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Relation between colonic proglucagon expression and metabolic response to oligofructose in high fat diet-fed mice

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Abstract

Several data suggest that fermentable dietary fiber could play a role in the control of obesity and associated metabolic disorders. The aim of this study was to investigate the putative role of short chain fructo-oligosaccharide (OFS) – a non-digestible oligosaccharide – in mice fed a standard diet and in mice fed two distinct high fat diets inducing metabolic disorders associated to obesity. We confirmed, in mice, several effects previously shown in rats fed a standard diet enriched with OFS, namely an increase in total and empty caecum weight, a significant decrease in epididymal fat mass, and an increase in colonic and portal plasma glucagon-like peptide-1 (GLP-1), a phenomenon positively correlated with a higher colonic proglucagon mRNA level. Curiously, 4-week treatment with OFS added at the same dose induced different effects when added in the two different high fat diets. OFS decreased energy intake, body weight gain, glycemia, and epididymal fat mass only when added together with the high fat–carbohydrate free diet, in which OFS promoted colonic proglucagon expression and insulin secretion. Our results support an association between the increase in proglucagon expression in the proximal colon and OFS effects on glycemia, fat mass development, and/or body weight gain. In conclusion, dietary oligosaccharides would constitute an interesting class of dietary fibers promoting, in certain conditions, endogenous GLP-1 production, with beneficial physiological consequences. This remains to be proven in human studies.

Keywords: Proglucagon; High-fat diet; GLP-1; Obesity; Diabetes; Dietary fibers; Oligofructose

Introduction

Current recommendations for the management of type 2 diabetes and obesity include an increase in dietary fiber intake (American Diabetes Association, 2000). Non digestible oligosaccharides (NDO) are often cited as being important dietary fibers in nutritional advice concerning specific disorders associated with the metabolic syndrome (Slavin, 2005). On the basis of studies in animals and humans, it has been proposed that intake of NDO, which are fermented in the caeco-colon, could be interesting way to modulate satiety, glucose or lipid metabolism, and hypertension (Delzenne and Cani, 2005). Among NDOs, short chain fructo-oligosaccharides (OFS), given at the dose of 10% in the diet of rats for a few weeks, reduces hepatic triglyceride content, post prandial glycemia and triglyceridemia in normal rats, lessens hepatic steatosis and fat mass development in obese Zucker Fa/Fa and rats fed a high fat diet. This phenomenon could be partly explained by a satietogenic effect of OFS (Cani et al., 2005b; Daubioul et al., 2002; Kok et al., 1998b). In streptozotocin-treated diabetic rats, OFS feeding during 4 to 6 weeks improves glucose tolerance, decreases glycemia, and partially restores insulin secretion (Cani et al., 2005a). Moreover, an improvement of glucose/insulin ratio has also been observed in rats receiving OFS added in a high-fructose diet (Busserolles et al., 2003).

Interestingly, in rats, these effects seem to be linked to the higher secretion of glucagon-like-peptide 1 (7–36) amide (GLP-

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1) in the portal vein (Cani et al., 2004; Kok et al., 1998a). This effect is positively correlated with increases of proglucagon mRNA and GLP-1 concentration in the proximal colon (Cani et al., 2004). This peptide is produced by intestinal endocrine L-cells through a specific post-translational processing of proglucagon gene. GLP-1 is considered a key peptide in the control of glucose tolerance, and insulin secretion by pancreatic β-cells (Drucker, 2002; Meier and Nauck, 2005). Moreover, we and other have demonstrated the key role of gut peptides in the metabolic effect of drugs or nutrients in specific mouse models or nutritional models of obesity (Burcelin et al., 2001, 2002; de Fourmestraux et al., 2004; Preitner et al., 2004; Knauf et al., 2005).

We have recently demonstrated that OFS treatment reduced the development of glucose intolerance following 4 weeks of high fat, carbohydrate free diet, a classical nutritional model leading to disorders associated with obesity. The antidiabetic effects of OFS were largely dependent on GLP-1 action, as disruption of GLP-1R function, by infusing Ex-9 or using GLP-1 receptor-/-mice, prevented the majority of beneficial effects observed following OFS treatment (Cani et al., 2006a).

The effects of OFS have not been studied in mice fed another type of a high fat diet (high fat, high carbohydrate). This type of diet is interesting since it is largely used for a long period of treatment (8 to 24 weeks) to assess the role of nutrients in metabolic alterations occurring through high fat feeding (Parekh et al., 1998; Petro et al., 2004; Surwit et al., 1988, 1995).

Therefore, we analyzed sequentially 1) the effect of OFS added in the standard diet of mice, on key parameters known to be modulated by this dietary fiber in rats (intestinal fermentation and GLP-1 synthesis), and 2) the capacity of OFS to counteract metabolic disorders induced by two distinct high fat diet treatments in mice.

Methods and materials

Animals

C57BL/6J mice (Charles River, Belgium) were housed in a controlled environment (inverted 12 h daylight cycle, lights off at 10 am) with free access to food and water in groups of four–five mice per cage, at 22 °C.

Experiment 1

Mice were fed a standard diet with or without OFS for 21 days: Twelve-week-old control mice (CT) were fed a powdered A04 standard diet (A04, UAR, Villemoisson-sur-Orge, France), whereas oligofructose (OFS) treated mice received a diet prepared by mixing 90 g A04 standard diet with 10 g corresponding fructan: Raftilose P_{95} (Orafti, Tienen, Belgium). The A04 standard diet contained the following (g/100 g dry diet): 19.3 protein (consisting of equivalent mix of soy and fish proteins); 70.4 total carbohydrates obtained from corn, wheat, barley and bran (including 38 starch, 3 saccharose, 5 cellulose and 8 non-digestible carbohydrates); 3 lipids; 6 of mineral mixture and 1.3 of vitamins (Cani et al., 2004).

Experiment 2

Mice were fed 2 types of high fat diet with or without OFS for 28 d:

1) HF-1: a high fat diet (UAR, Epinay-sur-Orge, France) (Table 1). Energy content (kcal/100g): 72% fat (corn oil and lard), 28% protein, and< 1% carbohydrates (HF-1–CT), (Burcelin et al., 2002; Cani et al., 2006a), or a mix of high fat diet and oligofructose (a gift from Orafti, Tienen, Belgium) in a proportion of 90:10 (weight/weight) (HF-1–OFS). The treatment with OFS started when mice were 12 weeks old, simultaneously with HF-1 diet, and continued for 28 d.
2) HF-2: a high fat diet (UAR, Epinay-sur-Orge, France) (Table 1). Energy content (kcal/100g): 58% fat, 16% protein, and 26% carbohydrates (Petro et al., 2004). All mice received the HF-2 diet for 8 weeks; at this end of this period, mice were 12 weeks old (same age as mice fed HF-1), and they were then randomized into two groups: one receiving the HF-2 diet as such (HF-2–CT), and the second one receiving a mix of HF-2 diet and oligofructose in a proportion of 90:10 (HF-2–OFS), for 28 d.

All mouse experiments were approved by the local committee and the housing conditions were as specified by the Belgian Law of November 14, 1993 on the protection of laboratory animals (agreement n° LA 1230314).

Chemicals

Raftilose P_{95} (Orafti, Tienen, Belgium) is a mixture of glucosyl-$(fructosyl)_n$-fructose and $(fructosyl)_m$-fructose but with an average degree of polymerization (DP) of 4.5. Other chemicals used in this study are of the purest grade available (Sigma, St. Louis, MO, USA; Merck, Darmstadt, Germany).

Blood samples

At the end of experiment (28 d), in Experiment 1, mice were anesthetized by intra-peritoneal injection of sodium pentobarbital solution (using 60 mg/kg of body weight, Nembutal®, Sanofi Santé Animale, Benelux, Brussels, Belgium). Portal vein blood samples were collected in EDTA tubes (Sarstedt, Nümbrecht, Germany) containing dipeptidyl peptidase IV inhibitor (Linco Research, St. Charles, MO, USA); after centrifugation, plasma was stored at −80 °C. Concentrations of GLP-1 (7–36) amide were measured using an ELISA kit, specific for GLP-1 (7–36) amide without cross reactivity towards GLP-1 (9–36) amide, GLP-2 and glucagon (GLP-1 active ELISA kit, Linco Research, St. Charles, MO, USA). In the other set of experiments, retro-orbital vein blood samples were collected in EDTA tubes and plasma was stored at −30 °C for further assessment.

Tissue samples

The caecum, and segments of the colon (proximal, medial, distal colon, corresponding to segments taken just after the caecal junction, in the middle of the colon, and just before the rectum, respectively), were immediately excised, flushed with ice-cold

Table 1
High fat diet composition

g/100 g dry diet	HF-1	HF-2
Proteins	37	23
Carbohydrates:	10	36
-Cellulose	10	0
-Maltodextrine	0	18
-Saccharose	0	18
Lipids	49.5	36
Mineral mix	2.5	4
Vitamin mix	1	1

saline, immersed in liquid nitrogen, and stored at −80 °C for further analysis of mRNA and peptides. Full and empty caecum, and epididymal fat pads were weighed.

Food intake assessment

Mice were housed five per cage. Food intake was recorded twice weekly for one month as described (Cani et al., 2004, 2005b). Pellets and spillage were weighed separately. The mean value for the weekly assessment was calculated.

Blood parameters

Plasma insulin concentration was determined at completion of the feeding period in the fasted (6 h) state in 5 µl of plasma collected from tail blood using an ELISA kit (Mercodia, Uppsala, Sweden). GLP-1 (7–36) amide were measured either in the plasma, or in tissue extracts, using an ELISA kit (GLP-1 active ELISA kit, Linco Research, St Charles, MO, USA), as previously described (Cani et al., 2004, 2005b). Concentrations of plasma triglycerides (TG) (Elitech Diagnostics, Brussels, Belgium) and non esterified fatty acids (NEFA) (Wako, Brussels, Belgium) were measured using kits coupling enzymatic reaction and spectrophotometric detection of reaction end-products.

Proglucagon and actin mRNA: RT–PCR

Total RNA from the different part of the colon was isolated and RT–PCR performed as previously described (Cani et al., 2004, 2005b). Briefly, after the RT reaction the PCR products were quantified using a fluorimetric method (Rediplate96Pico-Green® dsDNA Quantitation-Kit, Molecular Probes, Leiden, The Netherlands). Results are presented as mean ratio of relative fluorescence unit (RFU) of proglucagon mRNA/actin mRNA.

Table 2
Organ weight and body weight during standard diet treatment

	CT	OFS
Full caecum (g/100 g body weight)	1.54±0.09[a]	2.76±0.13[b]
Empty caecum (g/100 g body weight)	0.55±0.02[a]	0.87±0.04[b]
Body weight (g)	26.4±0.6[a]	26.6±0.4[a]
Epidydimal fat mass (g/100 g body weight)	1.41±0.1[a]	1.16±0.04[b]

Total caecum weight, empty caecum weight, body weight gain, and epididymal fat mass of mice treated for 3 weeks with a control diet (CT) or a control diet supplemented with OFS (OFS). Data are means±S.E.M. $n=8$ per group. Data with different superscript letters are significantly, $P<0.05$.

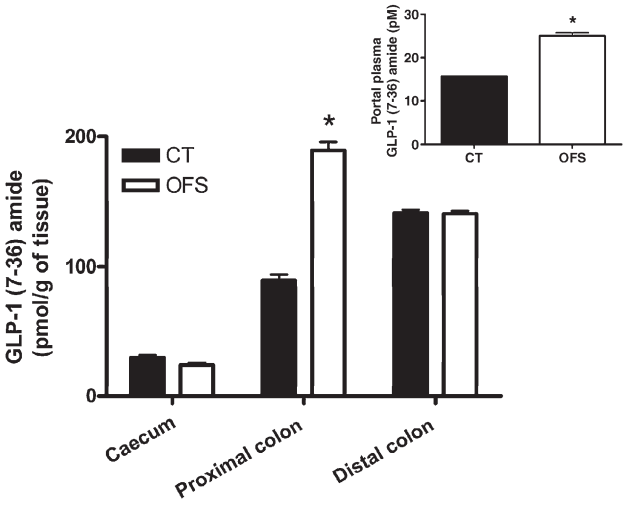

Fig. 1. Intestinal and portal plasma (insert) GLP-1 (7–36) amide concentration of mice treated with a control diet (CT) (black bars) or a diet supplemented with OFS (open bars) for 3 weeks. Data are mean±S.E.M. $n=8$ per group; *, $P<0.05$.

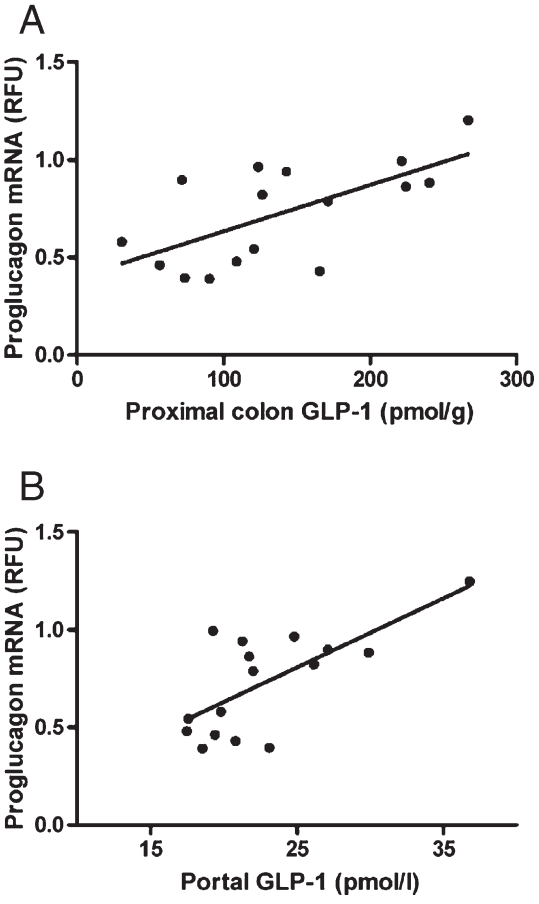

Fig. 2. Pearson's correlations between proximal colon GLP-1/proglucagon mRNA (A) and portal plasma GLP-1/proglucagon mRNA (B) of mice treated with a control diet or a diet supplemented with OFS for 3 weeks. Pearson's correlation values, (A): r squared value: 0.48; $P=0.002$. (B) r squared value: 0.42; $P=0.006$. $n=16$.

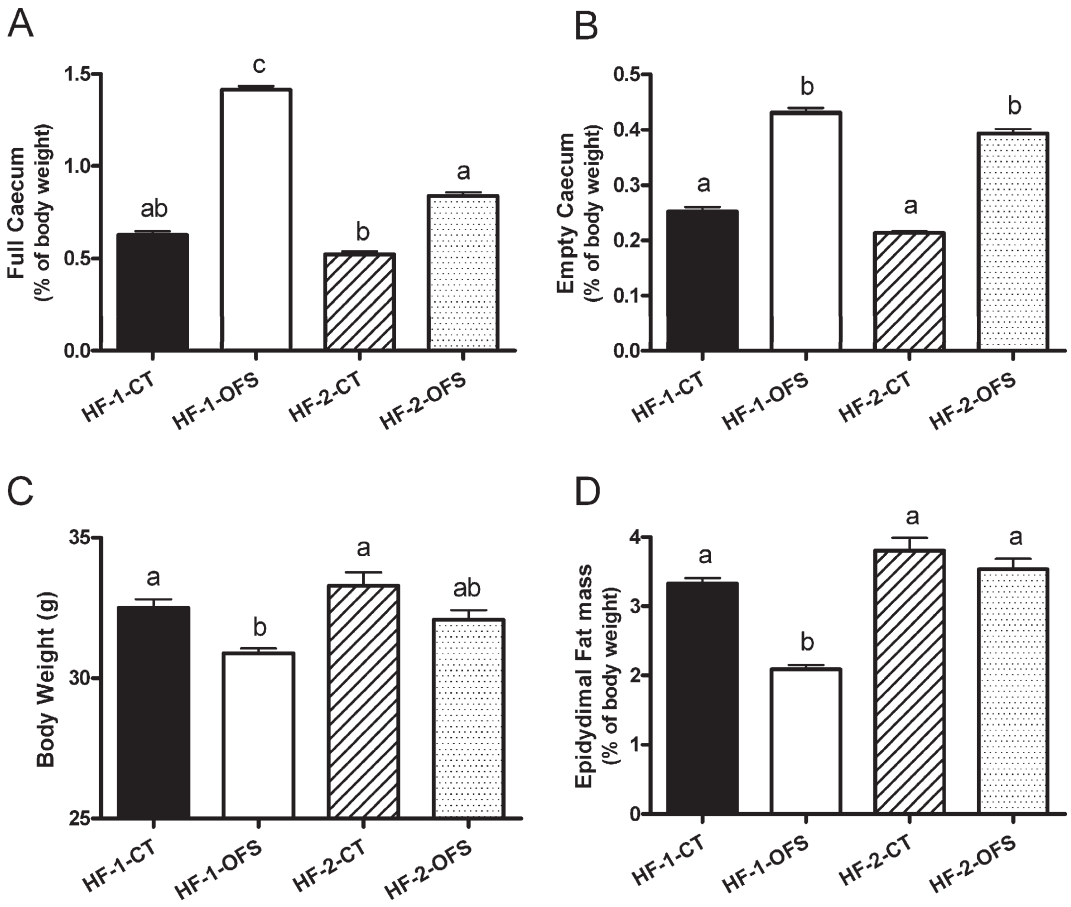

Fig. 3. Total caecum weight (A), Empty caecum weight (B), Body weight gain (C), and Epididymal fat mass (D) of mice treated with a high fat diet HF-1 (HF-1–CT) (black bars) or a high fat diet HF-1 supplemented with OFS (HF-1–OFS) (open bars), a high fat diet, HF-2 (HF-2–CT) (hatched bars) or a HF-2 diet supplemented with OFS (HF-2–OFS) (gray bars). Data are mean ± S.E.M. $n = 8$ per group. Data with different superscript letters are significantly different, $P < 0.05$, according to the post hoc ANOVA statistical analysis convention.

Statistical analysis

Results are presented as mean ± S.E.M. One-way ANOVA followed by post hoc (Tukey HSD) tests or Student's *t*-test were used to assess statistical significance between groups. $P < 0.05$ was considered as statistically significant.

Results

Experiment 1: Effect of OFS added to standard diet (A04)

Organ weight

Table 2 shows that full caecum and empty caecal tissue weights were doubled in OFS fed mice as compared to controls. Epididymal fat mass was significantly decreased by OFS treatment, without significant effect on body weight (Table 2).

GLP-1 and proglucagon mRNA concentrations

Portal plasma GLP-1 concentration was significantly increased by about 66% in OFS fed mice as compared to CT mice (Fig. 1 insert). GLP-1 concentration in the proximal colon was increased by about 100% in OFS fed mice as compared to CT mice. No effects were observed in the other intestinal segments. This colonic segment thus appears to be the major site of production of the peptide (Fig. 1).

Proglucagon mRNA measured in the proximal colon was increased by 80% in OFS treated mice (CT 100 ± 11.2% versus OFS 178.4 ± 8.8%, relative fluorescence unit, $P < 0.05$). Moreover, a positive linear correlation exists between proglucagon mRNA measured in the proximal colon, and the concentration of GLP-1 measured in the proximal colon and in the portal vein (Fig. 2).

Table 3
Blood parameters during high fat diet treatment

	HF-1–CT	HF-1–OFS	HF-2–CT	HF-2–OFS
Glucose (mmol/L)	7.1 ± 0.18^{a}	5.9 ± 0.24^{b}	8.3 ± 0.3^{a}	8.1 ± 0.3^{a}
Insulin (mmol/L)	163 ± 23^{a}	225 ± 34^{b}	214.8 ± 14.9^{b}	211.7 ± 41.3^{b}
Energy intake (kcal/d)	12 ± 0.2^{a}	10.3 ± 0.4^{b}	11.9 ± 0.2^{a}	11.4 ± 0.2^{a}

Plasma glucose (mmol/L) and insulin (mmol/L) measured in fasted state and mean daily energy intake (kcal/d) of mice treated with a high fat diet HF-1 (HF-1–CT) or a high fat diet HF-1 supplemented with OFS (HF-1–OFS), a high fat diet, HF-2 (HF-2–CT) or a HF-2 diet supplemented with OFS (HF-2–OFS). Data are mean ± S.E.M. $n = 8$ per group Data with different superscript letters are significantly different, $P < 0.05$, according to the post hoc ANOVA statistical analysis convention.

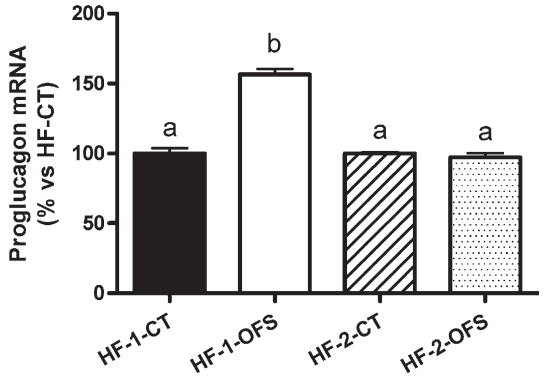

Fig. 4. Relative proglucagon mRNA content in the proximal colon of mice treated with a high fat diet HF-1 (HF-1–CT) (black bars) or a high fat diet HF-1 supplemented with OFS (HF-1–OFS) (open bars), a high fat diet, HF-2 (HF-2–CT) (hatched bars) or a HF-2 diet supplemented with OFS (HF-2–OFS) (gray bars). Data are mean±S.E.M. $n=8$ per group. Data with different superscript letters are significantly different, $P<0.05$, according to the post hoc ANOVA statistical analysis convention.

Experiment 2: effects of OFS added to different high fat diets

Two different protocols were applied. In the first one (HF-1), HF diet was given alone or together with the OFS treatment during 4 weeks. In the second one (HF-2), HF diet was first given for 8 weeks to all the mice, before the introduction of OFS. The period of 8 weeks induced metabolic disorders associated with obesity, since fasted glycemia (CT 5.2±0.2 mmol/L; $n=10$, HF-2 8.5±0.2 mmol/L; $n=24$, $P<0.01$), triglyceridemia (CT 0.68± 0.08 mmol/L; $n=10$, HF-2 1.05±0.04 mmol/L; $n=24$, $P<0.01$), as well as body weight (CT 26.4±0.6 g; $n=10$, HF-2 31.02± 0.46 g; $n=24$, $P<0.01$) were significantly increased as compared to control mice receiving standard A04 diet during the same period.

Fig. 3 clearly shows that the two different high fat diets, whatever the composition or the duration of the treatment, led to a decrease (by about 150%) in full caecum and caecal tissue weights, and to a large increase (by about 250%) in epididymal fat mass as compared to the standard control diet (Experiment 1), $P<0.05$.

However, food intake is differently modulated by OFS in both HF treatments, since it was significantly decreased in HF-1–OFS, but not in HF-2–OFS versus their respective control groups (Table 3).

OFS treatment for 4 weeks led to a similar increase (about 2 fold) in caecal tissue weight, in HF-1 and HF-2 protocols (Fig. 3B). The increase in total caecum weight was more pronounced when OFS was added in HF-1 diet than when added in HF-2 diet (Fig. 3A).

OFS induced a significant decrease of body weight, glycemia and epididymal fat mass when added in HF-1 diet, but not in HF-2 treated mice (Fig. 3C, D and Table 3). OFS increased insulinemia when added in HF-1 diet, whereas no modulation was observed following OFS treatment in HF-2 protocol.

As described in the presentation of results obtained with the standard diet, proglucagon mRNA is strongly correlated with proximal colon GLP-1 and portal plasma GLP-1 concentrations; therefore, we measured proglucagon mRNA in the proximal colon of high fat fed mice. OFS treatment significantly increased proglucagon mRNA in the proximal colon by about 50%, in HF-1 diet, but not in HF-2 diet (Fig. 4).

Discussion

Several data suggest that fermentable dietary fibers could play a role in the control of obesity and associated metabolic disorders (Englyst and Englyst, 2005; Mazur et al., 1990, 1992; van Loo et al., 1999). Indeed, fructo-oligosaccharides, recently recognized as fermentable dietary fibers, lower body weight, and improve blood lipids levels and/or glycemia, in rats (Busserolles et al., 2003; Delzenne, 2003).

The aim of this study was to investigate the putative role of OFS, on one hand, in mice fed a standard diet and on the other hand, in mice fed two distinct high fat diets classically used to induce metabolic disorders associated with obesity.

In the first experiment, we confirmed several effects previously shown in animals fed a standard diet enriched with OFS: an increase in total and empty caecum weight (Kok et al., 1998b; Cani et al., 2006a), a significant decrease in epididymal fat mass (Daubioul et al., 2002; Cani et al., 2006a), and an increase in colonic and portal plasma GLP-1, a phenomenon positively correlated with a higher colonic proglucagon mRNA level (Cani et al., 2004).

In rats fed with a high fat diet, OFS decreased body weight and fat mass development (Cani et al., 2005b; Kok et al., 1998b). In our second experiment, we used two types of diet, one high fat/carbohydrate free and one high fat/high carbohydrate, usually given in mice to induce fat mass accumulation and associated metabolic disorders (Burcelin et al., 2002; de Fourmestraux et al., 2004; Parekh et al., 1998; Petro et al., 2004; Surwit et al., 1988, 1995). Both high fat diet treatments led to a similar increase in fasting glycemia, body weight and epididymal fat mass after 4 weeks and 8 weeks for HF-1 and HF-2, respectively. Moreover, as compared to standard diet, a lower caecum weight was observed in mice: this may be explained by the fact that high fat diet contains much less fermentable substrate (fibers, resistant starch, etc.) than the standard diet.

Curiously, a 4-week treatment with OFS added at the same dose induced different effects in HF-1 and HF-2 protocols. OFS decreased energy intake, body weight gain, glycemia, and epididymal fat mass only when added together with the HF-1 diet, but it had no effect on those parameters when added in HF-2 protocol. Interestingly, caecal enlargement due to OFS treatment was much higher in HF-1 than in HF-2 treated animals. In several animal models, the intestinal fermentation induced by lactitol or dietary fibers is correlated with GLP-1 production (Gee and Johnson, 2005; Massimino et al., 1998; Reimer and McBurney, 1996). In accordance with those data, we observe that proglucagon mRNA was increased when OFS was added in HF-1, but not in HF-2 diet. GLP-1 is a physiological regulator of food intake, and glycemia, namely through its capacity to increase insulin secretion (Drucker, 2002; Meier and Nauck, 2005). According to this, OFS-HF-1 mice exhibited a higher insulin level in plasma, which can contribute to the lower glycemia and may be related to the higher

proglucagon expression. Such a relationship between OFS fermentation, proglucagon mRNA content, and insulin production had already been shown in diabetic rats (Cani et al., 2005a). Moreover, we have recently shown, in high fat fed mice, that the anti obesity/diabetic effects of OFS are linked to a higher proglucagon mRNA expression, and are dependent on a functional GLP-1 receptor (Cani et al., 2006). Here again, our results support the fact that an increase in proglucagon expression in the proximal colon is associated to OFS effects on glycemia, fat mass development, and/or body weight gain. Accordingly, OFS addition in the diet was able to counteract diabetes when given in streptozotocin-treated diabetic rats (Cani et al., 2005a) but was unable to improve diabetes occurring in rats exhibiting a defect in colonic proglucagon expression – the BioBreeding diabetes-prone rats (Perrin et al., 2003; Reimer et al., 1998).

We may suggest that an enrichment of the diet with OFS is less effective in more advanced states of metabolic disturbances, due to a longer period of high fat treatment (HF-2), and is not necessarily due to the difference in the composition of the high fat diets. However, we observed that an 8-week HF-1–OFS treatment gave results similar to those obtained in the present study (not shown).

OFS thus appears as a promising tool in the nutritional approach to control metabolic syndrome in obese patients. To date, only a few studies report the effects of fermentable carbohydrates, namely fructo-oligosaccharides, in humans. Interestingly, a recent study reports that OFS feeding (20 g/d) significantly increases plasma GLP-1 after a mixed meal (Piche et al., 2003). 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% lower total energy intake (Cani et al., 2005b, 2006b). Moreover, Archer et al have demonstrated that fermentable fructo-oligosaccharides, added to food as fat replacer, were able to lower energy intake during a test day (Archer et al., 2004). The relevance of OFS effects in obese patients remains to be investigated.

In conclusion, dietary oligosaccharides would constitute an interesting class of dietary fibers, promoting endogenous GLP-1 production, with beneficial physiological consequences.

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References

American Diabetes Association, 2000. Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care 23 (Suppl 1), S43–S46.

Archer, B.J., Johnson, S.K., Devereux, H.M., Baxter, A.L., 2004. Effect of fat replacement by inulin or lupin-kernel fibre on sausage patty acceptability, post-meal perceptions of satiety and food intake in men. British Journal of Nutrition 91, 591–599.

Burcelin, R., Da Costa, A., Drucker, D., Thorens, B., 2001. Glucose competence of the hepatoportal vein sensor requires the presence of an activated glucagon-like peptide-1 receptor. Diabetes 50, 1720–1728.

Burcelin, R., Crivelli, V., Dacosta, A., Roy-Tirelli, A., Thorens, B., 2002. Heterogeneous metabolic adaptation of C57BL/6J mice to high-fat diet. American Journal of Physiology: Endocrinology and Metabolism 282, E834–E842.

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

Cani, P.D., Dewever, C., Delzenne, N.M., 2004. Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. British Journal of Nutrition 92, 521–526.

Cani, P.D., Daubioul, C.A., Reusens, B., Remacle, C., Catillon, G., Delzenne, N.M., 2005a. Involvement of endogenous glucagon-like peptide-1(7–36) amide on glycaemia-lowering effect of oligofructose in streptozotocin-treated rats. Journal of Endocrinology 185, 457–465.

Cani, P.D., Neyrinck, A.M., Maton, N., Delzenne, N.M., 2005b. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1. Obesity Research 13, 1000–1007.

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

Cani, P.D., Joly, E., Horsmans, Y., Delzenne, N.M., 2006b. Oligofructose promotes satiety in healthy human: a pilot study. European Journal of Clinical Nutrition 60, 567–572.

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

de Fourmestraux, V., Neubauer, H., Poussin, C., Farmer, P., Falquet, L., Burcelin, R., Delorenzi, M., Thorens, B., 2004. Transcript profiling suggests that differential metabolic adaptation of mice to a high fat diet is associated with changes in liver to muscle lipid fluxes. Journal of Biological Chemistry 279, 50743–50753.

Delzenne, N.M., 2003. Oligosaccharides: state of the art. Proceedings of the Nutrition Society 62, 177–182.

Delzenne, N.M., Cani, P.D., 2005. A place for dietary fibre in the management of the metabolic syndrome. Current Opinion in Clinical Nutrition and Metabolic Care 8, 636–640.

Drucker, D.J., 2002. Biological actions and therapeutic potential of the glucagon-like peptides. Gastroenterology 122, 531–544.

Englyst, K.N., Englyst, H.N., 2005. Carbohydrate bioavailability. British Journal Nutrition 94, 1–11.

Gee, J.M., Johnson, I.T., 2005. Dietary lactitol fermentation increases circulating peptide YY and glucagon-like peptide-1 in rats and humans. Nutrition 21, 1036–1043.

Knauf, C., Cani, P.D., Perrin, C., Iglesias, M., Maury, J., Bernard, E., Benhamed, F., Grémeaux, T., Drucker, D.J., Kahn, C., Girard, J., Tanti, J., Delzenne, N.M., Postic, C., Burcelin, R., 2005. Brain glucagon-like peptide-1 increases insulin secretion and muscle insulin resistance to favor hepatic glycogen storage. Journal of Clinical Investigation 115, 3554–3563.

Kok, N.N., Morgan, L.M., Williams, C.M., Roberfroid, M.B., Thissen, J.P., Delzenne, N.M., 1998a. Insulin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and insulin-like growth factor I as putative mediators of the hypolipidemic effect of oligofructose in rats. Journal of Nutrition 128, 1099–1103.

Kok, N.N., Taper, H.S., Delzenne, N.M., 1998b. Oligofructose modulates lipid metabolism alterations induced by a fat-rich diet in rats. Journal of Applied Toxicology 18, 47–53.

Massimino, S.P., McBurney, M.I., Field, C.J., Thomson, A.B., Keelan, M., Hayek, M.G., Sunvold, G.D., 1998. Fermentable dietary fiber increases GLP-1 secretion and improves glucose homeostasis despite increased intestinal glucose transport capacity in healthy dogs. Journal of Nutrition 128, 1786–1793.

Mazur, A., Gueux, E., Felgines, C., Bayle, D., Nassir, F., Demigne, C., Remesy, C., 1992. Effects of dietary fermentable fiber on fatty acid synthesis and

triglyceride secretion in rats fed fructose-based diet: studies with sugar-beet fiber. Proceedings of the Society for Experimental Biology and Medicine 199, 345–350.

Mazur, A., Remesy, C., Gueux, E., Levrat, M.A., Demigne, C., 1990. Effects of diets rich in fermentable carbohydrates on plasma lipoprotein levels and on lipoprotein catabolism in rats. Journal of Nutrition 120, 1037–1045.

Meier, J.J., Nauck, M.A., 2005. Glucagon-like peptide 1 (GLP-1) in biology and pathology. Diabetes Metabolism and Research Reviews 21, 91–117.

Parekh, P.I., Petro, A.E., Tiller, J.M., Feinglos, M.N., Surwit, R.S., 1998. Reversal of diet-induced obesity and diabetes in C57BL/6J mice. Metabolism 47, 1089–1096.

Perrin, I.V., Marchesini, M., Rochat, F.C., Schiffrin, E.J., Schilter, B., 2003. Oligofructose does not affect the development of Type 1 diabetes mellitus induced by dietary proteins in the diabetes-prone BB rat model. Diabetes Nutrition and Metabolism 16, 94–101.

Petro, A.E., Cotter, J., Cooper, D.A., Peters, J.C., Surwit, S.J., Surwit, R.S., 2004. Fat, carbohydrate, and calories in the development of diabetes and obesity in the C57BL/6J mouse. Metabolism 53, 454–457.

Piche, T., des Varannes, S.B., Sacher-Huvelin, S., Holst, J.J., Cuber, J.C., Galmiche, J.P., 2003. Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. Gastroenterology 124, 894–902.

Preitner, F., Ibberson, M., Franklin, I., Binnert, C., Pende, M., Gjinovci, A., Hansotia, T., Drucker, D.J., Wollheim, C., Burcelin, R., Thorens, B., 2004. Gluco-incretins control insulin secretion at multiple levels as revealed in mice lacking GLP-1 and GIP receptors. Journal of Clinical Investigation 113, 635–645.

Reimer, R.A., McBurney, M.I., 1996. Dietary fiber modulates intestinal proglucagon messenger ribonucleic acid and postprandial secretion of glucagon-like peptide-1 and insulin in rats. Endocrinology 137, 3948–3956.

Reimer, R.A., Glen, S., Field, C.J., McBurney, M.I., 1998. Proglucagon and glucose transporter mRNA is altered by diet and disease susceptibility in 30-day-old biobreeding (BB) diabetes-prone and normal rats. Pediatric Research 44, 68–73.

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

Surwit, R.S., Kuhn, C.M., Cochrane, C., McCubbin, J.A., Feinglos, M.N., 1988. Diet-induced type II diabetes in C57BL/6J mice. Diabetes 37, 1163–1167.

Surwit, R.S., Feinglos, M.N., Rodin, J., Sutherland, A., Petro, A.E., Opara, E.C., Kuhn, C.M., Rebuffe-Scrive, M., 1995. Differential effects of fat and sucrose on the development of obesity and diabetes in C57BL/6J and A/J mice. Metabolism 44, 645–651.

van Loo, J., Cummings, J., Delzenne, N., Englyst, H., Franck, A., Hopkins, M., Kok, N., Macfarlane, G., Newton, D., Quigley, M., Roberfroid, M., van Vliet, T., van den Heuvel, E., 1999. Functional food properties of non-digestible oligosaccharides: a consensus report from the ENDO project (DGXII AIRII-CT94-1095). British Journal of Nutrition 81, 121–132.