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Unusual increase of Scd1 and Elovl6 expression in rat inguinal adipose tissue

Research Article

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Abstract: It is generally accepted that the location of body fat deposits may play an important role in the risk of developing some endocrine and metabolic diseases. We have studied the effect of food restriction and food restriction/refeeding, often practiced by individuals trying to lose body weight, on the expression of genes which are associated with obesity and certain metabolic disorders in inguinal, epididymal, and perirenal rat white adipose tissues. Gene expression was analyzed by real time semi-quantitative polymerase chain reaction and by Western blot. We found that prolonged food restriction caused a significant decrease of body and adipose tissue mass as well as the increase of Scd1 and Elovl6 gene expressions in all main rat adipose tissue deposits. Food restriction/refeeding caused increases of: a) Scd1 and Elovl6 mRNA levels in adipose tissue, b) Scd1 protein level and c) desaturation index in adipose tissue. The increased expression of both genes was unusually high in inguinal adipose tissue. The results suggest that the increase of Scd1 and Elovl6 gene expressions in white adipose tissue by prolonged food restriction and prolonged food restriction/refeeding may contribute to accelerated fat recovery that often occurs in individuals after food restriction/refeeding.

Keywords: *Scd1 • Elongase • Food restriction • Rat adipose tissue*

1. Introduction

Mammalian stearoyl-CoA desaturase 1 (Scd1) is the rate limiting enzyme catalyzing the conversion of saturated fatty acyl-CoAs to corresponding monounsaturated acyl-CoAs [1,2]. Two functional genes (Scd1 and Scd2) encoding desaturase were found in rats. Some data indicates that Scd1 activity has a significant impact on the ratio of saturated to monounsaturated fatty acids and consequently on membrane fluidity [1-3]. Variations of the ratio of saturated to monounsaturated fatty acids, as a consequence of changes in Scd1 activity, have been implicated in some diseases including obesity, type 2 diabetes and different types of cancer [1-4]. The highest expression of the Scd1 gene was found in liver and adipose tissues [5,6]. Scd1 is the major gene target of leptin – a central regulator of energy homeostasis [7]. Moreover, low Scd1 activity is associated with low body weight and low fat mass, increased insulin sensitivity, up-regulation of fatty acid oxidation and down-regulation of lipid synthesis [1-3]. Given these positive metabolic effects, Scd1 has become an attractive target for obesity treatment [8-10]. It has been shown that fasting, like some drugs, causes a significant decrease of mouse liver Scd1 gene expression [11]. Similar to Scd1, elongase 6 (Elovl6) is a gene regulated by fasting/refeeding [12]. The information about the effect of food restriction and food restriction/refeeding on Scd1 and

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Elovl6 gene expressions in adipose tissue depots could be of great importance because food restriction is often practiced by individuals trying to lose body weight as well as in prevention of insulin resistance and type 2 diabetes [13]. It has recently been shown that 50% food restriction exerts different effects on Scd1 mRNA level in various adipose tissue depots (no effect on epididymal adipose tissue, down regulation of retroperitoneal fat [14] and up regulation in perirenal adipose tissue [15]). These contradictory results led us to examine the effect of prolonged food restriction and prolonged food restriction/refeeding on Scd1 and Elovl6 gene expressions in main body depots of rat white adipose tissue. Considering that substrates for Scd1 and Elovl6 are synthesized *de novo* in rat adipose tissue, we also studied the effect of food restriction and food restriction/refeeding on gene expressions of ATP-citrate lyase (Acly), fatty acid synthase (Fasn), acetyl-CoA carboxylase α (Acaca), and NADP-linked malic enzyme (Me1).

2. Experimental Procedures

2.1 Animals

Ten-week-old, male Wistar rats, weighing approximately 245 g at the onset of the experiments, housed in individual wire-mesh cages, were maintained at 22°C under a light to dark (12:12 h) cycle with lights on at 7:00 a.m. The animals were treated as described recently [15]. Briefly, the rats were divided randomly into 2 groups. Control animals (n=10 rats) were allowed free access to food and tap water. The animals in the remaining group (n=20 rats) were allowed free access to tap water and obtained 50% of the total amount of food consumed by the control group. The food was replenished every day, 2 hours before the lights off period. The majority of food supplied was consumed within the first 2 hours of access. Thus, in contrast to control (*ad libitum* fed rats), the other rats maintained on a restricted diet ate when food was available regardless of the light cycle. An average daily food intake by the control group was measured by the difference in weight between the amount of food provided and the amount of food remaining over a period of 1 day. The average daily food intake by the control rats (rats fed *ad libitum*) was approximately 26 g throughout the period of experiment. The commercial diet used in all groups was the same as described in [15]. After one month of treatment, the rats kept on a restricted diet were randomly divided into two subgroups: a) 10 rats were kept for an additional 2 days on the restricted diet, and b) 10 rats were fed *ad libitum* for 2 days. A two day refeeding period after food restriction was chosen to be close to lipogenic enzymes gene reprogramming within the first days of catch-up fat.

After the treatment, rats were killed by decapitation under ketamine anesthesia (between 8:00 and 10:00 a.m.). Perirenal, epididymal, and inguinal white adipose tissues were collected, and rapidly frozen in liquid nitrogen for subsequent analyses of gene expressions. The tissues were stored at –80ºC until further analysis was performed. All animal procedures were conducted in agreement with our institutional guidelines for the care and use of laboratory animals.

2.2 RNA isolation

Total cellular RNA was extracted from frozen tissue by a guanidinium isothiocyanate-phenol/chloroform method [16]. The RNA concentration was determined from the absorbance at 260 nm. All samples had 260/280 nm absorbance ratios of about 2.0.

2.3 cDNA synthesis

First strand cDNA was synthesised from 4 µg of total RNA (RevertAid™ First Strand cDNA Synthesis Kit – Fermentas UAB, Lithuania). Prior to amplification of cDNA, each RNA sample was treated with RNase-free DNase I (Fermentas UAB, Lithuania) at 37°C for 30 min.

2.4 Determination of mRNA level

Determination of lipogenic enzymes mRNA levels were performed by real-time PCR as described recently [15].

2.5 Western blot analysis of Scd1

About 100 mg of frozen rat adipose tissue was homogenized in 20 mM Tris-HCl pH 7.8 with 0.2% Triton X-100. Aliquots of the homogenate containing 50 µg of protein were mixed with sample buffer, boiled, separated by SDS/PAGE and electroblotted to PVDF membrane (Bio-Rad Laboratories, Hercules, USA). The membrane was blocked, incubated with goat polyclonal anti-Scd1 antibody (E-15) (Santa Cruz Biotechnology Inc., USA), washed and incubated with HRP-conjugated secondary antibody. Signal was revealed by membrane incubation with SuperSignal West Pico chemiluminescent substrate (Thermo Scientific, USA). Actin was used as a loading control. Gels were calibrated with prestained molecular mass markers (Fermentas UAB, Lithuania).

2.6 Determination of desaturation index of white adipose tissue

Lipids were extracted using the Folch's method which included homogenization in chloroform/methanol (2:1 v/v) [17]. The fatty acids were hydrolysed by heating in a methanolic solution of 0.5 M KOH for 3 h at 70ºC in sealed ampoules and fatty acid methyl esters

formed (FAME) were extracted with *n*-hexane. Analyses of the FAME were carried out by gas chromatography mass spectrometry on a Hewlett Packard GC-MS 5890 (Finnigan Mat) equipped with a fused silica capillary column HP-5, 30 m x 0.25 mm i.d., and with film of thickness of 0.25 µm. The GC was programmed from 60ºC to 300ºC at the rate of 4°C/min with helium carrier gas at the column head pressure of 60 kPa. Desaturation index was calculated as the ratio of monounsaturated to saturated fatty acids (oleic – 18:1 to stearic – 18:0).

2.7 Statistics

The statistical significance of differences between the groups was assessed by one-way analysis of variance (ANOVA) to compare: i) control *versus* rats maintained on a restricted diet; ii) control *versus* rats maintained on a restricted diet and refed; iii) rats maintained on a restricted diet *versus* rats maintained on a restricted diet and refed. The Sigma Stat software (Sigma Stat Inc.) was used. Differences between the groups were considered significant when $P<0.05$.

3. Results

The mean body weight of rats fed *ad libitum* increased from approximately 245 to 320 g (Figure 1). The rats maintained on a restricted diet lost approximately 50 g as compared to body mass at the start of the experiments and about 100 g in comparison to body mass of rats fed *ad libitum* (Figure 1). During the first day after the restoration of food intake, rats maintained on a restricted diet consumed approx. 40 g per 24 h. This led to the increase of body weight during the 2 days of refeeding (Figure 1). The mass of epididymal, perirenal and inguinal adipose tissue depots of rats maintained on a restricted diet decreased significantly as compared to the control group (Figure 2). The approximately 6-fold decrease was found in the case of perirenal, 4-fold in the case of epididymal and 2.5-fold in the case of inguinal white adipose tissue (Figure 2). Refeeding *ad libitum* for 48 h of rats maintained on a restricted diet led to approximately 2-fold increase of perirenal and epididymal adipose tissue masses. Inguinal adipose tissue increased only approx. 50% after refeeding (Figure 2). Collectively, these results indicate that prolonged food restriction causes a significant decrease in body and white adipose tissue masses. The degree of the decrease of fat mass depends on the location of body fat deposits. Refeeding caused an increase in body weight and fat mass. In this case, the fold of the increase of fat mass was similar in perirenal and epididymal (approx. 2-fold increase) and markedly less in inguinal adipose tissue (approx. 50% of the increase).

Prolonged food restriction was accompanied by approximately 18-fold increase of Scd1 mRNA level in inguinal white adipose tissue as compared to control (Figure 3A). Upon refeeding, approx. 4-fold increase of Scd1 mRNA level in inguinal white adipose tissue was found in comparison to rats maintained on a restricted diet (Figure 3A). Altogether, food restriction/refeeding caused more than 70-fold (as compared to control rats) increase of Scd1 mRNA level in inguinal adipose tissue (Figure 3A).

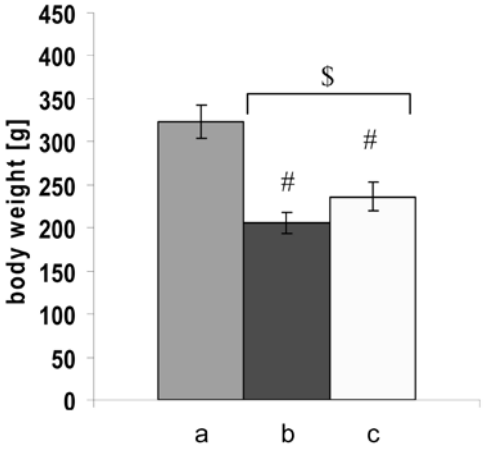

Figure 1. The effect of food restriction and food restriction/refeeding on rats' body weight. Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed ad libitum for 48 h (c). The data are presented as means ± SD. # $P<0.001$; $ $P<0.01$.

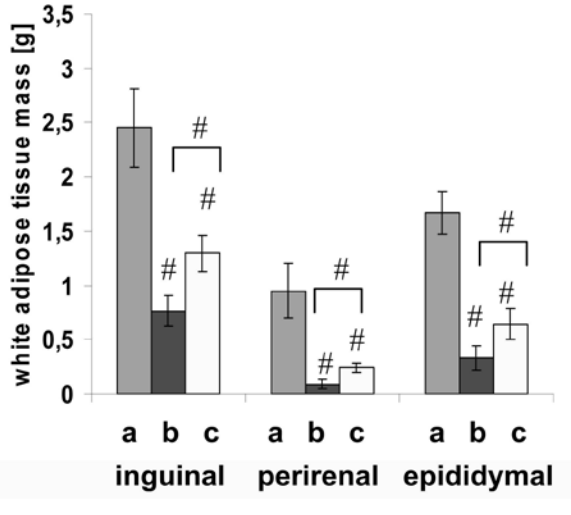

Figure 2. The effect of food restriction and food restriction/refeeding on perirenal, epididymal and inguinal rat fat mass. Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed *ad libitum* for 48 h (c). The data are presented as means ± SD. # $P<0.001$.

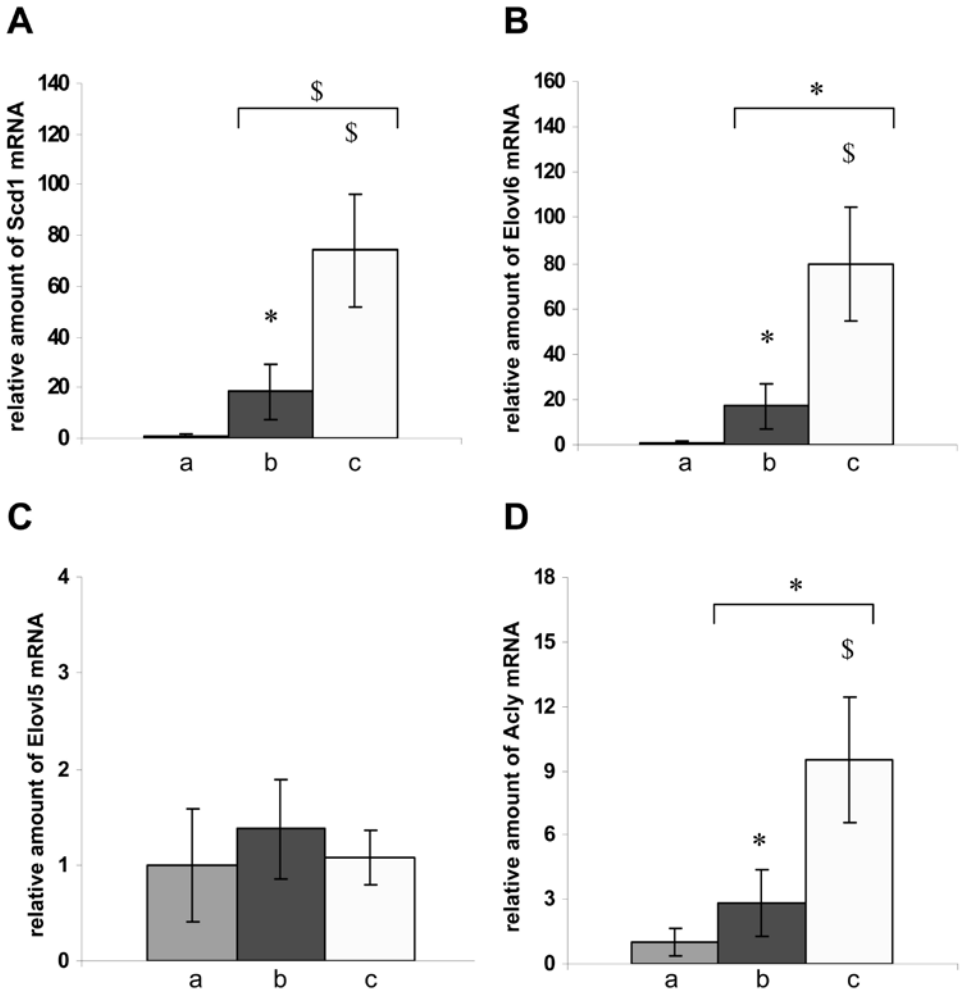

Figure 3. The effect of food restriction and food restriction/refeeding on inguinal white adipose tissue Scd1 (A), Elovl6 (B), Elovl5 (C) and Acly (D) mRNA levels. Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed *ad libitum* for 48 h (c). The data are presented as means ± SD. * $P<0.05$; $ $P<0.01$.

The pattern and magnitude of the change of inguinal adipose tissue Elovl6 mRNA level upon prolonged food restriction and prolonged food restriction/refeeding were essentially similar to the change of Scd1 mRNA level (Figure 3B). Despite an unusual increase of Elovl6 mRNA level, Elovl5 mRNA level did not change significantly in inguinal adipose tissue of rats maintained on a restricted diet or rats upheld on a restricted diet and refed (Figure 3C). The increase of other lipogenic enzyme mRNA levels in inguinal adipose tissue of rats maintained on a restricted diet and rats maintained on a restricted diet and refed were also found. However, the increase was less pronounced. For instance prolonged food restriction caused approximately 3-fold increase of ATP-citrate lyase (compared to approx. 18-fold increase of Scd1). Prolonged food restriction and refeeding caused approx. 9-fold increase of ATP-citrate lyase (compared to more than 70-fold increase of Scd1 mRNA level) (Figure 3D). Similar changes in fatty acid synthase (Fasn), acetyl-CoA carboxylase (Acaca) and malic enzyme (Me1) gene expressions were observed in inguinal adipose tissue of rats maintained on a restricted diet or rats maintained on a restricted diet and refed (not shown).

In epididymal white adipose tissue, prolonged food restriction caused only 2-fold (as compared to control) increase of Scd1 mRNA (Figure 4A). Upon refeeding, 7-fold higher (as compared to control) Scd1 mRNA level in epididymal white adipose tissue was found (Figure 4A). The increase of epididymal fat Elovl6 mRNA level upon prolonged food restriction and prolonged food restriction/refeeding was essentially similar to Scd1 mRNA level (Figure 4B). Similar to inguinal adipose tissue, Elovl5

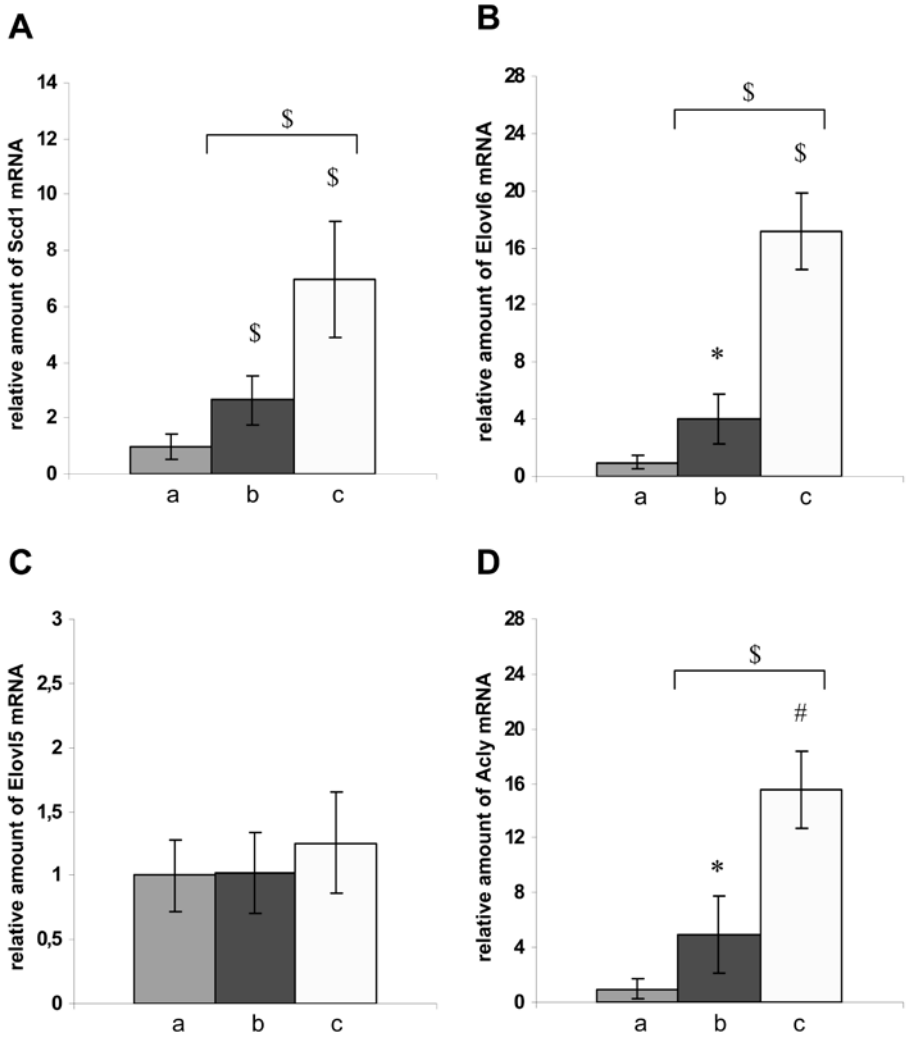

Figure 4. The effect of food restriction and food restriction/refeeding on epididymal white adipose tissue Scd1 (A), Elovl6 (B), Elovl5 (C) and Acly (D). Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed *ad libitum* for 48 h (c). The data are presented as means ± SD. * $P<0.05$; $^{\$}P<0.01$; $^{\#}P<0.001$.

mRNA level did not change significantly in epididymal adipose tissue of rats maintained on a restricted diet or rats maintained on a restricted diet and refed (Figure 4C). The increase of other lipogenic enzyme mRNA levels in epididymal adipose tissue of rats maintained on a restricted diet and rats maintained on a restricted diet and refed *ad libitum* were also found. For example, prolonged food restriction caused approximately 4-fold increase of ATP-citrate lyase and prolonged food restriction and refeeding was reflected to approx. 15-fold increase (Figure 4D). It should be noted that the pattern and magnitude of changes in ATP-citrate lyase in inguinal and epididymal white adipose tissue were essentially similar.

The magnitude and pattern of changes of Scd1, Elovl6, Elovl5 and ATP-citrate lyase in perirenal adipose white tissue resemble that observed in epididymal adipose tissue (Figures 5A-D). This is in accordance with the results reported recently [15].

As expected, the amount of Scd1 protein determined by Western Blot analysis in white adipose tissue reached the highest level in tissue of rats maintained on prolonged food restriction/refeeding according to Scd1 mRNA level (Figure 6). The increase of Scd1 gene expression was associated with the increase in desaturation index. In subcutaneous white adipose tissue, desaturation index (18:1/18:0) increased from 11.4 in control rats to 16.4 in rats maintained on a restricted diet and refed *ad libitum.* Essentially, similar results in perirenal and epididymal white adipose tissue was observed (not shown).

It should be noted that there was no significant differences in the relative levels of Scd1 and Elovl6 mRNA between perirenal and epididymal white adipose

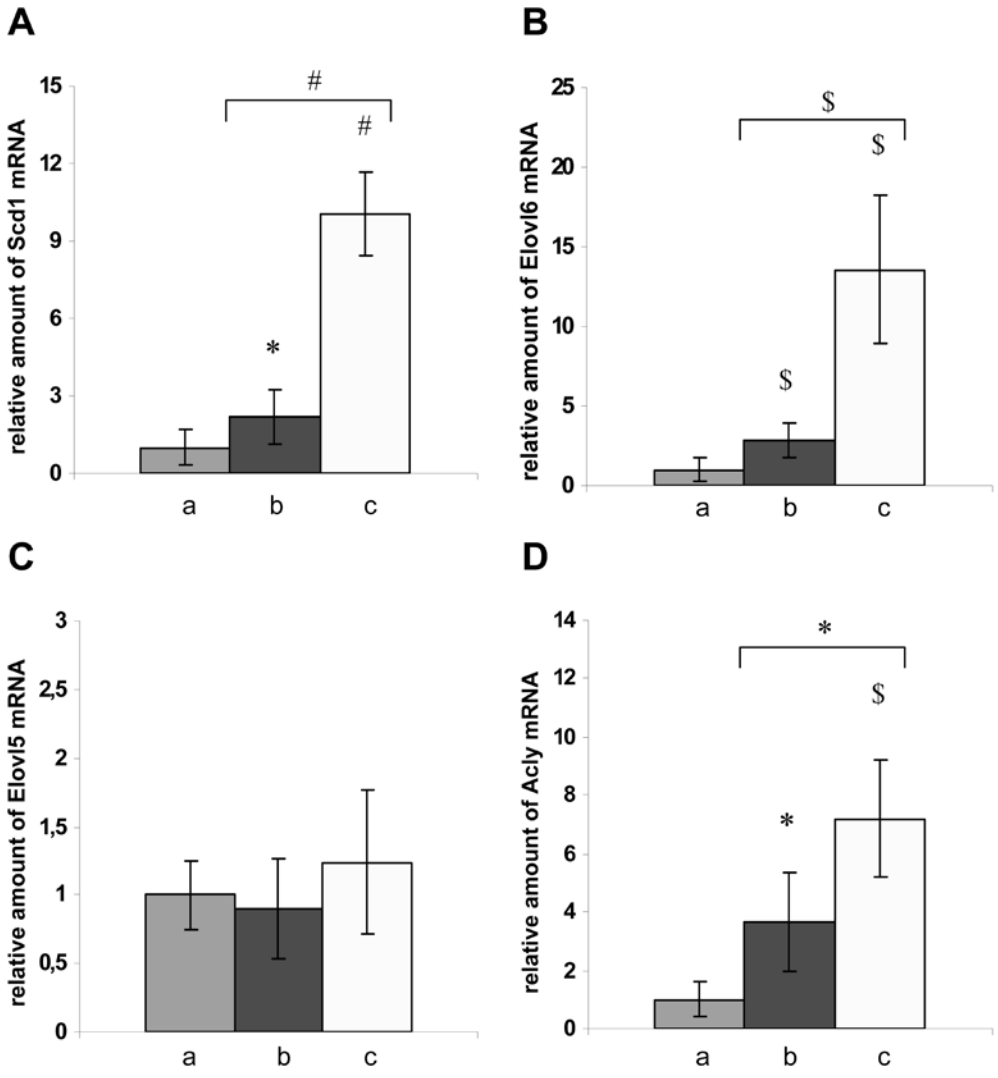

Figure 5. The effect of food restriction and food restriction/refeeding on perirenal white adipose tissue Scd1 (A), Elovl6 (B), Elovl5 (C) and Acly (D) mRNA levels. Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed *ad libitum* for 48 h (c). The data are presented as means ± SD. * $P<0.05$; $^{\$}P<0.01$; $^{\#}P<0.001$.

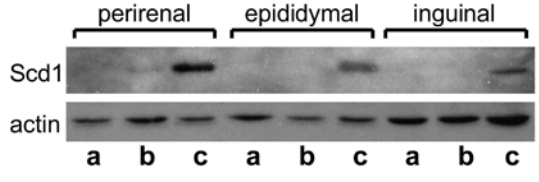

Figure 6. Western blot analysis of Scd1 protein levels in perirenal, epididymal and inguinal white adipose tissues of rats treated with food restriction and food restriction/refeeding. Control group (a); rats maintained on a restricted diet for one month (b); rats maintained on a restricted diet for 28 days and refed *ad libitum* for 48 h (c).

tissue of control rats (not shown). In inguinal adipose tissue the basal (observed in control rats) Scd1 and Elovl6 mRNA levels were approximately 40-fold lower than in perirenal and epididymal tissues (not shown). In rats maintained on a restricted diet, inguinal Scd1 and Elovl6 mRNA levels (despite several fold increase) did not reach the value observed in perirenal and epididymal white adipose (not shown).

4. Discussion

The results presented here indicate that both food restriction and food restriction/refeeding increase Scd1,

Elovl6 and other lipogenic enzyme gene expressions in all main depots of rat white adipose tissue. The magnitude of these changes is more pronounced in rats maintained on a restricted diet and refed than in rats maintained on a restricted diet alone. The novel findings presented here are: a) Scd1 and Elovl6 gene expressions are up-regulated in epididymal and inguinal depots of white adipose tissue by prolonged food restriction and prolonged food restriction/refeeding, b) the increase of Scd1 and Elovl6 gene expressions are unusually high in inguinal adipose tissue as compared to other lipogenic enzyme genes and c) the degree of the changes of fat mass in rats maintained on a restricted diet and on a restricted diet and refed depends on the location of body fat deposits. These findings extend previous knowledge that different fat depots have differential gene expression induced by the same conditions [18-24]. Moreover, the results presented here indicate that the increase of Scd1 gene expression (measured both at mRNA and protein level) was associated with the increase in desaturation index. Despite significant changes in Elovl6 gene expression in epididymal and inguinal depots of white adipose tissue, Elovl5 gene expression was not affected by food restriction and food restriction/refeeding. Different regulation of liver Elovl5 and Elovl6 have been observed [15,18]. In general, the changes of liver Elovl6 gene expression correlate with changes of other lipogenic enzyme gene expressions but not with Elovl5 [15,18]. Thus, the results presented here indicate that regulation of Elovl5 and Elovl6 gene expressions in white adipose tissue resembles the regulation found in the liver [15].

As already mentioned in the Introduction, Mainieri *et al*. [14] reported that food restriction causes significant decrease of Scd1 gene expression in retroperitoneal adipose tissue, whereas it is without effect on Scd1 gene expression in epididymal adipose tissue. Summermatter *et al.* reported that two weeks of semistarvation caused the decrease of Scd1 and Fasn mRNA level in epididymal adipose tissue [25]. In contrast our results clearly indicate that prolonged food restriction causes significant increase of Scd1, Elovl6 and other key lipogenic enzyme gene expressions in perirenal, epididymal and inguinal white adipose tissue (the main three depots of white adipose tissue). During preparation of this manuscript Bruss *et al*. [26] reported that food restriction caused significant up-regulation of Fasn and Acaca gene expressions both in liver and adipose tissue. Thus, both these studies, in contrast to Mainieri *et al*. [14] and Summermatter *et al.* [25] indicate a similar effect of prolonged food restriction on some lipogenic enzyme gene expressions.

Some experimental data has previously shown that increased expression of Scd1 in tissue contributes to abnormal lipid metabolism and progression of obesity [10,27]. One can suppose that the increase of Scd1 (and other lipogenic enzyme gene expressions) in white adipose tissue after prolonged food restriction/refeeding may also cause abnormal lipid synthesis and progression of obesity. It is not excluded that the increase of lipogenic enzyme gene expressions in white adipose tissue may be part of the molecular mechanism(s) by which the increase of fatty acid synthesis after food restriction/refeeding confers enhanced susceptibility to obesity and insulin resistance. However, one has to keep in mind that up-regulation of Scd1 and the knock-down of Elovl6 is beneficial for pancreatic beta cells by protecting them from saturated fatty acid-induced ER stress and apoptosis [28].

The results presented here indicate that prolonged food restriction causes a significant decrease in white adipose tissue mass. The degree of the decrease of fat mass depends on the location of body fat deposit. The decrease of perirenal and epididymal masses were approx. 4-5-fold, whereas the decrease of inguinal adipose tissue was only 2-fold. It is likely that inguinal adipose tissue is less responsive to the lipolytic effects of catecholamines [29] and/or more responsive to the antilipolytic effects of insulin [30]. However, it is not excluded that these differences result from the contradistinctive composition of adipose tissue between these depots. The increase of fat mass after refeeding was similar in perirenal and epididymal (approx. 2-fold increase) and less in inguinal adipose tissue (approx. 50% increase). It is unlikely that lower reduction of inguinal fat mass (compared to perirenal and epididymal adipose tissues) and less increase of inguinal fat mass after refeeding are related to the differences in Scd1 and Elovl6 gene expressions in this fat depot. The different effect of food restriction on inguinal and perirenal (as well as epididymal) fat lost may have pathophysiological significance. The location of body fat deposit rather than the degree of obesity may play an important role in the risk of developing some endocrine and metabolic diseases [31-34].

In conclusion, the increase of Scd1 and Elovl6 (and other lipogenic enzymes) gene expressions may be a part of the molecular mechanism(s) by which the increase of fatty acid synthesis after caloric restriction confers enhanced susceptibility to obesity and insulin resistance.

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