Effect of non-digestible fermentable carbohydrates on hepatic fatty acid metabolism
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Introduction
Several non-digestible but fermentable dietary carbohydrates are able to regulate lipaemia, and mainly triglyceridaemia. Among them, oligofructose (OFS), a mixture of non-digestible/fermentable fructo-oligosaccharides, is able to decrease triacylglycerols (TAGs) in very-low-density lipoproteins (VLDL) when it is given in the diet of rats. The triglycerides-lowering action of OFS is due to a reduction of de novo fatty acid synthesis in the liver, through inhibition of all lipogenic enzymes, namely acetyl-CoA carboxylase, fatty acid synthase (FAS), malic enzyme, ATP citrate lyase and glucose-6-phosphate dehydrogenase. Our results suggest that OFS decreases lipogenic enzyme gene expression. Postprandial insulin and glucose levels are lower in the serum of OFS-fed animals, and this fact could explain, at least partially, the metabolic effect of OFS. Moreover, some other events occurring in the gastrointestinal tract after OFS feeding could be involved in the antilipogenic effect of this fructan: the production of propionate through the fermentation; a modulation of the intestinal production of incretins, namely glucose-dependent insulinotropic peptide and glucagon-like peptide 1; and/or modifications of digestible carbohydrate availability.

Many attempts have been made to control serum TAGs concentration by modifying dietary habits. In that view, the hypotriglyceridaemic effect of non-digestible but fermentable carbohydrates, including resistant starch or fructo-oligosaccharides, has been described both in humans [1] and in animals [2–5]. The mechanism of their lowering effect on serum lipids is not fully elucidated.

Dietary TAGs are transported from lymph into the blood as chylomicrons, then hydrolysed by lipoprotein lipase; they may reach the liver as chylomicron remnants. The liver plays a key role in TAG-rich lipoprotein homeostasis, as it is able to 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 the circulation [6].

Since newly synthesized fatty acids are preferentially channelled into VLDL, the lipogenic activity of the liver is a key factor for the hepatic TAG-VLDL output [6–8]. Among the key enzymes that control lipogenesis, FAS is the most sensitive to nutrients and hormones [9].

Insulin and glucose have been shown to be important effectors regulating fatty acid and TAG synthesis, both in vivo [10,11] and in vitro [12].

Feeding rats a diet supplemented with 10% OFS, a non-digestible but fermentable oligomer of β-D-fructose obtained by enzymatic hydrolysis of chicory inulin, significantly lowers TAG and phospholipid (PL) serum concentrations [13]. This is almost exclusively due to a decrease in the concentration of plasma VLDL [14]. In the present paper, we review our recent results relevant to the mechanism of the hypotriglyceridaemic effect of OFS in rats, and discuss the relationship with the effect of other non-digestible carbohydrates. We also mention the effects described in humans to date.

Results and discussion
The effects of inulin-type fructans on triglyceridaemia have been studied in both human subjects and in animals. In rats, a decrease in serum

Abbreviations used: OFS, oligofructose; FAS, fatty acid synthase; TAG, triacylglycerol; PL, phospholipid, VLDL, very low density lipoproteins.

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triglyceridaemia (in both the fed and the fasted state) has consistently been reported in several
studies, whereas in healthy humans, only TAGs in the fasting state have been measured and they
were shown to be unmodified [15-17] in all but one study [18]. No data have yet been published
that report studies performed in hypertriglyceridaemic patients.

Feeding rats on a diet supplemented with OFS (10% in the diet) significantly lowers serum
TAGs and PL concentrations [19], but does not modify free fatty acid concentration in the serum.
The hypotriglyceridaemia is due mainly to a decrease in the concentration of plasma VLDL
[14]. This effect is likely to be the result of a decrease in the hepatic synthesis of TAGs rather
than to a higher catabolism of TAG-rich lipoproteins [20]. Hepatocytes isolated from OFS-fed
rats have a slightly lower capacity to esterify [14C]palmitate into TAGs and but a 40%
decreased capacity to synthesize TAGs from [14C]acetate [14,20]. These data support the
hypothesis that a decreased de novo lipogenesis in the liver, through a coordinate reduction of
the activity of all lipogenic enzymes, is a key event in the reduction of VLDL-TAG secretion
in fructan-fed rats: in fact the activity of acetyl-CoA carboxylase, FAS, malic enzyme, ATP
citrate lyase and glucose-6-phosphate dehydrogenase is decreased by about 50%. This coordi-
nate decrease of all enzymes, together with the lower activity of enzymes like FAS, which are
only regulated through modifications of protein and mRNA content, support the hypothesis that
OFS administration could modify lipogenic enzyme gene expression.

The fact that de novo lipogenesis is the basis for the hypotriglyceridaemic effect of fruc-
tans in rat liver might explain the lack of effect observed in healthy humans, in whom de novo
lipogenesis is relatively low due to the high levels of fats provided by the human diet. Future
experiments should be performed either in obese patients or in insulin-resistant individuals,
eating high carbohydrate–high caloric diets. Chronic feeding with OFS protected rats against fructose-
induced TAG accumulation in the liver. The lower lipogenic capacity of the liver could be the
key event in this protection since, even after the fructose load, FAS activity remained signifi-
cantly lower in OFS-fed rats. However, despite its protective effect on the liver, OFS was not able to
prevent fructose-induced hypertriglyceridaemia, suggesting that OFS feeding could not counter-
act the fructose-induced defect in VLDL–TAG clearance [21].

The hypotheses to explain a possible effect of inulin-type fructans on the modulation of
TAG metabolism are indirect effects mediated via several mechanisms.

(1) Modifications of glucose and/or insulin levels
Dietary modulation of lipogenesis is often linked to such physiological changes. Indeed, the induc-
tion of lipogenic enzymes by glucose, occurring via an increase in gene transcription, is poten-
tiated by insulin [22]. The association between glycaemia/insulinaemia and TAG has also been
demonstrated for resistant starch which, in rats, decreases the serum TAG concentration,
reduces FAS activity by 20%, and concomitantly lowers postprandial insulinaemia [23]. The
effects of inulin-type fructans on glycaemia and insulinaemia are not yet fully understood and
available data are sometimes contradictory indicating that these effects may depend on physiolo-
gical (fasting versus postprandial state) or disease (diabetes) conditions: OFS given at the
dose of 10% in the diet of rats for 30 days reduces postprandial glycaemia and insulinaemia
by 17 and 26%, respectively [20]. However, the glycaemic response during a glucose-tolerance
test after overnight fasting is identical in control and OFS-fed rats (N. Kok, unpublished work).
In streptozotocin-treated (diabetic) rats, feeding a diet containing 20% OFS for 2 months
decreases postprandial glycaemia, despite a lack of modification of the glycaemic/insulinaemic
response to a saccharose or maltose load [24]. Other non-digestible carbohydrates are known to
modify the kinetics of absorption of carbo-
hydrates, thus lowering glycaemia and insulinae-
mia [25-27].

(2) The production, in the large bowel, of short-
chain carboxylic acids
This leads to a greater than 2-fold increase in the portal concentrations of both acetate and
propionate in OFS-fed rats [13]. Propionate has been reported to inhibit fatty acid synthesis in vitro
[28-30], whereas acetate is a lipogenic sub-
strate.

(3) Glucose-dependent insulinotropic polypeptide
(GIP) and glucagon-like peptide-1 (7-36)amide
(GLP-1)
GIP and 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 \( \beta \)-cells (for a review see [31]). In addition to their insulinotropic effects, GIP and GLP-1 have direct anabolic insulin-like action on lipid metabolism: they stimulate de novo lipogenesis in both adipose tissue and liver and increase lipoprotein lipase activity [32-34]. The effects of OFS supplementation in the diet of rats on GIP and GLP-1 release will be studied further to analyse their putative role in the hypolipidaemic effect of such a non-digestible oligosaccharide.

In conclusion, the addition of fructans such as oligofructose, and also of other non-digestible carbohydrates such as resistant starch, to the diet of rats causes a decrease in lipogenesis in the liver, by lowering the activity of key enzymes which are only regulated through modifications of gene expression. The mechanism by which such non-digestible nutrients modify hepatic metabolism remains to be clarified. The relevance of these observations to humans requires trials to be performed in hypertriglyceridaemic patients in whom lipogenic homeostasis could be disturbed.


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