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Gene expression changes in rat white adipose tissue after a high-fat diet determined by differential display

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Abstract

The differences in gene expression pattern of visceral white adipose tissue between control and high-fat-fed rats were compared using the mRNA differential display methodology. The results, confirmed by Northern blot, showed eight genes upregulated: adiponectin, fibrillin-1, transferrin, Y-box binding protein-1, IgE receptor β chain (FcεRIβ), α-1 haemoglobin, and ribosomal proteins S10 and L7 and four genes downregulated: caveolin-2, lactate dehydrogenase-A, mitochondrial 16S rRNA, and mitochondrial cytochrome oxidase subunit I/serine tRNA. Two of these genes have been already related to obesity (adiponectin and caveolin-2) while the others are known to participate in metabolic, signalling or transcription regulation pathways that can be relevant in energy (lipid and/or carbohydrate) metabolism.

Keywords: Differential display; High-fat diet; Adipose tissue genes; Obesity

Obesity is a multifactorial disease under the influence of genetic and environmental factors. Indeed, more than 300 genes, markers, and chromosomal regions have been related to this disease [1]. On the other hand, obesity arises as the result of a positive energy balance and several studies have shown that a high saturated-fat intake can promote fat accumulation [2]. The diet-induced enlargement of fat depots is a complex process led by changes in gene expression that promote adipogenesis and fat storage [3]. A deeper knowledge of the participating processes is required to understand the mechanisms underlying the development of overweightness and, in this context, the high-fat cafeteria diet used in this work provides an appropriate model to study the onset and etiology of excessive weight gain in rodents [4].

Differential display (DD) has been used to study changes in gene expression allowing the comparative screening of mRNA pools from different tissues and making possible the simultaneous detection of either up- or downregulated genes [5,6].

The aim of this work was to identify white adipose tissue (WAT) genes whose expression change in high-fat diet-induced fat accumulation. For this purpose, we have used mRNA DD to compare the gene expression profiles of visceral WAT from lean rats, fed with a control diet, and from overweighed rats, fed with a cafeteria diet for a period of 11 days.

Methods and procedures

Animals and sample preparation. Five-week-old female Wistar rats weighing about 150 g were housed in cages under controlled conditions of light (12/12 h light/dark) and temperature (22 ± 2 °C). All experimental procedures were performed according to National and Institutional Guidelines for Animal Care and Use at the University of Navarra. Two groups (eight animals each) were fed for 11 days either with a control diet (C) containing 15,204 kJ/kg (6% calories from fat) or with a cafeteria diet (HF) containing 19,614 kJ/kg (65% calories from fat). The (C) group was given a standard laboratory pelleted diet and free access to water, while the (HF) group was given a fat-rich hypercaloric diet containing pate, chips, chocolate, bacon, biscuits,

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and chow in a proportion of 2:1:1:1:1:1 as previously published [7]. Food was offered ad libitum and food intake and body weight were measured daily. After the experimental feeding period, animals were euthanized and visceral WAT was immediately removed, weighted, and frozen in liquid nitrogen before being stored at −80 °C.

RNA extraction. Total RNA was isolated from rat visceral tissue following [8] and incubated with RNase-free DNase I (Sigma, Biochemicals) for 30 min at 37 °C. RNA concentration was measured spectrophotometrically and its quality was verified by ethidium bromide staining after agarose gel electrophoresis.

Differential display. The "Hyeroglyph mRNA profile Kit 1 for differential display analysis" (Genomyx) was used to perform the reactions following the manufacturer's instructions. Two hundred nanograms of total RNA was used for the reverse transcription reaction with the T7 (dT_{12})AP anchored primer. All PCRs were performed in duplicate following the cycling parameters recommended by the manufacturer and a total of 40 different combinations of primers were assayed for each tissue sample, using 10 different (dT_{12})AP anchored primers and four ARP arbitrary primers (Genomyx). Samples of each reaction were run on a Genomyx LR programmable DNA Sequencer Apparatus and the gels were dried at room temperature and exposed for 24 h to an X-ray film (Kodak).

Product cloning. Bands of interest were excised from the polyacrylamide gel and the DNA was reamplified with the same pair of primers. Reamplified products were cloned into pGEM-T cloning vector (Promega) using standard protocols. Sequencing was performed with the "Thermo Sequenase Fluorescent Labelled Primer Cycle Sequencing Kit" (Amersham–Pharmacia) in an ALF automatic laser sequencing apparatus. Sequences obtained were compared to GenBank nonredundant and EST databases using the BLAST algorithm.

Northern blotting. Probes were obtained from the recombinant plasmids by *Eco*RI digestion and labelled by random priming (Klenow DNA polymerase I, Promega) with [α-^{32}P]dCTP (3000 Ci/mmol, NEN). RNA electrophoresis and transfer were done following standard procedures loading 10 μg of total RNA in each lane. Hybridization was carried out using Express Hyb solution (Clontech) with 4×10^6 cpm/ml of labelled probe. Signals were quantified densitometrically and 18S rat ribosomal cDNA probe (Ambion) was used as normalizing control.

Results

Weight gain

Body weight was significantly increased (152%; $p < 0.05$) in those animals fed on the cafeteria diet for 11 days. Furthermore, the enlargement of the excised visceral fat depots was also statistically significant ($p < 0.001$) in cafeteria-fed rats as compared to the control group (Table 1).

Table 1
Weight-related parameters in control and high-fat (cafeteria) diet animals

	Control ($n = 8$)	High-fat diet ($n = 8$)
Initial body weight (g)	176.4 ± 6.2	179.8 ± 5.6
Final body weight (g)	202.7 ± 9.3	219.8 ± 13.9*
Weight gain (g)	26.3 ± 4.5	40.0 ± 9.8**
Visceral fat pad (g)	7.6 ± 1.7	11.4 ± 1.5***

Data are means ± SD.
Student's *t* test: $^{*}p < 0.05$; $^{**}p < 0.01$; and $^{***}p < 0.001$.

Differential display

Under standard DD conditions and after analysis of the autoradiographs, 76 differential bands were initially identified with sizes ranging between 100 and 1400 bp, 45 bands were upregulated, and 31 downregulated in the high-fat-fed animals.

Northern blot and sequencing

In order to confirm the differential expression of these genes and to estimate its transcript size, Northern blot analyses using the selected products as probes were performed. These analyses were carried out in different animals than those used for the DD experiment to assure that the observed differential expression is not due to a particular genetic background or response of one single animal to the high-fat diet. RNA from one to four separate animals of each group (C and HF) was used for this purpose. Of the initial 76 candidate products, 30 did not give any signal even after prolonged exposure (144 h), 24 did not show any significant difference in mRNA level between control and cafeteria-fed animals, and only the remaining 22 showed differential expression. The random priming of the PCR explains the high number of false positives usually obtained and the amplification step explains the isolation of poorly expressed products nondetectable by Northern blot [9]. Ten products were upregulated and 12 were downregulated in visceral WAT from the high-fat-fed animals. Unexpectedly, the expression pattern of six bands (22C8, 33C2, 24O3, 44O1, 52O1, and 53O1) was the opposite of that found by DD.

All the products showing differential expression by Northern blot were sequenced and compared against available databases. Three independently isolated products (43C1, 83C1, and 83C2) turned out to correspond to the same gene, rat caveolin-2, reducing the original 22 bands to 20 different genes (Table 2). Twelve of them matched rat genes already known (84O2, 83O4, 82O2, 22C8, 33C2, 84O5, 22O3, 24O2, 52O1, 43C1/83C1/83C2, 12C4, and 33C3), one encoded a rat cDNA found repressed in mammary adenocarcinoma in a microarray study [10] but whose function is not defined yet (11O4), two corresponded to rat ESTs (53O2 and 44O1), and three were similar to rat cDNAs either known (53C1 and 41C1) or predicted from the rat genome sequence (24O3). The last two (53O1 and 33C1) were similar to mouse uncharacterised cDNA clones (Table 2). Northern blot analyses confirmed 10 sequences as upregulated and 10 as downregulated in the WAT of high-fat-fed animals. Eight among the upregulated, and four among the downregulated, corresponded to rat genes already known (Table 2). Examples of upregulated (fibrillin-1) and downregulated (lactate dehydrogenase A) genes are shown in Fig. 1.

Table 2
Genes differentially expressed in high-fat-fed animals

DD product	Sequence	mRNA (kb)	Fold change
84O2	Rat Y-box protein 1 (YB-1), mRNA	4.5	130
83O4	IgE receptor β chain (FcεRIβ)	1.8	17
82O2	Rat ribosomal protein L7 mRNA	0.9	8.6
22C8	Rat transferrin mRNA	2.6	6.8
33C2	Rat adiponectin mRNA	2.5	6.6[a]
		1.7	3.0[a]
11O4	Rat mammary tumor 7 (RMT7) mRNA	4.5	3.4
84O5	Rat ribosomal protein S10 (Rps10) mRNA	0.7	3.2
22O3	Rat fibrillin-1 (FBN-1) mRNA	10	2.5
53O2	Rat EST. gb: BF404237	1.8	2.4
24O2	Rat haemoglobin, α1 (Hbα1), mRNA	0.6	2.0
24O3	Similar to LIM domain-binding factor-2. gb: NW_047427	2	−6.7
53O1	Rat clone similar to mouse RIKEN cDNA 5730469M10. gb: NW_047469	1.9	−5.3
53C1	Similar to rat osteoblast specific factor 2 (fasciclin I-like) mRNA	4	−4.8
44O1	Rat EST with moderate similarity to human hypothetical protein (gb: NP_115679) involved in binding sterols. gb: CB323494	2.2	−4.3
52O1	Rat mitochondrial cytochrome oxidase subunit I and serine tRNA	2	−4.3
43C1, 83C1, 83C2	Rat caveolin-2 mRNA	3.2	−3.8
41C1	Rat cDNA clone similar to rat cisplatin resistance-associated overexpressed protein (CROP)	1.9	−3.8
33C3	Rat mitochondrial 16S rRNA	1.8	−3.4
12C4	Rat lactate dehydrogenase A mRNA	1.8	−2.7
33C1	Rat clone similar to mouse RIKEN cDNA 4931406C07 gene. gb: XM_343349	1.9	−2.1

DD product: O, upregulated; C, downregulated in high-fat-fed animals. gb, GenBank accession number. Fold change: ratio between normalized O.D. values from Northern blots, positive for HF/C (upper part) and negative for C/HF (lower part).
[a] 33C2 renders two bands of different sizes.

Caveolins

It has been recently shown that caveolin-1 null mice, which have caveolin-2 expression severely reduced, are resistant to diet-induced obesity and show adipocyte abnormalities and hypertriglyceridemia [11]. Since caveolin-2 is one of the genes downregulated (−3.8 fold change) in this study, we have compared the expression level of caveolin-1 and 2 in control and high-fat-fed animals by Northern blot. A caveolin-1 specific probe was prepared by RT-PCR with primers based on the sequence available in the databases. Our results showed that the expression pattern of caveolin-1 is the opposite of caveolin-2, being upregulated (2.21 fold change) in the animals fed with the high-fat cafeteria diet (Fig. 1).

Discussion

Northern blot analysis confirmed the differential expression of only 22 of the 76 isolated DD-PCR products, but for six of them the difference in expression was in the opposite sense as detected initially. The sequences of some of these 22 products correspond to EST or cDNA clones not yet characterised, while others are similar to known genes or proteins (Table 2). The rest of the sequences correspond to known rat genes and among them we find two ribosomal proteins (L7 and S10), that were upregulated, and two mitochondrial genes (16S rRNA and cytochrome oxidase subunit I-serine tRNA), that were downregulated, in the WAT of the high-fat-fed animals.

Although ribosomal proteins and mitochondrial genes are considered housekeeping genes, is not unusual that they experience transcriptional regulation during differentiation and in response to specific stimuli, such as continuous muscle contraction [12].

Genes upregulated in WAT of high-fat-fed animals

Of the genes upregulated in WAT of cafeteria-fed animals, adiponectin is very representative since it is one of the main genes involved in obesity and therefore validates our approach as a method to search for new candidate obesity-related genes. The increase in adiponectin expression that we observe after 11 days of a high-fat diet is in agreement with the previous finding that adiponectin is induced in early stages of adipocyte differentiation [13] and might be part of an initial defensive response against obesity. On the other hand, it is well documented that adiponectin expression is reduced after a longer period when obesity and associated diabetes are already established [14]. Nevertheless, differences in gene expression have also been found as a consequence of differences in gender, period of feeding, and anatomical location of the adipose tissue [15].

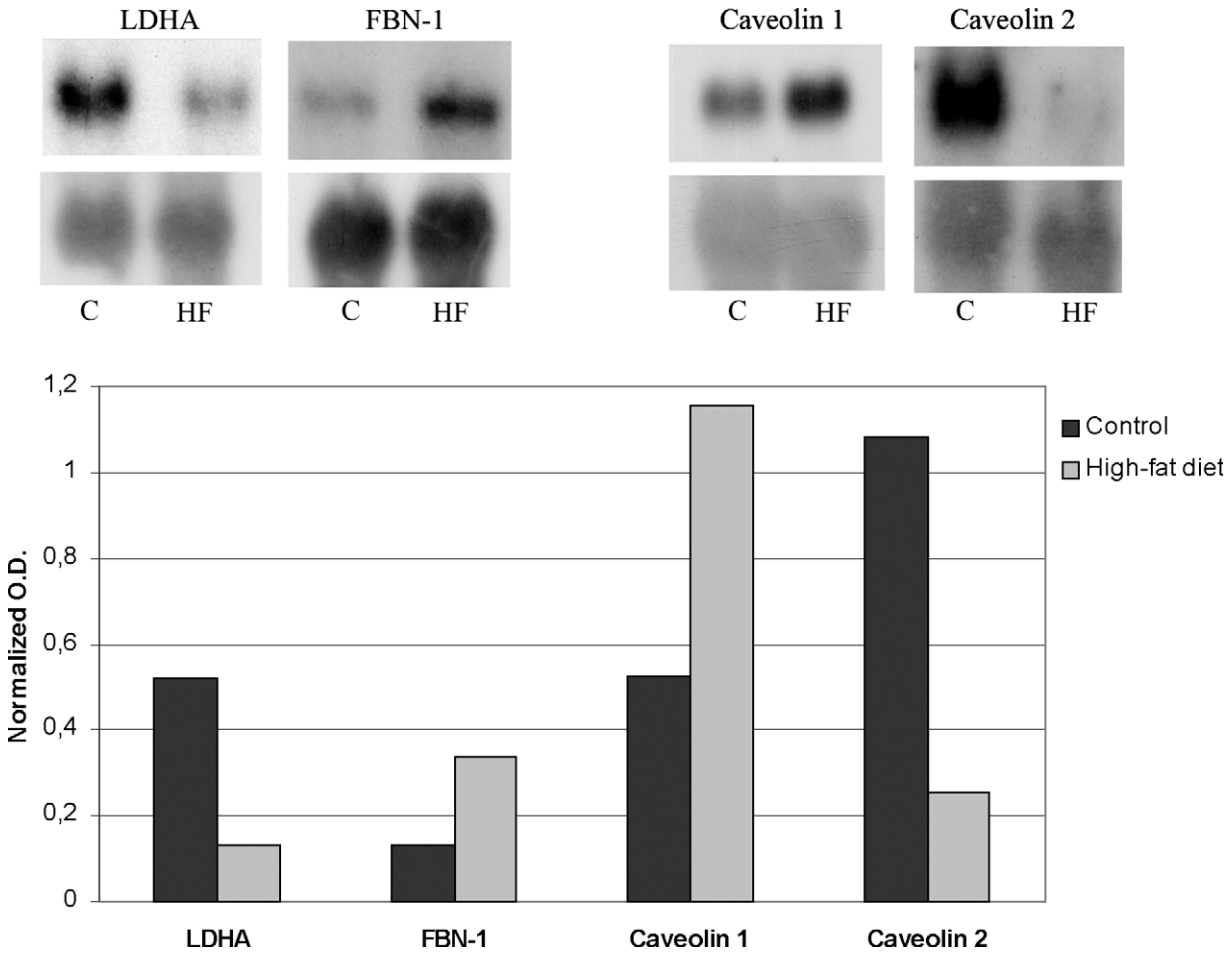

Fig. 1. Representative Northern blots of a downregulated (lactate dehydrogenase A, LDH-A) and a upregulated (fibrillin-1, FBN-1) genes and of caveolin-1 and 2 from rat visceral white adipose tissue. C, control; HF, high-fat diet.

In agreement with our study, microarray analyses using the WAT of diet-induced obese mice have previously shown the upregulation of fibrillin-1 gene [16]. Fibrillin-1 provides mostly force-bearing structural support but it has also been related with tissue homeostasis [17] since extracellular matrix is linked to the nucleus by cytoskeletal fibres facilitating hormonal signal transduction [18]. During adipose tissue enlargement structural changes take place that may affect cytoskeleton and extracellular matrix protein expression. With regard to this, it has been shown that cytoskeleton nonmuscle-type cofilin is differentially expressed in visceral WAT and may play a role in lipid accumulation [19].

We have also detected that transferrin expression is upregulated in the high-fat diet group, in agreement with a previous observation where this gene was overexpressed in adipocytes when compared to preadipocytes in in vivo and in vitro studies [20]. These results suggest that high-fat diet intake induces changes in iron metabolism that include transferrin gene regulation, possibly related to the higher iron content of cafeteria diet. Accordingly a recent report has also found a correlation between obesity and genes for iron homeostasis in the adipose tissue of BSB mice [21]. Furthermore, in other studies with genetically obese models, *ob*/*ob* mice were shown to absorb and retain approximately twice as much iron as lean mice [22], and Zucker rats presented higher concentration of iron in muscle than lean controls [23]. Insulin, that is usually elevated in these models of obesity, increases iron uptake by adipocytes [24] and stimulates transferrin mRNA synthesis in Sartoli cells [25]. Therefore, changes in iron metabolism related to a high-fat diet may be accompanied with changes in the expression level of important iron transport proteins such as transferrin.

The Y-box protein 1 (YB-1) gene shows the strongest induction (130-fold) in the WAT of the cafeteria-diet fed animals (Table 2). YB-1 protein is a DNA and RNA binding protein that controls specific gene expression positively or negatively at both transcriptional and translational levels [26], and therefore, it can have multiple effects on different targets. With regard to this, it has been reported that transcription factor YB-1

induces protein tyrosine phosphatase PTP1B expression by binding directly to its promoter [27], and that inactivation of this enzyme is related to obesity resistance. Studies in mice fed with a high-fat diet show that inhibition of PTP1B results in increased phosphorylation of the insulin receptor inducing enhanced sensitivity to insulin which elevates basal metabolic rate and energy expenditure and favours resistance to obesity [28]. Other reports show that PTP1B may be involved in the resistance to leptin associated with obesity [29]. Therefore, and despite it has not been definitively demonstrated that increasing PTP1B level or activity could promote obesity, all these data make our finding very interesting, since YB-1 can induce PTP1B transcription.

It is also interesting that YB-1 interacts with the protein IRP2 preventing it from binding to the iron response element (IRE) of ferritin mRNA which in turn would block its translation [30]. Thus, YB-1 can mediate an increase in the translation of ferritin and this may be relevant in the context of an altered iron metabolism, since as stated before, we have seen an upregulation of transferrin.

Another highly overexpressed (17 fold change) gene in WAT of the high-fat-fed animals is the IgE receptor β chain (FcεRIβ) which is part of a tetrameric receptor complex (α, β, and γ_2) that binds IgE-bound antigens leading to inflammatory responses. In this context, it is interesting that obesity has been considered as an inflammatory disorder, since adipocytes can secrete pro- and anti-inflammatory factors such as adiponectin TNFα, and several types of interleukins [31].

The α-1 chain of haemoglobin is in the limit of significant overexpression (2 fold change). This protein has not been related with obesity, but a special type of haemoglobin called HbA1c which binds glucose is increased two to three times in diabetes mellitus patients becoming a marker of hyperglycaemia.

Genes downregulated in WAT of high-fat-fed animals

One of the most interesting genes found as downregulated is caveolin-2, which together with caveolin-1, is a building block of caveolae. These membrane structures are particularly abundant in adipocytes and lung endothelial cells, and have been implicated in endocytosis, signal transduction [32], and glucose homeostasis [33]. Recently, caveolin-1 deficient mice were shown to present abnormalities in lipid metabolism that prevent a correct triglyceride storage in adipose tissue, making them somehow resistant to obesity [11]. On the other hand, caveolin-2 deficient mice have normal weight, adipose tissue morphology, and serum metabolites [34], although they suffer from exercise intolerance. Interestingly, our results suggest that the expression of both caveolins is counterbalanced and caveolin-1 becomes upregulated while caveolin-2 is downregulated in the WAT of animals fed on the high-fat diet for 11 days. All these data indicate that caveolins have a role in lipid metabolism and storage and point them as candidate genes involved in diet-induced obesity.

Another interesting downregulated gene is lactate dehydrogenase A (LDH-A) suggesting a decreased anaerobic degradation of glucose in adipose tissue. As a result, pyruvate would be directed to acetyl-CoA production, which in turn would fuel fatty acid biosynthesis and triglyceride storage. However, it has also been reported that in differentiated adipocytes long-term regulation may act in the opposite direction, activating or overexpressing LDH-A and therefore reacting against lipid accumulation by deviating pyruvate to lactate [20,35].

In summary, most of the genes identified in this study, whose expression level was modified in the WAT of rats that have been fed during 11 days with a high-fat cafeteria diet, are related to energy metabolism. Furthermore, three of them, adiponectin, LDH-A, and caveolin-2, are directly involved in lipid and/or carbohydrate pathways. In relation to this, it is also important to emphasise that the nature of the data obtained from dietary induced obesity models, like the one used in this work [36], constitute a more physiological approach than those arising from other experimental strategies such as knock-out or genetic models of obesity.

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