Effects of fructans-type prebiotics on lipid metabolism\textsuperscript{1–4}

Nathalie M Delzenne and Nadine Kok

ABSTRACT Several nondigestible but fermentable dietary carbohydrates are able to regulate lipemia and triglyceridemia in both humans and animals. The mechanism of their serum lipid–lowering effect remains to be elucidated. Oligofructose, which is a mixture of nondigestible and fermentable fructans, can decrease triacylglycerol in VLDL when given to rats. The triacylglycerol-lowering action of oligofructose is due to a reduction of de novo fatty acid synthesis in the liver through inhibition of all lipogenic enzymes, namely acetyl-CoA carboxylase (EC 6.4.1.2), fatty acid synthase, malic enzyme (EC 1.1.1.40), ATP citrate lyase (EC 4.1.3.8), and glucose-6-phosphate dehydrogenase (EC 1.1.1.49). Our results suggest that oligofructose decreases lipogenic enzyme gene expression. Postprandial insulin and glucose concentrations are low in the serum of oligofructose-fed animals and this could explain, at least partially, the metabolic effect of oligofructose. Moreover, some events occurring in the gastrointestinal tract after oligofructose feeding could be involved in the antilipogenic effect of this fructan: the production of propionate through fermentation, a modulation of the intestinal production of incretins (namely glucose-dependent insulinotropic peptide and glucagon-like peptide-1), or the modification of the availability of digestible carbohydrates. Recent studies showed that the hypotriglyceridemic effect of fructans also occurs in humans. Am J Clin Nutr 2001;73(suppl):456S–8S.

KEY WORDS Triacylglycerol, lipogenesis, fructans, rat, liver

REGULATION OF TRIGLYCERIDEMIA BY NUTRIENTS AND HORMONES

Many attempts have been made to control serum triacylglycerol concentrations through the modification of dietary habits. The hypotriglyceridemic effect of nondigestible but fermentable carbohydrates, including resistant starch or fructooligosaccharides, has been described both in humans (1–3) and in animals (4–7). The mechanism of these carbohydrates serum-lipid lowering effect remains to be elucidated. Dietary triacylglycerols are transported from lymph to the blood as chylomicrons and then hydrolyzed by lipoprotein lipase; they may reach the liver as chylomicron remnants. The liver plays a key role in triacylglycerol-rich lipoprotein homeostasis because it can assemble and secrete VLDL. The hepatic synthesis of VLDL involves the biosynthesis of both lipids and apoproteins, their assembly into nascent VLDL particles, and the secretion of mature VLDL into circulation (8). Because newly synthesized fatty acids are preferentially channeled into VLDL, the lipogenic activity of the liver is a key factor for the hepatic triacylglycerol-VLDL output (8–11). Among the key enzymes that control lipogenesis, fatty acid synthase (FAS) is the most sensitive to nutrients and hormones (12). Insulin and glucose have been shown to be important effectors regulating fatty acid and triacylglycerol synthesis, both in vivo (13, 14) and in vitro (15–17).

BIOCHEMICAL MECHANISMS UNDERLYING THE EFFECT OF NONDIGESTIBLE AND FERMENTABLE CARBOHYDRATES ON LIPID METABOLISM: THE CASE OF OLIGOFRUCTOSE

Feeding rats a diet supplemented with 10% oligofructose, a nondigestible but fermentable oligomer of β-d-fructose that has been obtained by enzymatic hydrolysis of chicory inulin, significantly lowers triacylglycerol and phospholipid serum concentrations (18–20). This is almost exclusively due to a decrease in the concentration of plasma VLDL (19). This effect is likely to result from a decrease in the hepatic synthesis of triacylglycerol rather than from a high catabolism of triacylglycerol-rich lipoproteins (21). Hepatocytes isolated from oligofructose-fed rats have a slightly lower capacity to esterify [\textsuperscript{14}C]palmitate into triacylglycerol but a 40% lower capacity to synthesize triacylglycerol from [\textsuperscript{14}C]acetate than in control rats (19, 21). These data support the hypothesis that decreased de novo lipogenesis in the liver, through a corresponding reduction of the activity of all lipogenic enzymes, is a key event in the reduction of VLDL-triglyceride secretion in fructan-fed rats. In fact, the activities of acetyl-CoA carboxylase, FAS, malic enzyme, ATP citrate lyase, and glucose-6-phosphate 1-dehydrogenase are decreased by \textasciitilde 50%. This coordinated decrease of all enzymes, in combination with the low activity of enzymes (eg, FAS, which are only regulated through modifications of protein and mRNA content) supports the hypothesis that oligofructose administration could modify lipogenic enzyme gene expression.

\textsuperscript{1}From the UCL-Université catholique de Louvain, School of Pharmacy, Brussels.

\textsuperscript{2}Presented at the symposium Probiotics and Prebiotics, held in Kiel, Germany, June 11–12, 1998.

\textsuperscript{3}Supported by the International Life Sciences Institute–Human Nutrition Institute and by the EEC Fair Program (grant 96/3 011).

\textsuperscript{4}Address correspondence to NM Delzenne UCL-Université catholique de Louvain, School of Pharmacy, UCL-PNMT 7369, 73 Avenue Mounier, B-1200, Brussels, Belgium. E-mail: delzenne@pnmt.ucl.ac.be.
Chronic feeding of oligofructose to rats prevented triacylglycerol accumulation induced by fructose in the liver (22). The low lipogenic capacity of the liver could be the key mechanism in this protection because even after the fructose load, FAS activity remained significantly low in oligofructose-fed rats. However, despite its protective effect on the liver, oligofructose was not able to prevent fructose-induced hypertriglyceridemia, which suggests that the consumption of oligofructose cannot counteract the fructose-induced defect in VLDL-triacylglycerol clearance. In a more recent study, we showed that when oligofructose was added to a diet composed of 10% lard, 4% corn oil, and 0.15% cholesterol for 3 wk, postprandial triglyceridemia was reduced by 50% and the increase in free cholesterol concentrations in the serum, which is usually induced by a high fat diet, was prevented. These results suggest that oligofructose is also able to decrease serum triacylglycerol concentrations through an extra-hepatic event, namely by enhancing triacylglycerol-rich lipoprotein catabolism (23). The hypotheses to explain a possible effect of inulin-type fructans on the modulation of triacylglycerol metabolism as an indirect effect mediated via several mechanisms is outlined below.

Modifications of glucose and insulin concentrations

Dietary modulation of lipogenesis is often linked to physiologic changes. Indeed, the induction of lipogenic enzymes by glucose, occurring via an increased gene transcription, is potentiated by insulin (12). The association between glycemia or insulinemia and triacylglycerol has also been shown for resistant starch which, in rats, decreases serum triacylglycerol concentrations, reduces FAS activity by 20%, and concomitantly lowers postprandial insulinemia (24). The effects of inulin-type fructans on glycemia and insulinemia are not yet fully understood, and available data are sometimes contradictory, indicating that these effects may depend on physiologic (fasting compared with postprandial) or disease (eg, diabetes) conditions. Oligofructose given to rats at a dose of 10% for 30 d reduces postprandial glycemia and insulinemia by 7% and 26%, respectively (25). However, the glycemic response during a glucose-tolerance test after overnight fasting is identical in control and oligofructose-fed rats (N Kok, personal communication, 1998). Feeding streptozotocin-treated (diabetic) rats a diet containing 20% oligofructose for 2 mo decreased postprandial glycemia despite a lack of modification of the glycemic or insulinemic response to a saccharose or maltose load (25). Other nondigestible carbohydrates are known to modify the kinetics of absorption of carbohydrates, thus decreasing the incidence of glycemia and insulinemia (26, 27).

Production of short-chain carboxylic acids in the large bowel

The production of short-chain carboxylic acids in the large bowel of oligofructose-fed rats leads to a >2-fold increase in the portal concentration of both acetate and propionate (28). Propionate was reported to inhibit fatty acid synthesis in vitro (29–31), whereas acetate is a lipogenic substrate.

Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 amide

Glucose dependent insulinotropic polypeptide (GIP) and glucagon-like peptide1(7–36)amide (GLP-1) are the major hormonal mediators regulating postprandial insulin release. Both peptides are released from endocrine cells in the intestinal mucosa after ingestion of carbohydrates and enhance postprandial insulin release from the pancreatic β cells (32). In addition to their insulinoic effects, GIP and GLP have direct anabolic insulin–like actions on lipid metabolism. They stimulate de novo lipogenesis in both adipose tissue and liver and increase lipoprotein lipase activity (33–35). Oligofructose supplementation in the diet of rats on GIP and GLP-1 release will be further studied to analyze their putative role in the hypolipidemic effect of such a nondigestible oligosaccharide.

CONCLUSIONS

The addition of fructans (eg, oligofructose) and other nondigestible carbohydrates (eg, resistant starch) to the diet of rats can decrease lipogenesis in the liver by lowering the activity of key enzymes regulated only through modifications of gene expression. The mechanism by which such nondigestible nutrients modify hepatic metabolism remains to be clarified. What about an effect of fructans in humans? Some studies performed in normo- and hyperlipidemic patients showed a hypotriglyceridemic effect of dietary inulin (2, 3), whereas other studies showed no effect of long-chain fructans on triglyceridemia (36–38). As suggested by Jackson et al (2), several factors need to be accounted for in the interpretation of results in human studies, such as the duration of the treatment, the dietary intake of carbohydrates compared with lipids, and the serum lipid composition at the beginning of treatment. Studies need to be performed in hypertriglyceridemic patients, in whom lipogenic homeostasis could be disturbed, to determine the relevance of fructans in decreasing lipogenesis in humans.

REFERENCES