Modulation of Glucagon-like Peptide 1 and Energy Metabolism by Inulin and Oligofructose: Experimental Data[1–5]

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Abstract

Inulin-type fructans have been tested for their capacity to modulate lipid and glucose metabolism in several animal models. Oligofructose (OFS) decreases food intake, fat mass development, and hepatic steatosis in normal and in obese rats; moreover, it exerts an antidiabetic effect in streptozotocin-treated rats and high-fat-fed mice. In most cases, the beneficial effects of OFS are linked to an increase of glucagon-like peptide-1 (GLP-1) level in the portal vein and of GLP-1 and proglucagon mRNA, its precursor, in the proximal colon. In this organ, OFS increases the number of GLP-1-positive L cells by promoting factors (Neurogenin 3 and NeuroD) involved in the differentiation of stem cells into L cells. The chronic administration of GLP-1 receptor antagonist exendin 9–39 totally prevents the beneficial effects of OFS (improved glucose tolerance, fasting blood glucose, glucose-stimulated insulin secretion, insulin-sensitive hepatic glucose production, and reduced body weight gain). Furthermore GLP-1 receptor knockout mice are completely insensitive to the antidiabetic actions of OFS. These findings highlight the potential interest of enhancing endogenous GLP-1 secretion by inulin-type fructans for the prevention/treatment of obesity and type 2 diabetes. Moreover, OFS is also able to modulate other gastrointestinal peptides (such as PYY and ghrelin) that could be involved in the control of food intake. Several studies in humans already support interest in OFS in the control of satiety, triglyceridemia, or steatohepatitis. The link with gut peptides production in humans remains to be proven. J. Nutr. 137: 2547S–2551S, 2007.

Modulation of lipid and glucose metabolism by dietary inulin-type fructans: an effect linked to the control of food intake?

Several data suggest that prebiotics could play a role in the control of obesity and associated metabolic disorders (1). This applies especially to inulin-type fructans, fermentable dietary fibers that lower body weight and improve blood lipids levels and/or glycemia in rats (2,3).

The effects of inulin-type fructans on glucose and lipid metabolism have been reviewed in several articles (3,4). When added in the diet of rats, mice, or hamsters, inulin-type fructans modulate hepatic lipid metabolism with consequences on triglyceride accumulation in the liver and/or serum lipids. In rats, reduced triglyceridemia is linked to a decrease in de novo lipogenesis in hepatic tissue and to a decrease in the expression of key hepatic lipogenic enzymes, reflected by a decrease in fatty acid synthase mRNA (5). In obese Zucker rats, dietary supplementation with oligofructose (OFS,[6] a chicory inulin-type fructan with a low degree of polymerization) reduces hepatic steatosis (6). This effect is likely to result mainly from a lower availability of nonesterified fatty acids coming from adipose tissue because fat mass and body weight are decreased by the

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[5] In these proceedings, the term inulin-type fructan shall be used as a generic term to cover all β–(2←1) linear fructans. In any other circumstances that justify the identification of the oligomers vs. the polymers, the terms oligofructose and/or inulin or eventually long-chain or high-molecular-weight inulin will be used, respectively. Even though the oligomers obtained by partial hydrolysis of inulin or by enzymatic synthesis have a slightly different DP_{av} (4 and 3.6, respectively), the term oligofructose shall be used to identify both. Synergy will be used to identify the 30/70 mixture (wt:wt) of oligofructose and inulin HP otherwise named oligofructose-enriched inulin.

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[6] Abbreviations used: DPPIV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; NDO, nondigestible oligosaccharides; OFS, oligofructose.

treatment. The protection against steatosis is strongly dependent on fermentation pattern (7). The high proportion of propionate produced in the cecum, which reaches the liver through the portal vein, is, at least in animals, a key event explaining a lower hepatic triglyceride synthesis resulting from nondigestible oligosaccharide (NDO) feeding (4,8).

Rats fed OFS also exhibit a lower fat mass development (6,9). Indeed, the epididymal, inguinal, and visceral adipose tissue fat masses are reduced by 30–40% in OFS-fed rats as compared with controls (10–12).

Carbohydrate digestibility and glucose homeostasis are important phenomena to take into account when assessing the influence of OFS on metabolism (see Jenkins, this Supplement). An improvement of glucose/insulin ratio has been observed in rats receiving OFS added to a high-fructose diet (13). OFS improves glycemia and plasma insulin both in the postprandial state and after an oral glucose load in streptozotocin-treated diabetic rats. Moreover, the treatment with OFS improves pancreatic insulin production and increases β-cell mass (14). In diabetic mice fed a high-fat diet, OFS treatment for 4 wk improves glucose tolerance reverses hepatic insulin resistance but does not improve insulin-stimulated whole-body or individual tissue glucose utilization (15).

In most studies showing a beneficial effect of OFS or other inulin-type fructans on lipid homeostasis, on glucose metabolism, and on fat mass development, the animals supplemented with OFS exhibited a lower energy intake, suggesting a satietogenic effect. It has thus been hypothesized that the production of satietogenic gut peptides could be a relevant mechanism to explain such effects.

Gut peptides: biochemical relay explaining the effect of dietary fructans on satiety and metabolic disorders associated with obesity

The understanding of the biochemical mechanism by which inulin-type fructans modulate satiety or glucose or lipid metabolism is essential to propose key nutritional advice for specific disorders associated with the metabolic syndrome. It was proposed more than 30 y ago that dietary fibers act as a physiological obstacle to energy intake by an effect on satiation and/or satiety (16). The mechanism and relevance of endogenous modulation of gut peptide production by dietary fibers are poorly documented. Some experimental data, however, suggest that those peptides could constitute a link between fermentation in the lower part of the gut and systemic consequences of "colonic food" intake. An example is given through the analysis of the metabolic and satietogenic effect of chicory inulin-type fructans (9,10,14,17).

We first focused on glucagon-like peptide-1 (GLP-1) as a target. GLP-1 is a key hormone released from enteroendocrine L cells in response to nutrient ingestion. It is produced by tissue-specific posttranslational processing of its precursor proglucagon peptide by prohormone convertase-1. It promotes insulin secretion and β-cell proliferation in the pancreas, controls glycogen synthesis in muscle cells, and promotes satiety. These actions make GLP-1 highly attractive as a therapeutic agent, but its rapid enzymatic degradation by dipeptidyl peptidase-IV (DPPIV) makes it unsuitable for injection therapy (18–20).

In rats fed a standard diet enriched with OFS, exhibiting a high fermentation as shown by an increase in total and empty cecum weight, there is a significant increase in colonic and/or portal plasma GLP-1 (10,11,14,21). The high intestinal GLP-1 content was corroborated by a higher colonic proglucagon mRNA level (11).

GLP-1 (7–36) amide production occurs in different parts of the distal intestine (22), and the site of production might influence the systemic distribution of GLP-1 (7–36) amide through the portal vein. Therefore, we have analyzed the modulation of portal GLP-1 (7–36) amide in the sera of rats fed 3 types of inulin-type fructans, differing through their main site and extent of fermentation. We have also identified the major intestinal site of proglucagon expression and GLP-1 (7–36) amide synthesis after fructan feeding and established a relation between peptide modulation and fructan effect on energy intake and fat mass development (11). Rats were fed a standard diet supplemented (10%) with 1 of 3 inulin-type fructans (Orafti, Oreye, Belgium) with different degrees of polymerization, i.e., OFS, containing mainly short-chain inulin-type fructans inulin HP, containing mainly long-chain fructans; and Synergy, a mix of both short- and long-chain fructans. Our data show that GLP-1(7–36) amide, even in control rats, is mainly produced in the proximal and median colon. Inulin-type fructans containing short-chain oligosaccharides (OFS and Synergy) preferentially increased both mRNA proglucagon and GLP-1(7–36) amide concentration in the proximal and, to a lesser extent, in the median colon. GLP-1(7–36) amide concentration per gram of cecal tissue remained unchanged after inulin-type fructan feeding, but, and because of cecum enlargement, mainly observed in rats fed OFS, GLP-1(7–36) amide content increased 3-fold in the whole organ as compared with controls.

This study led us to postulate that the proximal colon is the main location where OFS and OFS containing inulin-type fructans increase proglucagon mRNA and GLP-1 content.

Another study, performed in mice fed different types of high-fat diets supplemented with OFS, supports the fact that an increase in proglucagon expression in the proximal colon is a prerequisite to allow OFS to exert favorable effects on glycemia, fat mass development, and/or body weight gain (23). Two types of diet, a high-fat/carbohydrate-free (72% energy from fat, 28% from protein; contains 10% wt:wt microcrystalline cellulose) and a high-fat/high-carbohydrate [58% energy from fat, 16% from protein, 26% from carbohydrates (maltrodextrin:saccharose 1:1)] were given to mice and caused a similar increase in fasting glycemia, body weight, and epididymal fat mass. A 4-wk treatment with OFS decreased energy intake, body weight gain, glycemia, and epididymal fat mass only when added together with the high-fat/carbohydrate-free diet, but it had no effect on those parameters when added in a high-fat/high-carbohydrate diet. Interestingly, cecal enlargement caused by OFS treatment was much higher ($\times$2.2) in animals fed a high-fat/carbohydrate-free diet than in those fed a high-fat/high-carbohydrate diet ($\times$1.6). We observed that proglucagon mRNA was increased when OFS was added in a high-fat/carbohydrate-free diet but not in a high-fat/high-carbohydrate diet. GLP-1 is a physiological regulator of food intake and glycemia, mainly through its capacity to increase insulin secretion (18–19). According to this, a link could exist between OFS fermentation, proglucagon mRNA content, and insulin production, as already shown in diabetic rats (15).

Accordingly, OFS addition in the diet is able to counteract diabetes when given in streptozotocin-treated diabetic rats (15) but is unable to improve diabetes occurring in rats exhibiting a defect in colonic proglucagon expression [the BioBreeding diabetes-prone rats (24,25)].

We suggest that an increase in proglucagon mRNA and GLP-1 levels in the proximal colon is a key event allowing fermentable inulin-type fructans to modulate food intake, body weight, and glucose homeostasis. Moreover, the composition of the diet in which OFS is added might be important to allow an

adequate fermentation, leading to increased proglucagon expression.

The relevance of GLP-1 as a key factor in the control of food intake, fat mass development, and associated metabolic disorders by OFS was recently demonstrated in collaboration with Burcelin et al. (15). Indeed, in high-fat-fed mice, the antiobesity/diabetic effects of OFS clearly depend on a functional GLP-1 receptor (GLP-1R) (15). In mice exhibiting a functional GLP-1 receptor, the following beneficial effects of OFS were observed: decreases in food intake, in fat mass, and in body weight gain, an improved glucose tolerance during oral glucose tolerance test, and improved hepatic insulin resistance as assessed by euglycemic/hyperinsulinemic clamp technique and, at the molecular level, through the increase in the liver content of phosphorylated IRS2 and Akt . The disruption of GLP-1R function by chronic infusion of Exendin-9 prevents the majority of the beneficial effects of OFS treatment. Furthermore, the importance of GLP-1R-dependent pathways for the actions of OFS was confirmed using GLP-1R$^{-/-}$ mice fed a high-fat diet, which did not benefit from the OFS treatment.

These results are consistent with a model whereby OFS feeding increases the colonic content and release of GLP-1, leading to stimulation of insulin secretion and to the reduction of hepatic glucose production, fasting glycemia, and glucose intolerance.

The available evidence suggests that GLP-1 released from intestinal L cells may interact with afferent sensory nerve fibers arising from the nodose ganglion, which send impulses to the nucleus of the solitary tract and onward to the hypothalamus, which may be transmitted to the pancreas (26,27). Consequently, releasing GLP-1 directly into the portal vein may represent an important feature of the mechanisms related to OFS-improved glucose homeostasis.

Modulation of GLP-1 production/availability by dietary inulin-type fructans: role of L cells and DPPIV activity

GLP-1 is a short-living peptide in vivo because it is rapidly cleaved into an inactive form by DPPIV. Interestingly, DPPIV activity, measured in the portal serum of rats fed a standard diet, is lower in animals fed with OFS (10% in the diet) for 7 wk than in controls (11). OFS also decreases DPPIV activity in the serum of rats fed a high-fat diet (11).

If GLP-1 plays a key role in the systemic effects of inulin-type fructans, the question of the mechanism by which OFS increases intestinal and portal GLP-1 remains open. L cells, which are thought to arise from pluripotent stem cells in the crypts that also give rise to enterocytes, goblet cells, and Paneth cells, are abundant in the colon. Now it is accepted that stem cells located in the crypts differentiate into the 4 epithelial cell types through the action of specific differentiation factors. Among them, NGN-3 and NeuroD specifically drive cells into enteroendocrine cell types such as L cells (28) that express the proglucagon gene and synthesize the active form of GLP-1 as well as other peptides such as PYY and oxyntomodulin, which are also implicated in the control of food intake.

Some authors have proposed that it is the fermentation of nondigestible carbohydrates into short-chain fatty acids (mainly butyrate) that promotes proglucagon expression in mature intestinal L cells (29–31). In a recent study, we have tested the hypothesis that OFS could also target the enteroendocrine L-cell differentiation pathway (32). We have demonstrated that the doubling of L-cell number in the proximal colon after OFS feeding (4 wk in male Wistar rats fed a standard diet containing 10% OFS) is associated with a significant increase of NGN3 and NeuroD mRNA content. These results suggest a promotion of L-cell differentiation in the proximal colon by OFS. This is a novel mechanism by which nondigestible carbohydrates may modulate GLP-1 production.

Relevance to humans of inulin-type fructans effects on GLP-1 production

Based on animal data, it can be hypothesized that OFS appears to be a promising tool in the nutritional approach to controlling metabolic syndrome in obese patients, but to date, only a few studies have been reported that tested such effects of fermentable carbohydrate, namely inulin-type fructans, in humans. Interestingly, a recent study reports that OFS feeding (20 g/d) significantly increases plasma GLP-1 after a mixed meal (33), and we have recently shown, in healthy humans, that feeding 16 g/d OFS promotes satiety following breakfast and dinner and reduces hunger and prospective food consumption after the dinner. This was accompanied by a significant 10% reduction in total energy intake (34). Moreover, Archer et al. have demonstrated that

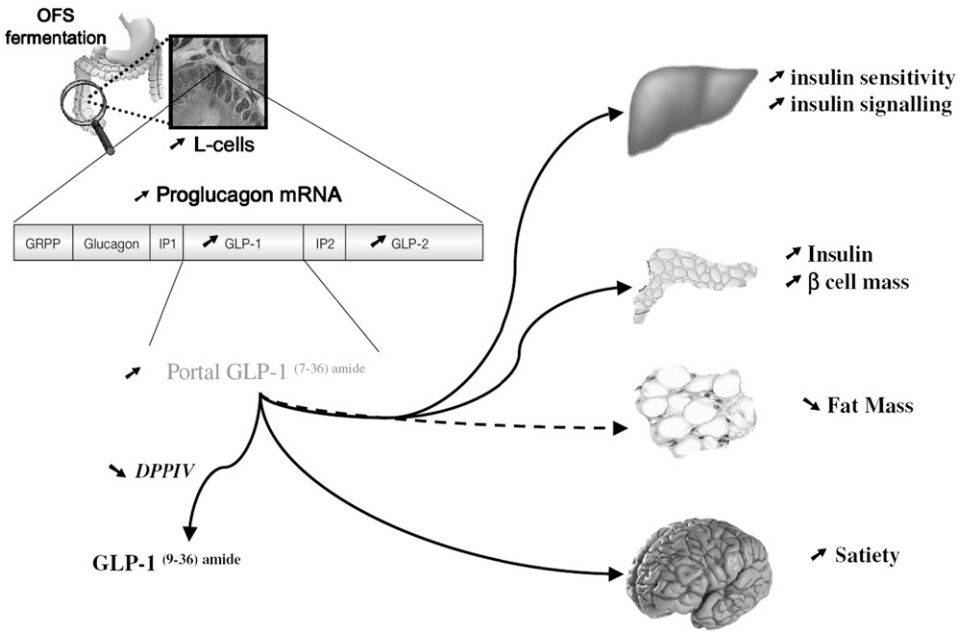

FIGURE 1 Physiological effects of the increased colonic GLP-1 production from OFS feeding.

fermentable inulin-type fructans, added in food as fat-replacers, were able to lower energy intake during a test day (35). The role of fermentable dietary fibers in the management of appetite in healthy humans has been recently confirmed (36).

In this article, we have summarized our experimental data showing that the effect of dietary inulin-type fructans on food intake and metabolic disorders associated with obesity could be related to the promotion of GLP-1 synthesis in the lower part of the gut (see **Fig. 1** for the summary of the effects). Several comments/questions should be taken into account for further research in this area.

There is no answer to the question: Is the prebiotic effect of inulin-type fructans responsible for the modulation of GLP-1 production and energy homeostasis? Studies performed in gnotobiotic animals would help to verify that the metabolic response to inulin or OFS is dependent on the resident bacteria.

If GLP-1 has a crucial role in the modulation of food intake or glucose tolerance in animals, some effects could also be driven by other mediators. Interestingly, a 2-fold reduction of hepatic levels of phosphorylated IKK-β and NF-κB was observed in OFS-fed mice vs. controls, suggesting a reduction in the hepatic inflammatory status in diabetic mice; this effect might be related to the improvement of insulin sensitivity, as shown by the increased tyrosine phosphorylation of IRS2 (15). Importantly, the lowering of the inflammatory mediators IKK-β and NF-κB in the liver was not prevented by Ex-9 treatment. This suggests that OFS may modulate immunity/inflammation by a mechanism that would not be dependent on GLP-1 production. It remains to be determined through which mechanisms OFS reduces hepatic inflammation. We have previously shown that OFS treatment increases the number of large phagocytic Kupffer cells with increased capacity to clear proinflammatory agents such as LPS in the liver (37). The effect of OFS on inflammatory processes occurring in the liver is an interesting perspective in the understanding of new systemic effects associated with the ingestion of prebiotic inulin-type fructans.

GLP-1 was the first gut peptide studied to relate events occurring in the colon through OFS ingestion to the modulation of energy, lipid, and glucose homeostasis. Other peptides could also be of interest. We have shown an increase in portal PYY and a decrease in serum ghrelin after OFS supplementation in rats, both events that could also participate in the satietogenic effect of OFS or related compounds (10). Other authors have shown that events occurring in the colon (fermentation; modulation of gut microbiota) exert a key influence on the overall host metabolism by modulating peptides such as fasting-induced adipose-tissue factor (38,39). The door is thus open to the discovery of new targets allowing fermentable inulin-type fructans and related food components to build a bridge between the colon and the rest of the body.

Finally, the modulation of gut peptides by colonic nutrients such as OFS or other NDOs would lead to a new nutritional approach (including functional food development) devoted to improving insulin sensitivity, satiety, and body weight gain in obese and type 2 diabetes patients. But further human studies are clearly necessary to prove the relevance of the animal data available until now.

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