Invited commentary

The hypolipidaemic effect of inulin: when animal studies help to approach the human problem

The paper by Jackson *et al*. (1999) in the present issue of the *British Journal of Nutrition* is devoted to the analysis of the effect of inulin on blood lipids in moderately hyperlipidaemic men and women. The hypolipidaemic effect of dietary inulin-type fructans has been suggested by many animal studies, in which either a hypotriacylglycerolaemic, or a hypocholesterolaemic effect was observed when animal diets were enriched with such non-digestible, fermentable carbohydrates (for review, see Roberfroid & Delzenne, 1998). Jackson *et al*. (1999) show in their human study the occurrence of a rather punctual hypotriacylglycerolaemic effect, which is observed after 8 weeks of treatment with 10 g inulin/d and is preceded by decreased insulinaemia, observed after 4 weeks. They also suggest an inter-individual variability in the response to inulin, which is dependent on the plasma triacylglycerol level at the beginning of the treatment. Interestingly, they present a table in which several human studies are reported, and indicate clearly that in some experiments, inulin-type fructans decrease cholesterolaemia and/or triacylglycerolaemia, whereas in some other studies, no effect can be seen, as recently shown in hyperglycaemic patients (Alles *et al*. 1999). The data obtained in animals could help to clarify those discrepancies.

First, in animals, the type of diet in which inulin-type fructans are incorporated influences the metabolic response.

(1) With a standard diet, rich in digestible carbohydrates or with a diet enriched in sucrose, a decrease in triacylglycerolaemia is observed, which mainly occurs through a decrease in the hepatic lipogenesis, defined as *de novo* fatty acid synthesis from hexoses. This process involves a modification of the expression of genes coding for lipogenic enzymes (Aghelli *et al*. 1998; Delzenne & Kok, 1998). Could lipogenesis constitute a key target for the hypolipidaemic effect of inulin in human subjects? This question remains open, as only a few studies to date have been devoted to the analysis of lipogenesis in man. Interesting results have been obtained recently within the context of the EEC-funded research project (Nutrigene FAIR CT97-3011) suggesting that, depending on the carbohydrate content of the diet, lipogenesis has to be considered as a non-negligible pathway involved in triacylglycerol secretion in man (Michel Beylot, personal communication).
(2) When inulin-type fructans are added to a high-fat diet, resembling a human Western diet, they decrease triacylglycerolaemia in rats and hamsters by a completely different biochemical mechanism, involving higher triacylglycerol-rich lipoprotein catabolism (Kok *et al*. 1998; Trautwein *et al*. 1998).
(3) The influence of inulin-type fructans on cholesterol homeostasis has also been reported in rats and hamsters fed on high-fat diets (Levrat *et al*. 1994; Trautwein *et al*. 1998). This effect seems to result from a higher turnover and modifications of bile acid synthesis (Levrat *et al*. 1994; Moundras *et al*. 1994).

All these findings show that several metabolic pathways may be influenced by inulin (bile acid synthesis and excretion, lipogenesis, lipoprotein catabolism), leading to differential effects on serum lipids (decrease in LDL-cholesterol or triacylglycerols).

Besides the diversity in the metabolic goals, the link between the events occurring in the gastrointestinal tract and the systemic effect of inulin or other fructans on lipid metabolism remains unclear.

Several mechanisms could be evoked, in view of experiments performed in animals or *in vitro*, and could take place concomitantly.

(1) Feeding of fructans modifies the availability of the other nutrients present in the diet through their effect on gastrointestinal 'kinetics' (gastric emptying, motility), on digestion (dissacharidase activity, bile acid homeostasis), or on absorption (for example, Ca or Mg) (Roberfroid & Delzenne, 1998). The qualitative and quantitative modifications of the digestion products (glucose, chylomicrons, minerals) in the systemic circulation could act as metabolic modulators.
(2) Fructans are prebiotics, as they are highly fermented and modify the gut microflora composition. The influence of microflora composition on lipid homeostasis is unknown; however, several studies suggest that some end-products of fructan fermentation, such as acetate and propionate, reach the systemic circulation and are able to modify the glucose and lipid metabolism in several cell types (Demigné *et al*. 1995).
(3) Finally, the intestine may be considered as an endocrine organ, as in response to dietary components, several peptides and hormones are secreted from the intestinal cells. Their role as putative mediators of the systemic effect of fructans merits attention. For example, a higher secretion of glucose-dependent insulinotropic peptide occurs in fructan-fed rats, where it is able to modify the activity of lipoprotein lipase (*EC* 3.1.1.34) involved

in circulating triacylglycerol catabolism (Knapper *et al*. 1995; Kok *et al*. 1998).

Another important factor to consider, when a systemic effect of inulin is studied, is the duration of the treatment; the hypotriacylglycerolaemic effects appears only after several (3–4) weeks in rats. In human subjects Jackson *et al*. (1999) show a hypotriacylglycerolaemic effect after 8 weeks; in the conclusion of their paper, Alles *et al*. (1999) incriminate the short duration of the treatment to explain the lack of effect in their studies. This 'lag phase' could be justified by the fact that several physiological effects of fructans require time for adaptation (modification of gut microflora, of gene expression etc.).

In conclusion, several papers support the idea that inulin-type fructans could constitute interesting nutrients, not only because of their 'local' effect inside the gastrointestinal tract, but also through their systemic effects, namely on glucose, Ca, or lipid homeostasis. Concerning their hypolipidaemic effects, recent data obtained in human studies, like the one published in this issue of *British Journal of Nutrition* are encouraging. Despite the great interest it could constitute in terms of human health, the mechanism of the effect of non-digestible, fermentable carbohydrates on lipid metabolism in human subjects remains to be elucidated, not only because the road from the gut to the liver and the blood is long and complicated, but also because the putative metabolic targets of inulin, relatively well known and described in animal models, are more difficult to study in man. As suggested by experimental studies in animals, and by Jackson *et al*. (1999), several factors should be taken into account in the human studies; for example, dietary intakes of carbohydrates *v*. lipids, the duration of the treatment, and the serum lipid composition at the beginning of the treatment. We hope that all the future experimental studies devoted to analysing the systemic effect of inulin and related carbohydrates will bring key pieces into the puzzle, and will help to identify the 'health' effects of inulin-type fructans in man.

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