Eur J Nutr (2014) 53:413–419
DOI 10.1007/s00394-013-0538-2

ORIGINAL CONTRIBUTION

Adipose tissue remodeling in rats exhibiting fructose-induced obesity

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Received: 14 January 2013 / Accepted: 17 May 2013 / Published online: 2 June 2013

Abstract
Purpose To explore the effect of a fructose-rich diet on morphological and functional changes in white adipose tissue (WAT) that could contribute to the development of insulin resistance.
Methods Adult sedentary rats were fed a fructose-rich diet for 8 weeks. Glucose tolerance test was carried out together with measurement of plasma triglycerides, non-esterified fatty acids and lipid peroxidation. In subcutaneous abdominal and intra-abdominal WAT, number and size of adipocytes together with cellular insulin sensitivity and lipolytic activity were assessed.
Results Rats fed a fructose-rich diet exhibited a significant increase in plasma insulin, triglycerides, non-esterified fatty acids and lipid peroxidation, together with significantly increased body lipids and epididymal and mesenteric WAT, compared to controls. Mean adipocyte volume in subcutaneous abdominal WAT was significantly lower, while mean adipocyte volume in intra-abdominal WAT was significantly higher, in rats fed a fructose-rich diet compared to controls. A significant increase in larger adipocytes and a significant decrease in smaller adipocytes were found in intra-abdominal WAT in rats fed a fructose-rich diet compared to controls. Insulin's ability to inhibit lipolysis was blunted in subcutaneous abdominal and intra-abdominal adipocytes from fructose-fed rats. Accordingly, lower p-Akt/Akt ratio was found in WAT in rats fed a fructose-rich diet compared to controls.
Conclusions Long-term consumption of high levels of fructose elicits remarkable morphological and functional modifications, particularly in intra-abdominal WAT, that are highly predictive of obesity and insulin resistance and that contribute to the worsening of metabolic alterations peculiar in a fructose-rich, hypolipidic diet.

Keywords Fructose · White adipose tissue · Insulin resistance · Lipolysis · p-Akt

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Introduction

Caloric excess and sedentary lifestyle in Western society are major contributors to epidemic of obesity and associated metabolic disorders. In fact, obesity induces tissue alterations that result in systemic insulin resistance, with a strong risk factor for the development of type 2 diabetes and cardiovascular disease [1]. Obesity develops under conditions of high energy and fat intake [2], but lipid overflow toward white adipose tissue (WAT) could also arise from disproportionate de novo lipogenesis in hepatic tissue [3]. In both conditions, visceral and subcutaneous adipocytes must be able to deal with large amounts of lipids being delivered as chylomicrons or very-low-density lipoproteins (VLDL) to the WAT.

We have previously shown [4] that even low-fat diet can be responsible for the development of diet-induced obesity in adult laboratory rats that display a sedentary behavior resembling the Western human lifestyle. In fact, by keeping dietary fats low but partly substituting starch with fructose, we were able to obtain a diet-induced phenotype [4] very similar to that usually observed in high-fat-fed rats [5, 6], that is, increased body lipid and energy gain despite the same level of energy intake, together with increased

energetic efficiency and decreased insulin sensitivity [4]. In this condition, a significant increase was found in hepatic lipogenic capacity that could contribute to increased lipid flow to adipose tissue [4]. The resulting increasing adiposity could be linked to insulin resistance and increased risk of type 2 diabetes, mainly when the adipose tissue does not fully incorporate increased energy influx [7].

The role of WAT in the development of impaired glucose homeostasis and insulin sensitivity typical of adult rats fed a fructose-rich diet is not well defined, and therefore, the present study was performed in rats fed a fructose-rich diet to explore its effect on morphological and functional changes in WAT that could contribute to the development of insulin resistance. To achieve this goal, we used adult sedentary rats made obese by long-term high fructose feeding and we investigated the number, the size and the distribution of cells together with cellular insulin sensitivity and lipolytic activity in subcutaneous abdominal and intra-abdominal adipocytes.

Research methods and procedures

Male Sprague–Dawley rats (Charles River, Italy) of 90 days of age were caged singly in a temperature-controlled room (23 ± 1 °C) with a 12-h light/dark cycle (06.30–18.30) and divided in two groups matched for weight, which were fed a high-fructose or control diet (Mucedola 4RF21; Settimo Milanese, Milan, Italy) for 8 weeks. The composition of the two diets is shown in Table 1. Treatment, housing and killing of animals met the guidelines set by the Italian Health Ministry. All experimental procedures involving animals were approved by "Comitato etico-scientifico per la sperimentazione animale" of the University "Federico II" of Naples.

At the end of the experimental period, the animals were killed by decapitation, samples of plasma, subcutaneous abdominal (abdominal), intra-abdominal (epididymal) and visceral (mesenteric) WAT harvested, and the carcasses used for body composition determination.

Glucose tolerance test

At the end of the experimental period, glucose tolerance test was carried out. Rats were fasted for 6 h from 08.00. A point 0 sample was obtained from venous blood from a small tail clip, and then, glucose (2 g/kg body weight) was injected intraperitoneally. Blood samples were collected after 20, 40, 60, 90, 120 and 150 min. The blood samples were centrifuged at 1,400×g_{av} for 8 min at 4 °C. Plasma was removed and stored at −20 °C until used for determination of substrates and hormones. Plasma glucose concentration was measured by colorimetric enzymatic method (Pokler Italia, Genova, Italy). Plasma insulin concentration was measured using an ELISA kit (Mercodia AB, Uppsala, Sweden) in a single assay to remove inter-assay variations.

Table 1 Composition of experimental diets

	Control diet	Fructose diet
Component (g/100 g)		
Standard chow	100.0	50.5
Sunflower oil		1.5
Casein		9.2
Alphacel		9.8
Fructose		20.4
Water		6.4
AIN-76 mineral mix		1.6
AIN-76 vitamin mix		0.4
Choline		0.1
Methionine		0.1
Gross energy density, kJ/g	17.2	17.2
Metabolizable energy density, kJ/g[a]	11.1	11.1
Protein (J/100 J)	29.0	29.0
Lipids (J/100 J)	10.6	10.6
Carbohydrates (J/100 J)	60.4	60.4
Of which		
Fructose	–	30.0
Starch	45.3	22.8
Sugars	15.1	7.6

[a] Estimated by computation using values (kJ/g) for energy content as follows: protein 16.736, lipid 37.656 and carbohydrate 16.736

Plasma lipid profile and lipid peroxidation

Plasma concentrations of total cholesterol, triglycerides and non-esterified fatty acids (NEFA) were measured by colorimetric enzymatic method using commercial kits (SGM Italia, Italy, and Randox Laboratories Ltd., UK). Lipid peroxidation was determined according to Fernandes et al. [8].

Body lipid content

Guts were cleaned of undigested food, and the carcasses were then autoclaved. After homogenization of the carcasses with a Polytron homogenizer (Kinematica, Luzern, Switzerland), the resulting homogenates were frozen at −20 °C until the day of measurements. Total body lipid content was measured by the Folch extraction method [9]. Metabolizable energy (ME) intake was determined [10] by subtracting the energy measured in feces and urine from the gross energy intake, determined from daily food consumption and gross energy density of the diet.

Adipocyte counting and sizing

Intra-abdominal and subcutaneous abdominal WAT samples were fixed in paraformaldehyde 4 % and sectioned to 10 μm on a rotary microtome. Sections were then stained by Mallory's trichrome stain, and images were acquired on a microscope Axioskop through a CCD camera AxioCamR 5 and the software Axiovision 4.7 (Zeiss). Sampling of sections was performed following the physical fractionator method to ensure a uniformly random systematic sampling [11]. Images were then processed using ImageJ 1.44 software to estimate the number of adipocytes/mm^3 and the diameter of the adipocytes of the investigated area.

Isolation of subcutaneous abdominal and intra-abdominal adipocytes and measurement of in vitro lipolytic capacity

Adipocytes were isolated from subcutaneous abdominal or intra-abdominal WAT by a modification of the method of Wang et al. [12]. Briefly, 2.5 g of WAT was rapidly excised and placed in a buffer solution, containing 130 mM NaCl, 4.7 mM KCl, 1.24 mM $MgCl_2$, 2.5 mM $CaCl_2$, 10 mM Hepes, pH 7.4, 2.5 mM KH_2PO_4, 2 % bovine serum albumin, 5 mM glucose and 200 nM adenosine. Tissue was finely minced with scissors, then collagenase (10 mg/g tissue) was added, and samples were incubated at 37 °C for 45 min in a shaking bath. At the end of the incubation, samples were centrifuged at 1,000 rpm for 3 min, supernatant was taken and washed twice with the above solution, and the final supernatant containing adipocytes was used for subsequent counting and incubation.

Cell counting was carried out with a light microscope NIKON ECLIPSE E1000. Aliquots corresponding to 15,000 cells were then incubated in 1 ml of the above solution without adenosine in the presence of 1 μM isoproterenol, with or without 0.1 μM insulin, for 2 h at 37 °C in a shaking bath. At the end of the incubation, aliquots were used for the determination of glycerol production, by incubating samples with Sigma glycerol reagent at 37 °C for 15 min and then monitoring absorbance at 540 nm against appropriate standards.

Western blot quantification of adipose tissue Akt and p-Akt

Samples were denatured in a buffer (60.0 mM Tris pH 6.8, 10 % saccharose, 2 % SDS and 4 % β-mercaptoethanol) and loaded onto a 12 % SDS–polyacrylamide gel. After the run in electrode buffer (50 mM Tris, pH 8.3, 384 mM glycine, 0.1 % SDS), the gels were transferred onto PVDF membranes (Immobilon-P, Millipore, MA, USA) at 0.8 mA/cm^2 for 90 min. The membranes were preblocked in blocking buffer (PBS, 5 % milk powder, 0.5 % Tween 20) for 1 h and then incubated overnight at 4 °C with polyclonal antibody for Akt or p-Akt (Cell Signaling, MA, USA, diluted 1:1,000 in blocking buffer). Membranes were washed 3 times 12 min in PBS/0.5 % Tween 20 and 3 times 12 min in PBS, and then incubated 1 h at room temperature with an anti-mouse, alkaline phosphatase-conjugated secondary antibody (Promega, WI, USA). The membranes were washed as above described, rinsed in distilled water and incubated at room temperature with a chemiluminescent substrate, CDP-Star (Sigma-Aldrich, MO, USA). Data detection was carried out by exposing autoradiography films (Kodak, Eastman Kodak Company, NY, USA) to the membranes. Quantification of signals was carried out by Un-Scan-It gel software (Silk Scientific, UT, USA).

Chemicals

All chemicals utilized were of analytical grade and were purchased from Sigma (St. Louis, MO, USA).

Statistical analysis

Data are provided as means ± SEM. Statistical analyses were performed using two-tailed unpaired Student's *t* test or by two-way ANOVA for main effects and interactions followed by Bonferroni post-test. Correlation between selected parameters was evaluated by linear regression analysis. All analyses were performed using GraphPad Prism 4 (GraphPad Software Inc., San Diego, CA, USA).

Results

Plasma lipid profile determination shows that rats fed a fructose-rich diet exhibited a significant increase in triglycerides, NEFA and lipid peroxidation (+59, +42 and +22 %, respectively, $P < 0.05$), while no variation was found in total cholesterol (Table 2).

Table 2 Plasma lipid profile in rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
Triglycerides, mg/100 ml	73 ± 5	116 ± 10*
Total cholesterol, mg/100 ml	38.6 ± 1.3	38.9 ± 3.2
NEFA, mM	0.57 ± 0.02	0.81 ± 0.02*
Lipid peroxidation, nmol/ml	18.8 ± 1.1	23.0 ± 1.5*

Values are the mean ± SEM of six different experiments

NEFA non-esterified fatty acids

* $P < 0.05$ compared to controls (two-tailed unpaired Student's *t* test)

Basal, postabsorptive plasma insulin levels and integrated insulin response to glucose load were significantly higher in rats fed a fructose-rich diet compared to controls (+44 and +34 %, respectively, $P < 0.05$), while no significant variation was found in the integrated glucose response, although values found in fructose-fed rats tended to be higher (Table 3).

Body composition determinations revealed that fructose feeding significantly increased total body lipid content, as well as epididymal and mesenteric WAT weight (+29, +34 and +31 %, respectively, $P < 0.05$) compared to rats fed a control diet (Table 4). As for WAT structural characterization, mean adipocyte volume was significantly lower (−38 %, $P < 0.05$), while number of cells per unit volume was significantly higher (+62 %, $P < 0.05$), in subcutaneous abdominal WAT from rats fed a fructose-rich diet compared to controls (Table 4). On the other hand, mean adipocyte volume was significantly higher (+44 %, $P < 0.05$), while number of cells per unit volume was significantly lower (−30 %, $P < 0.05$), in intra-abdominal WAT from rats fed a fructose-rich diet compared to controls (Table 4). Analysis of diameter distribution of intra-abdominal adipocytes revealed a significant increase in the proportion of larger (>75 and >100 μm) adipocytes (+44 and +286 %, respectively, $P < 0.05$), as well as a significant decrease in the proportion of smaller (<25 μm) adipocytes (−69 %, $P < 0.05$) in rats fed a fructose-rich diet compared to controls (Table 5).

Linear regression analysis revealed that mean volume of intra-abdominal adipocytes was strongly positively correlated to plasma insulin response to glucose load ($r^2 = 0.862$, $P < 0.001$), as well as to body lipids ($r^2 = 0.963$, $P < 0.0001$) (Fig. 1a, b). On the other hand, no correlation was found between mean volume of subcutaneous abdominal adipocytes and body lipids ($r^2 = 0.277$, $P = 0.225$) or plasma insulin response to glucose load ($r^2 = 0.1079$, $P = 0.472$).

Tissue insulin sensitivity in subcutaneous abdominal and intra-abdominal WAT was assessed through western blot determination of p-Akt/Akt ratio, and the obtained results show a significant decrease in the above ratio in intra-abdominal but not in subcutaneous abdominal WAT (−24 %, $P < 0,05$) (Table 6). When p-Akt/Akt ratio was normalized to plasma insulin levels, significantly lower values were found in fructose-fed rats both in intra-abdominal and in subcutaneous abdominal WAT (−48 and −31 %, respectively, $P < 0.05$) (Table 6).

In vitro lipolytic activity of subcutaneous abdominal and intra-abdominal WAT cells was assessed in the absence and in the presence of insulin, and the results show that in subcutaneous abdominal adipocytes, lipolysis was not affected by fructose feeding, while insulin's ability to inhibit lipolysis was blunted in adipocytes from fructose-fed rats (−84 %, $P < 0.05$). In intra-abdominal adipocytes, lipolysis was significantly higher (+16 %, $P < 0.05$) and insulin inhibitory effect was absent in fructose-fed rats compared to controls (Table 7).

Table 3 Basal, postabsorptive plasma insulin levels and integrated response to glucose load test in rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
Postabsorptive plasma insulin, μg/l	2.17 ± 0.18	3.13 ± 0.14*
AUC glucose	28,833 ± 2,368	32,100 ± 2,930
AUC insulin	543 ± 30	729 ± 45*

Values are the mean ± SEM of six different experiments

AUC area under the curve

* $P < 0.05$ compared to controls (two-tailed unpaired Student's *t* test)

Table 4 Body lipid mass and cell volume and number of subcutaneous and intra-abdominal WAT in rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
Body weight, g	540 ± 22	543 ± 25
Body lipids, g	60.5 ± 4.1	78.2 ± 5.1*
Body lipids, g/100 g b.w.	11.2 ± 0.8	14.4 ± 0.9*
Epididymal fat, g	4.27 ± 0.15	5.71 ± 0.22*
Epididymal fat, g/100 g b.w.	0.79 ± 0.03	1.05 ± 0.04*
Mesenteric fat, g	4.8 ± 0.2	6.4 ± 0.2*
Mesenteric fat, g/100 g b.w.	0.89 ± 0.03	1.17 ± 0.03*
Subcutaneous WAT		
Cells/mm^3	24,420 ± 2,000	39,600 ± 3,000*
Mean cell volume, μm^3	40,950 ± 2,490	25,200 ± 1,593*
Intra-abdominal WAT		
Cells/mm^3	50,432 ± 2,204	35,068 ± 683*
Mean cell volume, μm^3	19,870 ± 868	28,540 ± 556*

Values are the mean ± SEM of six different experiments

* $P < 0.05$ compared to controls (two-tailed unpaired Student's *t* test)

Table 5 Cell diameter distribution in intra-abdominal WAT from rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
<25 μm	26 ± 1	8 ± 1*
25–50 μm	23 ± 1	17 ± 1
50–75 μm	26 ± 1	23 ± 1
75–100 μm	18 ± 1	26 ± 1*
>100 μm	7 ± 1	27 ± 1*

Values are the mean ± SEM of six different experiments

* $P < 0.05$ compared to controls (two-tailed unpaired Student's *t* test)

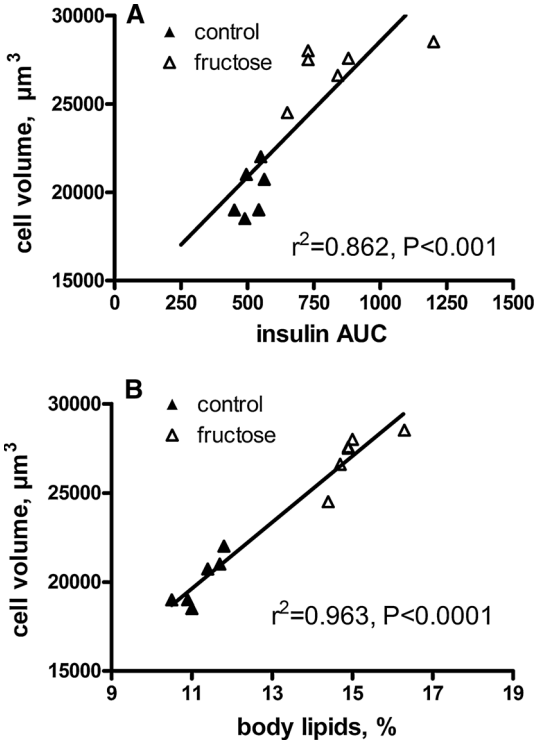

Fig. 1 Correlation between intra-abdominal adipocyte volume and area under the curve (AUC) of insulin response to glucose load (**a**) or body lipids (**b**) in rats fed a high-fructose or control diet. Values are reported as mean ± SEM of six different experiments

Table 6 p-Akt/Akt ratio in intra-abdominal and subcutaneous WAT from rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
Intra-abdominal WAT		
p-Akt/Akt	0.29 ± 0.02	0.22 ± 0.02*
(p-Akt/Akt)/plasma insulin	0.134 ± 0.01	0.070 ± 0.003*
Subcutaneous WAT		
p-Akt/Akt	1.1 ± 0.2	1.1 ± 0.2
(p-Akt/Akt)/plasma insulin	0.507 ± 0.022	0.348 ± 0.028*

Values are the mean ± SEM of six different experiments

* $P < 0.05$ compared to controls (two-tailed unpaired Student's t test)

Discussion

The results of the present study show, in a rat model resembling sedentary adults in Western societies, that long-term fructose feeding is associated with insulin resistance in intra-abdominal and, to a lesser extent, in subcutaneous abdominal adipocytes. This metabolic impairment leads to increased lipolysis and consequent increase in plasma NEFA, which in turn could impact on other metabolically important tissues, thus determining systemic insulin resistance.

We have previously characterized our animal model of obesity induced by long term feeding a diet low in fat but high in fructose [4] and here we confirm that, despite similar ME intake between the two groups of rats (control rats = 19,000 ± 544 kJ, fructose-fed rats = 19,200 ± 335 kJ), the above dietary regimen elicits the development of obesity in terms of increased fat mass. In addition, here we show that enhanced whole-body fat deposition is accompanied by a selective increase in intra-abdominal and visceral WAT, a condition commonly associated with the development of insulin resistance and metabolic syndrome [13]. The increased whole-body fat mass probably arises from the increased hepatic lipogenesis previously found by us in fructose-fed rats [4] and that is usually associated with high intake of fructose [14, 15]. Accordingly, notwithstanding the low fat content of the diet, plasma lipid profile in fructose-fed rats is characterized by increased concentrations of triglycerides, in agreement with others [16]. Therefore, elevated levels of fructose present in low-fat diet elicit a dangerous metabolic link between liver and adipose tissue, where fat synthesized in liver from fructose metabolism is delivered to adipocytes for storage. Plasma lipid profile also evidenced significantly higher lipid peroxidation, indicating that oxidative imbalance occurs in fructose-fed rats, in agreement with the current idea that oxidative stress is a mechanism contributing to elevated blood pressure and insulin resistance typical of animal models of metabolic syndrome [17]. A further deleterious impact of lipids derived from hepatic lipogenesis on WAT can be hypothesized, taking into account the recent findings [18] of a "Randle-like" competition between lipid flux and glucose flux in WAT, with lipid-induced suppression of WAT de novo lipogenesis resulting in reduced glucose-buffering capacity by WAT, which could therefore contribute to glucose intolerance.

Table 7 In vitro lipolytic activity in subcutaneous and intra-abdominal adipocytes from rats fed a high-fructose or control diet for 8 weeks

	Control	Fructose
Subcutaneous adipocytes		
− insulin	32.0 ± 2.0	33.9 ± 2.0
+ insulin	20.6 ± 2.1#	31.9 ± 2.0*
% inhibition	33.7 ± 2.2	5.4 ± 1.1§
Intra-abdominal adipocytes		
− insulin	29.2 ± 1.0	33.8 ± 1.0*
+ insulin	23.8 ± 1.0#	32.9 ± 2.0*
% inhibition	21.9 ± 2.0	1.0 ± 1.0§

Values are expressed as µg glycerol/($h \times 10^{-6}$ cells) and are the mean ± SEM of 6 different experiments

* Significant effect ($P < 0.05$) of fructose feeding; # significant effect ($P < 0.05$) of insulin (two-way ANOVA for main effects and interactions followed by Bonferroni post-test); § $P < 0.05$ compared to controls (two-tailed unpaired Student's t test)

To investigate potential alterations in WAT determined by excessive fat deposition, we firstly looked at morphological alterations in WAT depots, since it is well known that adipocyte morphology is linked to its function. In particular, we found that in rats fed a fructose-rich diet, the increased whole-body lipid content is associated with an increase in the number of subcutaneous abdominal adipocytes, whose mean diameter decreases, while intra-abdominal adipocyte diameter increases, leading to a decrease in the number of cells per unit of volume. The above morphological alterations in the two populations of adipocytes are in agreement with the well-established response of these cells to lipid overflow to adipose tissue. In fact, it is well known that subcutaneous adipocytes are more prone to hyperplasia when challenged with increased lipids [19], while intra-abdominal fat cells react to increased lipid supply preferentially with hypertrophy [20, 21]. Thus, it appears that independently from the source (diet or hepatic synthesis) and hence from the typology (chylomicron or VLDL), the response of fat cells to increased lipid flow is similar. The increased mean cell volume of intra-abdominal adipocytes is the result of a shift in the composition of the cell population, with a significant increase in larger adipocytes, whose percent contribution to total cells is about doubled (from 25 to 53 %). In addition, we found a strong correlation between mean cell volume and plasma insulin response to glucose load, as well as between mean cell volume and body lipids, thus indicating that in this dietary model of non-genetic obesity and insulin resistance, the morphology of intra-abdominal adipose cells is a good predictor of whole-body metabolic imbalance.

It is well known that adipocyte size is strictly correlated with cell function and sensibility to the action of insulin [22], especially in visceral WAT [23], and therefore increased cell size in this adipose depot after long-term fructose feeding is predictive of changes in cell function. To address this issue, we assessed insulin sensitivity in terms of p-Akt levels in the two WAT depots and the results confirm the higher insulin sensitivity typical of subcutaneous adipocytes when compared to intra-abdominal ones [23]. In addition, our present results also show that intra-abdominal fat cells in fructose-fed rats display decreased p-Akt levels, while no variation was found in subcutaneous abdominal fat cells. However, considering that fructose-fed rats exhibit higher plasma insulin levels, the normalized adipose tissue p-Akt levels reveal that reduced insulin signaling is also present in subcutaneous abdominal cells, although the degree of impairment (31 %) is lower than that found in intra-abdominal fat (52 %), so that normal insulin signaling can be maintained through higher plasma insulin.

Subcutaneous abdominal and intra-abdominal fat cells also displayed a different metabolic behavior and a different regulation both in control and in fructose-fed rats. In fact, in control rats, the inhibitory effect of insulin on the cellular lipolytic activity is significantly higher in subcutaneous abdominal than in intra-abdominal adipocytes, in agreement with the higher insulin sensitivity of subcutaneous abdominal fat [23] as well as with the higher p-Akt levels here found by us. In addition, different responses to fructose feeding are evident in the two fat depots, since in subcutaneous abdominal fat, a significant decrease in the inhibitory effect of insulin is found, while in intra-abdominal adipocytes, the loss of insulin inhibition is coupled with a significant increase in lipolysis. This latter result could be explained taking into account that larger adipocytes have a higher lipolytic rate than smaller adipocytes [24, 25] and that intra-abdominal adipocyte size is higher in fructose-fed rats compared to controls. The lower insulin effect on lipolysis inhibition here found is similar to that found after long-term sucrose feeding [26], and it is responsible for the enhanced plasma NEFA levels found in fructose-fed rats [this work, 4], since plasma NEFA levels depend on WAT metabolic activity [27]. This is particularly interesting because there is accumulated evidence that the increased availability of NEFA in muscle, pancreas and liver is associated with a reduced ability of insulin to stimulate the utilization and storage of glucose (insulin resistance) [28, 29]. Therefore, it appears that high fructose intake not only causes metabolic alterations in the liver, which metabolize about 90 % of the ingested fructose [15], but could also have a deep impact on other metabolically relevant tissues, thus contributing to metabolic disturbance found by us in fructose-fed rats [4].

In conclusion, there is evidence that high fructose feeding elicits remarkable morphological and functional modifications, particularly in intra-abdominal WAT, that are highly predictive of obesity and insulin resistance and that contribute to the worsening of metabolic alterations peculiar in a fructose-rich, hypolipidic diet.

Acknowledgments This work was supported by a grant from University "Federico II" of Naples and by P.O.R. Campania FSE 2007-2013, Project CREME. The authors thank Dr. Emilia De Santis for skillful management of animal housing.

Conflict of interest The authors declare no conflict of interest.

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