Short-chain fructooligosaccharides do not alter glucose homeostasis but improve the lipid profile in obese rats

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ABSTRACT. The present study investigated the effects of short-chain fructooligosaccharides (scFOS) feeding on body weight, fat accumulation, glucose homeostasis and lipid profile in cafeteria (CAF) obese rats. Male Wistar rats were divided randomly into two groups: control group (CTL, n = 10), which received a chow diet and water and CAF (n = 20), which received the cafeteria diet, standard chow and soda. After 30 weeks of diet, 10 animals of CAF group received scFOS in the diet (50 g kg⁻¹ of diet) over a period of 50 days, forming the CAF FOS group. Were evaluated the body weight, fat pad as well as, quantity of feces, glucose tolerance, insulin resistance (IR) and serum lipids levels. Animals submitted to the CAF diet displayed obesity, hyperglycemia, glucose intolerance, hyperinsulinemia and IR. The scFOS feeding   not altered obesity, glucose intolerance, hyperinsulinemia and IR. CAF rats also presented hypertriglyceridemia and lower levels of HDL-cholesterol. The CAF FOS animals had reduced serum triglycerides (TG) and increased HDL-cholesterol. Thus, the use of scFOS in the diet can be considered as a hypolipidemic agent in the obese state.

Keywords: fructooligosaccharides. obesity. cafeteria diet. triglycerides. HDL-cholesterol.

Frutooligossacarídeos de cadeia curta na dieta não altera homeostase glicêmica, porém melhora o perfil lipídico em ratos obesos

RESUMO. O presente estudo investigou os efeitos da adição de frutooligossacarídeos de cadeia curta (scFOS) sobre o peso corporal, acúmulo de gordura, homeostase glicêmica e perfil lipídico em ratos obesos pela dieta de cafeteria (CAF). Ratos *Wistar* foram divididos em dois grupos: controle (CTL, n = 10), que receberam dieta padrão e água e CAF, que receberam dieta de CAF, ração padrão e refrigerante (n = 20). Após 30 semanas, dez animais do grupo CAF receberam 50 g kg⁻¹ de dieta de scFOS na ração padrão durante 50 dias, formando o grupo CAF FOS. Foram avaliados o peso corporal e o peso das gorduras, bem como, quantidade de fezes, homeostase glicêmica e concentração de lipídios séricos. Animais do grupo CAF apresentaram obesidade, hiperglicemia, intolerância à glicose, hiperinsulinemia e RI. A adição scFOS não alterou a obesidade, intolerância à glicose, hiperinsulinemia e RI no grupo CAF FOS comparado ao grupo CAF. Animais CAF também apresentaram hipertrigliceridemia e redução na concentração de HDL-colesterol. Os animais CAF FOS apresentaram redução na concentração sérica de triglicerídeos (TG) e aumento no HDL-colesterol. Desta forma, a utilização de scFOS na dieta pode ser considerado como um agente hipolipidêmico nos estados de obesidade.

Palavras-chave: frutooligossacarídeos. obesidade. dieta de cafeteria. Triglicerídeos. HDL-colesterol.

Introduction

Obesity is a world-wide epidemic present in the developed and developing countries (PRENTICE, 2006; CABALLERO, 2007). In 2008, approximately 1.5 billion adults aged over 20 years were overweight and about 200 and 300 million of men and women, respectively, presented obesity (WHO, 2014). In 2011, 45% of the Brazilian population was overweight and 16% were obese (BRASIL, 2014). Obesity contributes to the development of chronic degenerative diseases such as dyslipidemia, hypertension, cardiovascular disease and type 2 diabetes mellitus (T2DM) (MAYES; WATSON, 2004).

T2D is a heterogeneous clinical syndrome characterized by partial or absolute deficiency of insulin secretion by the pancreas and /or impaired

insulin action in target tissues, causing further alterations in the metabolism of lipids, proteins and carbohydrates (ALBERTI; ZIMMET, 1998). Studies have shown the effects of short-chain fructooligosaccharides (scFOS) on health, particularly in the case of diabetes and obesity (BHARTI et al., 2013; YAMASHITA et al., 1984). scFOS are non-viscous β-fructan fibers with prebiotic properties (ROBERFROID, 2007) that are not degraded by digestive enzymes and, consequently, do not increase blood glucose and insulin levels (SABATER-MOLINA et al., 2008). Bifidobacteria and lactobacilli in the intestines can metabolize scFOS to produced short-chain fatty acids (SCFA) (SABATER-MOLINA et al, 2008; HOSOYA et al., 1988). scFOS improve gastrointestinal conditions, mineral absorption, dyslipidemia, hypertension and decrease the risk of colon cancer (PASSOS; PARK, 2003). Nevertheless, the effects of scFOS on glycemia and insulinemia are contradictory (SABATER-MOLINA et al., 2008) and their effects on obesity have not yet been fully described (MERINO-AGUILLAR et al., 2014).

In experimental animals, cafeteria diet (CAF)-induced obesity closely resembles the human obesity that is induced by overfeeding with high-energy food (SAMPEY et al., 2011). The CAF diet promotes rapid weight gain, fat accumulation, dyslipidemia, hyperglycemia, insulin resistance and a fatty liver (SAMPEY et al., 2011; MARTIRE et al., 2013). There are currently no data to demonstrate the effects of scFOS on this experimental model of obesity. As such, the current study was carried out to determine the effects of scFOS on obesity, glucose homeostasis and the lipid profile in CAF obese rats.

Material and methods

Experimental Animals

All experiments were approved by the University's Committee on Ethics in Animal Experimentation (CEEAAP/UNIOESTE, protocol nº61/10).Thirty male Wistar rats aged 8 weeks were divided randomly into two groups: control group (CTL, n = 10), which received a standard diet and water and Cafeteria Group (CAF, n = 20), which received the cafeteria diet and soda. After 30 weeks of diet, 10 animals of CAF group received scFOS in the diet (50 g kg^{-1} of diet) over a period of 50 days, forming the CAF FOS group. The rats were maintained under controlled temperature (22 ± 1ºC) and light (12 hours of light and 12 hours of darkness - 7 a.m.-7 p.m.).

Diets

CTL group received a standard diet (Biobase, Brazil), consisting of 3.8 kcal g-1 (70% carbohydrate, 20% protein and 10% fat) and water ad libitum. The CAF group received a cafeteria diet, as described by Goularte et al. (2012), with some modifications. The addition of scFOS was made in the standard diet. Table 1 presents the nutritional composition of foods offered to the animals in the cafeteria diet.

Evolution of Body Weight and Stool Production

Once a week during the experimental period, all animals were weighed to monitor body weight. At 43 weeks of life, animals were placed in metabolic cages to measure the production of stools during 12 hours.

Intraperitoneal Glucose Tolerance Test

All rats were submitted to the intraperitoneal glucose tolerance test (ipGTT) following an 8-hour overnight fast. Before administration of glucose, animals were weighed and fasting glucose (time 0) was measured using a glucose analyzer (One Touch Ultra®, Johnson & Johnson). A glucose load of 2 g kg^{-1} body weight was then administered by 'ip' injection and additional blood samples were collected at 15, 30, 60, 120 and 180 min. after administration of the sugar.

Table 1. Nutritional composition of foods in the cafeteria diet.

	Energy (kcal g^{-1})	Carboydrates g 100 g^{-1}	Protein g100 g^{-1}	Fat g 100 g^{-1}	Sodium mg 100 g^{-1}
Standard chow (Biobase, Brazil)	3.8	70	20	10	0
Cheetos Balls snack (Cheetos, Pepsico, Brazil)	4.65	72	6.4	17.2	676
Bacon snack (Troféu, Santa Helena, Brazil)	5.25	56	8.8	30	1040
Cookie cornstarch (Zadimel, Brazil)	4.28	73	8	10.7	300
Chocolate cake (Renata, Selmi, Brazil)	4.29	55	5	21.7	141.7
Coca-Cola (Coca-Cola, Brazil)	0.43	11	0	0	5
Guaraná (Antarctica, AmBev, Brazil)	0.4	10	0	0	5.5
Italian salami (Sadia, Brazil)	4.35	2	22	38	1140
Mixed Sausage (Sadia, Brazil)	3.71	1.4	16	34	1342
Nutrella bread (Nutrella, Brazil)	3.17	54	11.2	6.2	300
Chocolate wafer (Bauducco, Brazil)	5.2	63	5	27	113
Mortadella (Frimesa, Brazil)	2.02	2	12	16	1545
Marshmallow (Fini, Brazil)	3.4	80	5	0	46

Serum analyses

During euthanasia and after 8 hours of fasting, whole blood was collected in a glass tube and placed in water bath at 37ºC for one hour. Then, the blood was centrifuged for 10 min at 3.000 rpm and serum was collected for subsequent analysis of serum parameters. Concentrations of triglycerides (TG), total cholesterol (CHOL) and HDL-cholesterol were measured by enzymatic colorimetric methods, according to the manufacturer's instructions. Briefly, the CHOL total, HDL-cholesterol and TG were analyzed by the VITROS® technology Microslides, using multilayer film and dry chemical with colorimetric detection. Insulin was measured by radioimmunoassay (RIA).

Obesity parameters

During euthanasia, the body weight was verified and the retroperitoneal and peritoneal fats pads were removed and weighed.

Insulin sensitivity

Tissue insulin sensitivity was also evaluated by the previously validated (BONORA et al., 2000) homeostasis model assessment (HOMA) method, using the HOMA index of insulin resistance (HOMA-IR) = fasting insulin (μU mL^{-1}) x fasting glucose (mM)/22.5, described by Matthews et al. (1985).

Statistical analyses

Results are presented as means ± mean standard error (SEM) for the number of determinations (n) indicated. Statistical analyses were carried out using one way analysis of variance (ANOVA) followed by the Tukey post-test and the level of significance was $p < 0.05$. Tests were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software®).

Results and discussion

The cafeteria diet, also called the 'Western diet', is an experimental diet that is more closely related to the variety of palatable and caloric foods that are prevalent in Western society and associated with the current obesity epidemic. This experimental rodent diet model best fits human obesity as it demonstrates a closer similarity to human food intake and leads to an increase in adiposity (SAMPEY et al., 2011). In addition, this obesity model also shows features of T2DM such as hyperglycemia, glucose intolerance and insulin resistance (VANZELA et al., 2010; PRADA et al.,

2005). In this study, CAF rats presented higher body weight, increased fat pad accumulation, demonstrated hyperglycemia, glucose intolerance, hyperinsulinemia, IR, hypertriglyceridemia and reduction of HDL-cholesterol. For the first time using this model of obesity, was showed that the addition of scFOS in the diet over a period of 50 days did not alters obesity parameters and glucose homeostasis, however, improved values of serum lipids levels.

Animals that were submitted to the CAF diet demonstrated an increase in body weight of approximately 10% from the second week after administration of diet; this increase in body weight was accentuated throughout the experimental period, when compared to the CTL group ($p < 0.05$). The area under the curve (AUC) of the evolution of body weight was higher in the CAF (8381 ± 117, n = 09), compared to the CTL animals (7135 ± 127, n = 10, $p < 0.001$). The CAF FOS group did not present any changes in body weight when compared with the CAF group. The AUC of the evolution of the weight of these animals reinforces this finding (CAF FOS, 8531 ± 168, n = 10). The retroperitoneal and perigonadal fat pad weights were 4.5 and 2-fold higher in the CAF group than in the CTL group ($p < 0.05$, Table 2). The CAF FOS animals demonstrated similar augmentations in the fat deposits, when compared to the CAF group. Ours data are in accordance with different reports which presented that supplementation with scFOS do not affect the body weight of rats (SHINOKI; HARA, 2011; FUKAWASA et al., 2010; KOK et al., 1998), obese dogs (RESPONDEK et al., 2008a and b) or obese horses (RESPONDEK et al., 2011).

In our study, CAF rats presented a 62% reduction in the quantities of stools in 12 hours, compared to the CTL group and this parameter was completely normalized in CAF FOS animals (Table 2). This improvement is probably due to the fact that the scFOS ameliorates the microflora in the colon, resulting in increased intestinal motility (MUSSATO; MANCHILHA, 2007). FOS reach the colon unchanged, where they are readily fermented by the intestinal microflora, resulting in changes in this flora, as shown by the increased number of potentially beneficial microorganisms, while suppressing the number of harmful bacteria (SABATER-MOLINA et al., 2008). In addition, fermentation of FOS increases the bacterial biomass, which consequently ameliorates gastrointestinal conditions (JENKINS et al., 1999).

Table 2. Effect of cafeteria diet and scFOS feeding on fats pad weights and quantity of feces.

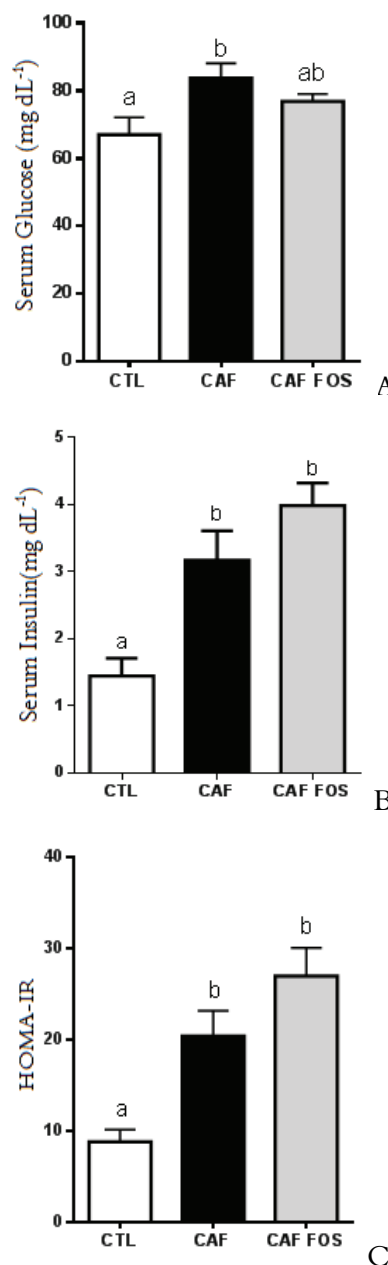|	CTL	CAF	CAF FOS
Retroperitoneal fat pad (% body weight)	6 ± 0.4[a]	27 ± 2.5[b]	24 ± 1.6[b]
Perigonadal fat pad (% body weight)	7 ± 0.5[a]	14 ± 1.0[b]	14 ± 1.0[b]
Quantity of feces (g 12 hours^{-1})	4.2 ± 0.6[a]	1.6 ± 0.15[b]	3.5 ± 0.4[a]

Data are means ± SEM obtained from 8-9 rats for each group. Different letters represent significant differences (p < 0.05; One-way ANOVA with Tukey post hoc test).

Since reports show that scFOS has beneficial effects on diabetes (BHARTI et al., 2013; YAMASHITA et al., 1984) we investigated, for the first time, the effect of scFOS supplementation on glucose homeostasis in obese rats during a period of 50 days. The plasma glucose concentration reached maximal levels at 15 min in both groups. CAF and CAF FOS rats presented higher glucose values at 15 min, compared with CTL rats (p < 0.03, Figure 1A). The AUC of the glucose plasma levels during the ipGTT in CAF group was 50% higher than in the CTL group (p < 0.02; Figure 1B). The administration of scFOS did not alter glucose intolerance in obese CAF FOS rats, compared with CAF animals (Figure 1B).
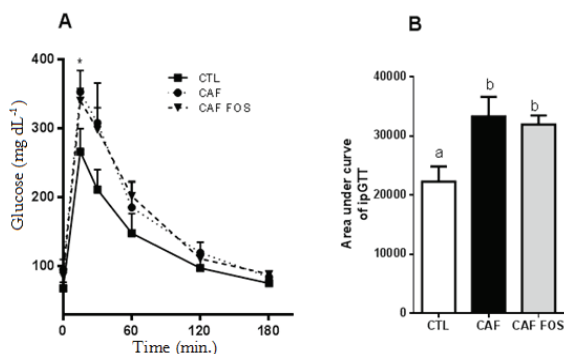
Figure 1. Plasma glucose concentrations (A) and AUC (B) during 'ip' GTT in CTL, CAF and CAF FOS rats. Data are means ± SEM obtained from 8-9 rats for each group. *Significant difference between CAF and CAF FOS groups, compared to controls in graph A. Different letters represent significant differences in graph B (p < 0.05; One-way ANOVA with Tukey post hoc test).

After 8 hours of fasting, we evaluated glucose and insulin serum levels. CAF rats presented higher glucose and insulin serum levels when compared to CTL rats (p < 0.03 and p < 0.0001, respectively, Figure 2A and B). The HOMA index in the CAF rats was 2.3 fold-higher than in CTL animals (p < 0.0001, Figure 2C). Serum glucose in CAF FOS rats was similar with CAF and CTL rats. Insulin levels and the HOMA index did not change in CAF FOS when compared with CAF rats (Figure 2A, B and C,

respectively). In this way, scFOS administration did not alter glucose homeostasis in cafeteria obese rats.

Figure 2. Levels of serum fasting glucose (A) and insulin (B) and HOMA-IR (C) in CTL, CAF and CAF FOS rats. Data are means ± SEM obtained from 8-9 rats for each group. Different letters represent significant differences (p < 0.05; One-way ANOVA with Tukey post hoc test).

Chronic administration of oligofructose (OFS) in normal rats improved glucose disposal and authors speculated that this result may be associated with an increase in GLP-1 levels stimulated by OFS in cecum (KOK et al., 1998). In the present work, we used a mixture of scFOS with different molecular chains which probably not increases

GLP-1, subsequently not changing glucose homeostasis. Furthermore, the effect of scFOS on glycemia and insulinemia are contradictory (SABATER-MOLINA et al., 2008). A daily intake of FOS (8 g day⁻¹) for a period of 14 days reduced blood glucose in diabetic patients (YAMASHITA et al., 1984). Rats that received a diet supplemented with 10% oligofructose for 30 days presented a reduction in postprandial glucose and insulin; however no changes in glucose tolerance were observed (ROBERFROID, 1993; ROBERFROID; DELZENNE, 1998). In obese dogs, dietary supplementation with scFOS reduced basal insulin resistance (RESPONDEK et al., 2008a, b). FOS supplementation in rats for 3 or 5 weeks did not alter glucose levels but improved blood insulin and insulin sensitivity (SHINOKI; HARA, 2011). Diabetic rats that received FOS at two different concentrations for a period of 6 weeks demonstrated significantly decreased glucose levels (BHARTI et al., 2013). No effect of scFOS supplementation on plasma glucose has been reported in obese horses, although scFOS moderately improved insulin sensitivity (RESPONDEK et al., 2011).

After analyze glucose homeostasis, we verified the effects of scFOS on serum lipids. Serum total cholesterol was similar in all groups (Figure 3A). However, CAF animals presented lower levels of HDL cholesterol and higher triglyceride levels than the CTL rats (p < 0.04 and p < 0.001, Figure 3B and C, respectively). Administration of FOS during the period of 50 days normalized HDL cholesterol and reduced TG serum in the CAF FOS rats, when compared with HDL-cholesterol and TG serum concentrations, to levels that were similar to those observed in CTL rats.

Studies have shown that scFOS administration reduces TG and CHOL, in association with LDL and VLDL values (DELZENNE et al., 1993; FIORDALISO et al., 1995; KOK et al., 1998). In addition, all SCFA produced are absorbed quickly in the large intestine and metabolized by different tissues, producing principally propionate (BLAUT, 2002), which in turn inhibits the cholesterogenesis and lipogenesis pathways (SABATER-MOLINA et al., 2008). Modification of the glucose or insulin concentrations may also be involved in this mechanism since both are involved in expression and regulation of enzymes associated with lipogenesis *de novo* and beta oxidation pathway (BERLANGA et al., 2014). More studies will be necessary to investigate the

exact pathways mediating the reduction of TG and the increase of HDL-cholesterol in this model of obesity.
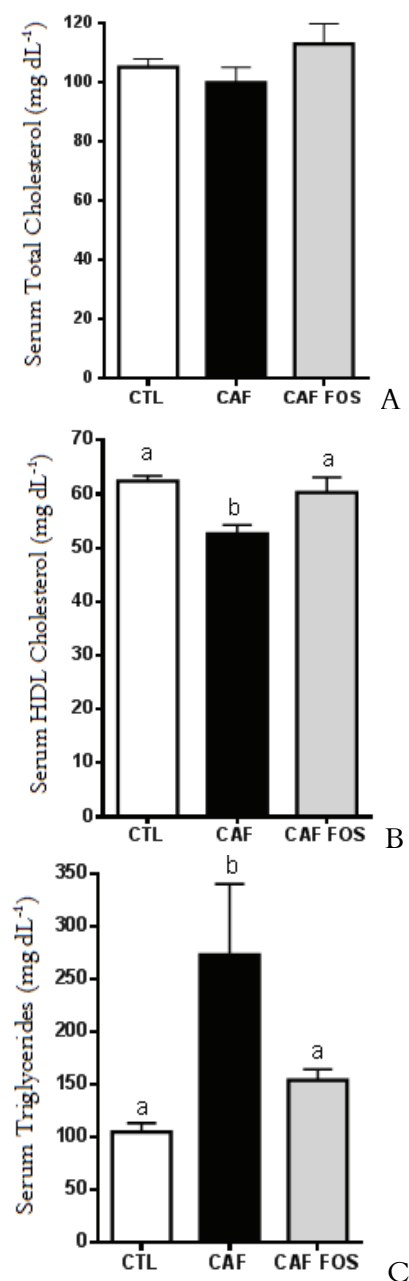

Figure 3. Changes in serum total cholesterol (A), HDL cholesterol (B) and triglycerides (C) in CTL, CAF and CAF FOS fasting rats. Data are means ± SEM obtained from 8-9 rats for each group. Different letters represent significant differences (p < 0.05; One-way ANOVA with Tukey post hoc test).

Conclusion

scFOS supplementation during a period of 52 days not changes glucose homeostasis but ameliorated serum TG levels and increased HDL-cholesterol in rats obese by CAF diet. Our results indicate that scFOS

can be used as a diet supplement, representing a potential hypolipidemic agent.

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Authors contribution

FSSM, MCM: execution of all experiments and data interpretation;

PYF: biochemical analyses;

MLB, SLB, MKK: conception, experimental design, provided materials and reagents, data interpretation and manuscript writing.

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