accumulation in the cecum of rats adapted to different levels of inulin. *J. Nutr.* 121:1730–1737.

Ley, R. E., F. Backhed, P. Turnbaugh, C. A. Lozupone, R. D. Knight, and J. I. Gordon. 2005. Obesity alters gut microbial ecology. *Proc. Natl. Acad. Sci. USA* 102:11070–11075.

Ley, R. E., P. J. Turnbaugh, S. Klein, and J. I. Gordon. 2006. Microbial ecology: human gut microbes associated with obesity. *Nature* 444:1022–1023.

Lopez, H. W., M. A. Levrat, C. Guy, A. Messager, C. Demigne, and C. Remesy. 1999. Effects of soluble corn bran arabinoxylans on cecal digestion, lipid metabolism, and mineral balance (Ca, Mg) in rats. *J. Nutr. Biochem.* 10:500–509.

Lopez, H. W., M. A. Levrat-Verny, C. Coudray, C. Besson, V. Krespine, A. Messager, C. Demigne, and C. Remesy. 2001. Class 2 resistant starches lower plasma and liver lipids and improve mineral retention in rats. *J. Nutr.* 131:1283–1289.

Lovegrove, J. A., A. Clohessy, H. Milon, and C. M. Williams. 2000. Modest doses of beta-glucan do not reduce concentrations of potentially atherogenic lipoproteins. *Am. J. Clin. Nutr.* 72:49–55.

Luo, J., S. W. Rizkalla, C. Alamowitch, A. Boussairi, A. Blayo, J. L. Barry, A. Laffitte, F. Guyon, F. R. Bornet, and G. Slama. 1996. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. *Am. J. Clin. Nutr.* 63:939–945.

Luo, J., M. Van Yperselle, S. W. Rizkalla, F. Rossi, F. R. Bornet, and G. Slama. 2000. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. *J. Nutr.* 130:1572–1577.

McNaught, C. E., and J. MacFie. 2001. Probiotics in clinical practice: a critical review of the evidence. *Nurs. Res.* 21:343–353.

Morrison, D. J., W. G. Mackay, C. A. Edwards, T. Preston, B. Dodson, and L. T. Weaver. 2006. Butyrate production from oligofructose fermentation by the human faecal flora: what is the contribution of extracellular acetate and lactate? *Br. J. Nutr.* 96:570–577.

Mortensen, A., M. Poulsen, and H. Frandsen. 2002. Effect of a long-chained fructan Raftiline HP on blood lipids and spontaneous atherosclerosis in low density receptor knockout mice. *Nutr. Res.* 22:473–480.

Pedersen, A., B. Sandstrom, and J. M. M. VanAmelsvoort. 1997. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. *Br. J. Nutr.* 78:215–222.

Pomeroy, S., R. Tupper, M. Cehun-Aders, and P. Nestel. 2001. Oat beta-glucan lowers total and LDL-cholesterol. *Aust. J. Nutr. Diet.* 58:51–55.

Queenan, K. M., M. L. Stewart, K. N. Smith, W. Thomas, R. G. Fulcher, and J. L. Slavin. 2007. Concentrated oat beta-glucan, a fermentable fiber, lowers serum cholesterol in hypercholesterolemic adults in a randomized controlled trial. *Nutr. J.* 6:6.

Rault-Nania, M. H., E. Gueux, C. Demougeot, C. Demigne, E. Rock, and A. Mazur. 2006. Inulin attenuates atherosclerosis in apolipoprotein E-deficient mice. *Br. J. Nutr.* 96:840–844.

Rawls, J. F., M. A. Mahowald, R. E. Ley, and J. I. Gordon. 2006. Reciprocal gut microbiota transplants from zebrafish and mice to germ-free recipients reveal host habitat selection. *Cell* 127:423–433.

Roberfroid, M. B., and N. M. Delzenne. 1998. Dietary fructans. *Annu. Rev. Nutr.* 18:117–143.

Sakakibara, S., T. Yamauchi, Y. Oshima, Y. Tsukamoto, and T. Kadowaki. 2006. Acetic acid activates hepatic AMPK and reduces hyperglycemia in diabetic KK-A(y) mice. *Biochem. Biophys. Res. Commun.* 344:597–604.

Schaafsma, G., W. J. Meuling, W. Van Dokkum, and C. Bouley. 1998. Effects of a milk product, fermented by *Lactobacillus acidophilus* and with fructo-oligosaccharides added, on blood lipids in male volunteers. *Eur. J. Clin. Nutr.* 52:436–440.

Scheppach, W., H. Luehrs, and T. Menzel. 2001. Beneficial health effects of low-digestible carbohydrate consumption. *Br. J. Nutr.* 85(Suppl. 1):S23–S30.

Slavin, J. L. 2005. Dietary fiber and body weight. *Nutrition* 21:411–418.

St Onge, M. P., E. R. Farnworth, and P. J. Jones. 2000. Consumption of fermented and nonfermented dairy products: effects on cholesterol concentrations and metabolism. *Am. J. Clin. Nutr.* 71:674–681.

Sugatani, J., T. Wada, M. Osabe, K. Yamakawa, K. Yoshinari, and M. Miwa. 2006. Dietary inulin alleviates hepatic steatosis and xenobiotics-induced liver injury in rats fed a high-fat and high-sucrose diet: association with the suppression of hepatic cytochrome P450 and hepatocyte nuclear factor 4alpha expression. *Drug. Metab. Dispos.* 34:1677–1687.

Takase, S., T. Goda, and M. Watanabe. 1994. Monostearoylglycerol-starch complex: its digestibility and effects on glycemic and lipogenic responses. *J. Nutr. Sci. Vitaminol.* (Tokyo) 40:23–36.

Taylor, G. R. J., and C. M. Williams. 1998. Effects of probiotics and prebiotics on blood lipids. *Br. J. Nutr.* 80:S225–S230.

Tokunaga, T., T. Oku, and N. Hosoya. 1986. Influence of chronic intake of new sweetener fructooligosaccharide (Neosugar) on growth and gastrointestinal function of the rat. *J. Nutr. Sci. Vitaminol.* (Tokyo) 32:111–121.

Trautwein, E. A., K. Forgbert, D. Rieckhoff, and H. F. Erbersdobler. 1999. Impact of beta-cyclodextrin and resistant starch on bile acid metabolism and fecal steroid excretion in regard to their hypolipidemic action in hamsters. *Biochim. Biophys. Acta* 1437:1–12.

Trautwein, E. A., D. Rieckhoff, and H. F. Erbersdobler. 1998. Dietary inulin lowers plasma cholesterol and triacylglycerol and alters biliary bile acid profile in hamsters. *J. Nutr.* 128:1937–1943.

Turnbaugh, P. J., R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis, and J. I. Gordon. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444:1027–1031.

Usman, K. E., and A. Hosono. 2000. Effect of administration of *Lactobacillus gasseri* on serum lipids and fecal steroids in hypercholesterolemic rats. *J. Dairy Sci.* 83:1705–1711.

Vogt, J. A., K. B. Ishii-Schrade, P. B. Pencharz, P. J. Jones, and T. M. Wolever. 2006. L-rhamnose and lactulose decrease serum triacylglycerols and their rates of synthesis, but do not affect serum cholesterol concentrations in men. *J. Nutr.* 136:2160–2166.

Wang, Z., G. Xiao, Y. Yao, S. Guo, K. Lu, and Z. Sheng. 2006. The role of bifidobacteria in gut barrier function after thermal injury in rats. *J. Trauma* 61:650–657.

Wang, Z. T., Y. M. Yao, G. X. Xiao, and Z. Y. Sheng. 2004. Risk factors of development of gut-derived bacterial translocation in thermally injured rats. *World J. Gastroenterol.* 10:1619–1624.

Whelan, K., G. R. Gibson, P. A. Judd, and M. A. Taylor. 2001. The role of probiotics and prebiotics in the management of diarrhoea associated with enteral tube feeding. *J. Hum. Nutr. Diet.* 14:423–433.

Williams, C. M., and K. G. Jackson. 2002. Inulin and oligofructose: effects on lipid metabolism from human studies. *Br. J. Nutr.* 87:S261–S264.

Xiong, Y., N. Miyamoto, K. Shibata, M. A. Valasek, T. Motoike, R. M. Kedzierski, and M. Yanagisawa. 2004. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc. Natl. Acad. Sci. USA* 101:1045–1050.

Yamamoto, Y., Y. Takahashi, M. Kawano, M. Iizuka, T. Matsumoto, S. Saeki, and H. Yamaguchi. 1999. In vitro digestibility and fermentability of levan and its hypocholesterolemic effects in rats. *J. Nutr. Biochem.* 10:13–18.

Yamashita, K., M. Itakura, and K. Kawai. 1984. Effects of fructo-oligosaccharides on blood glucose and serum lipids in diabetic subjects. *Nutr. Res.* 4:961–966.