Upregulation of Lipogenesis and Protein Tyrosine Phosphatase-1B Expression in the Liver of Wistar Rats with Metabolic Syndrome Chronically Induced by DrinkingSucrose Water

Chun-Yin Huang\(^{a,b}\) Yu-Shun Lin\(^{a}\) Gou-Chun Chen\(^{a}\) Hui-Ling Huang\(^{c}\) Shu-Han Chuang\(^{b}\) Pei-Min Chao\(^{a,b}\)

\(^{a}\)Institute of Nutrition and \(^{b}\)Department of Nutrition, China Medical University, Taichung, and \(^{c}\)Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan, ROC

Key Words
Metabolic syndrome · Sucrose-containing drinking water · Sterol regulatory element-binding protein-1c · Carbohydrate response element-binding protein · Protein tyrosine phosphatase-1B

Abstract
Background: Establishing animal models with metabolic disorders similar to human metabolic syndrome (MS) is important. In terms of eliciting a full array of MS, we have previously shown that Wistar rats are more responsive to sucrose water drinking than are C57BL/6J mice. This study was aimed at investigating the underlying molecular mechanism of sucrose water-induced MS in Wistar rats. Methods: Male Wistar rats were divided into 2 groups (n = 8 for each group) which were given plain water (C group) or 30% sucrose water (SW group) to drink ad libitum. After 20 weeks, the transcriptional levels and protein translocation of hepatic sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP) as well as the protein levels of protein tyrosine phosphatase-1B (PTP-1B) in insulin-responsive tissues (liver, muscle, and adipose tissue) were measured. Results: The sucrose water regimen successfully elicited visceral obesity, hypertriglyceridemia, insulin resistance, and high blood pressure. The upregulation of de novo lipogenesis in the liver of the sucrose water-treated rats was demonstrated by an increased activity of enzymes, mRNA levels of lipogenic proteins, and nuclear levels of SREBP-1c and ChREBP. Moreover, in the sucrose water-treated rats, protein levels of PTP-1B were significantly increased in liver and skeletal muscle but decreased in adipose tissue. Conclusion: The susceptibility of Wistar rats to sucrose water-induced MS is associated with the transactivation of SREBP-1c and ChREBP in the liver, and PTP-1B is involved in the upregulation of de novo lipogenesis in the liver and the pathology of systemic insulin resistance in rats with MS chronically induced by drinking sucrose water.

Introduction
Metabolic syndrome (MS), indicated by the clustering of certain risk factors including insulin resistance, central obesity, hypertension, and dyslipidemia, is a global health problem with a soaring morbidity [1, 2]. For the manage-
ment and prevention of this disease, it is important to establish animal models with metabolic disorders similar to human MS. We and others have shown that symptoms associated with human MS can be elicited in rodents by giving them sucrose water (10–30%) to drink [3–8]. Due to the energy content of sucrose water and a lower satiating effect of liquid carbohydrates compared to solid food [9], sucrose water-treated animals consistently show a reduction in solid food intake but a marked increase in energy consumption [3, 4, 6, 8]. Thus, a situation of a positive energy balance accompanied by a poor nutrient value occurs in response to drinking sucrose water. From this viewpoint, rodents exposed to sucrose-containing drinking water are exposed to a similar environmental temptation as humans (i.e. the overconsumption of empty-calorie foods or sucrose-sweetened beverages) and provide an appropriate diet-induced model for studies on MS [8].

In our previous study [8], a species difference in terms of susceptibility to MS elicited by sucrose water drinking was observed, with the sucrose water regimen causing great metabolic derangement in Wistar rats but having a less aggravating effect in C57BL/6J mice. The predisposition of Wistar rats to sucrose water-induced metabolic disorders might be associated with the inducibility of the expression of sterol regulatory element-binding protein-1c (SREBP-1c) and carbohydrate response element-binding protein (ChREBP), 2 posttranslationally modulated transcriptional factors which play a pivotal role in transforming overloaded carbohydrates into triacylglycerol (TG) [10, 11]. Susceptibility to fructose-induced hepatic steatosis is associated with a single nucleotide polymorphism at bp −468 in the promoter region of SREBP-1c [12]. In a study of 10 strains of inbred mice, the C57BL/6J and DBA strains were found to be resistant to sucrose-/fructose-induced fatty liver because they have adenine instead of guanine at this site, which prevents the increase in liver SREBP-1c mRNA levels in response to a high-fructose diet [12]. With guanine at this site, ddY mice given sucrose water to drink show increased body weight gain and liver lipid accumulation, along with increased mRNA levels for SREBP-1c, ChREBP, and their target genes in the liver [6].

Recently, protein tyrosine phosphatase-1B (PTP-1B) has received significant attention in investigating the pathology of MS. PTP-1B is abundantly expressed in all insulin-responsive tissues and acts as a negative regulator of the tyrosine phosphorylation of the insulin receptor and insulin receptor substrate 1 [13]. Mice lacking PTP-1B not only show a markedly increased insulin sensitivity but are also protected from diet-induced obesity [14–16], implying that PTP-1B is also involved in energy homeostasis. Indeed, PTP-1B has been shown to play substantial roles in leptin resistance and the upregulation of lipogenesis via, respectively, the dephosphorylation of Jak2 in the leptin signaling cascade [16] and the activation of protein phosphatase 2A (PP2A) to enhance SREBP-1c gene expression [17] and ChREBP nuclear translocation [11]. Although PTP-1B overexpression in animals with obesity and insulin resistance is not unexpected, reports of PTP-1B overexpression in tissues of insulin-resistant, obese, and diabetic animals and humans are somewhat inconsistent [18–21].

As the present study was aimed at investigating the underlying molecular mechanism in Wistar rats with MS induced by the chronic administration of sucrose-containing drinking water, the transcriptional levels and protein translocation of hepatic SREBP-1c and ChREBP were examined. Protein levels of PTP-1B in insulin-responsive tissues (liver, muscle, and adipose tissue) in sucrose water-induced MS rats were also measured.

Materials and Methods

Animals and Diets

Sixteen male Wistar rats, aged 7 weeks, were purchased from the National Applied Research Laboratories (Taipei, Taiwan). After acclimation to a standard rodent chow diet [6 g of water, 51 g of crude carbohydrates, 23.5 g of crude protein, 4.5 g of crude lipids, 6 g of crude fiber, and 9 g of ash/100 g diet (14 MJ/kg); Fwusow Industry Co. Ltd., Taichung, Taiwan] for 1 week, the rats were divided into 2 groups which were given plain water (C group) or 30% sucrose in water (SW group) as drinking water. The animals were exposed to a similar environmental temptation to electric sensor to detect blood flow in the tail [BP 2000; Visitech Systems, Apex, N.C., USA] that uses a photoelectric sensor to detect blood flow in the tail [22]; the rats were familiarized with the procedure for 7 days (weeks 18–19) before blood pressure and heart rate recordings were made on day 8. For each rat, at least 1 set of 10 measurements with 9 or more successful readings was obtained. For the measurement of insulin sensitivity, the oral glucose tolerance test (OGTT) and insulin tolerance test (ITT) were performed on rats after 18 weeks on the diets. For the OGTT, the animals were fasted overnight (only plain water was supplied to all animals), and then tail blood was collected before (0 min) and 30, 60, 90, and 120 min after the oral administration of a 2.5 g glucose solution (1.5 g/kg body weight). For the ITT, the animals were fed for 3 h after overnight fasting, and then tail blood was collected before (0 min) and 5, 10, 30, and 60 min
after the intraperitoneal injection of a 0.1 U/ml solution of insulin (0.75 U/kg body weight). The area under the curve for serum glucose (AUC$_\text{glu}$) over 2 or 1 h, respectively, was calculated for the OGTT and the ITT.

**Tissue Sampling and Preparation of Biomedical Indices**

After 20 weeks of treatment, all animals were killed by carbon dioxide asphyxiation. The Lee index, an index of obesity in rodents, was calculated based on body weight and nasoanal length [23]. Blood was collected from the orbital sinus. The visceral fat (epididymal and retroperitoneal fat) was excised and weighed. The liver, gastrocnemius muscle, and epididymal fat tissue were frozen at −70°C for RNA isolation, enzyme activity assay, and immunoblotting. Serum samples were obtained by centrifugation of blood at 3,000 g for 10 min and stored at −20°C for analysis of glucose, insulin, lipids, and leptin. For the measurement of biomedical indices, serum glucose was measured via the glucose oxidase method (Randox Laboratories, Crumlin, UK). TG and cholesterol were measured enzymatically using commercial kits (Randox Laboratories). Enzyme-linked immunosorbent assays were used to measure insulin and leptin in serum (Linco, St. Charles, Mo., USA, and R&D, Minneapolis, Minn., USA, respectively) and TNF-α in adipose homogenate (e Bioscience, San Diego, Calif., USA). A 0.5 cm$^3$ cube of epididymal fat was fixed in 10% formaldehyde, embedded and 60 μm sections, and examined under a light microscope (OLYMPUS IX71) equipped with a SPOT RT Color 2000 digital camera (Diagnostic Instruments, Inc., Sterling Heights, Mich., USA) to obtain images for cell size determination.

**RNA Isolation and mRNA Detection**

Total RNA was extracted from the liver using TRIZOL reagent according to the manufacturer’s instructions (Invitrogen, New York, N.Y., USA). The quality of the extracted RNA was confirmed by a value of 2 for the 28S ribosomal RNA/18S ribosomal RNA ratio after ethidium bromide staining. Levels of mRNA for a house-keeping gene (β-actin) and lipogenic genes [fatty acid synthase (FAS), acetyl-CoA carboxylase-1 (ACC-1), stearoyl-CoA desaturase 1 (SCD1), ChREBP, and SREBP-1c] were measured by real-time PCR. Total RNA (1 μg) was reverse transcribed into first-strand cDNA using 200 U of MMLV-RT (Promega, Madison, Wis., USA). PCR was performed using 50 ng of cDNA, 2X SYBR® Green PCR Master Mix (Applied Biosystems, Foster, Calif., USA), and 200 nM of the primer pair in a total volume of 25 μl. The sequences of the PCR primers used for ACC-1, FAS, SREBP-1c, and β- actin have been described previously [24, 25]. The ChREBP primer sequences used were 5’-TGATGCCTGAA-TACCACAACT-3’ (forward) and 5’-CTGCTTGAGCCAGGAA-3’ (reverse). For SCD1, the inventory primer and probe (Applied Biosystems) were used following a TaqMan gene expression assay. Amplification using 40 cycles of 2 steps (95°C for 15 s and 60°C for 1 min) was performed on an ABI Prism TM model 7900HT sequence detection system. To confirm the amplification of specific transcripts, melting curve profiles were produced at the end of each run.

**ACC and FAS Activity**

The liver was homogenized at 4°C in 10 mM potassium phosphate buffer containing 0.25 M sucrose, 5 mM 2-mercaptoethanol, 1 mM EDTA, and 1% protease inhibitor cocktail (Sigma, Saint Louis, Mo., USA). After centrifugation at 13,000 g for 45 min at 4°C, the supernatant was collected for enzyme activity assays. ACC activity was measured using the $^{14}$CO$_2$ fixation method [26] and FAS activity was measured using a spectrophotometric method [27]. The details of these assays have been described by Chen et al. [28]. One unit of ACC activity is defined as the amount which catalyzes the formation of 1 μmol of malonyl-CoA per minute. One unit of FAS activity is defined as the amount required to synthesize 1 nmol of palmitic acid (equivalent to the oxidation of 14 nmol of NADPH) per minute. The protein content of the liver extract was determined using the Bradford method.

**Immunoblotting**

For ChREBP and SREBP-1 immunoblots, a liver homogenate was prepared as described above and nuclear and cytosolic proteins separated using NE-PER™ Nuclear and Cytoplasmic Extraction Reagents (Pierce, Rockford, Ill., USA). For PTP-1B immunoblots, a whole tissue homogenate from liver, skeletal muscle, or epididymal fat was used. Briefly, 80 μg (cytosolic fraction) or 50 μg (nuclear fraction or whole tissue homogenate) of protein was subjected to electrophoresis on 10% SDS gels, transferred to a polyvinylidene fluoride-plus transfer membrane (NE Life Science, Boston, Mass., USA), and immunoblotted. The primary antibodies used were rabbit antibodies against mouse SREBP-1 (Affinity Bioreagents, Golden, Colo., USA), mouse ChREBP (Novus Biologicals, Littleton, Colo., USA), and mouse PTP-1B (Upstate, Lake Placid, N.Y., USA). Mouse antibodies against chicken β-acin or human histone H1 protein (Chemicon International, Temecula, Calif., USA) were used to verify the cytosolic and nuclear fractions obtained since β-acin and histone are, respectively, specifically located in the cytosol or nucleus. Horseradish peroxidase-labeled donkey anti-rabbit immunoglobulin G or horseradish peroxidase-labeled goat anti-mouse immunoglobulin G antibodies (Amersham International, Amersham, UK) were used as the secondary antibody. Bound antibodies were detected using an enhanced chemiluminescence Western blotting kit (Amersham International) and the images quantified by densitometric analysis using a Multimage Light Cabinet (Alpha Innotech Corporation, San Leandro, Calif., USA).

**Statistical Analysis**

Data are expressed as means ± SD. The significance of differences between the experimental group and the control group was analyzed using Student’s t test. The data were transformed to log values for the statistical analysis if the variances were not homogeneous. The General Linear Model of the SAS package (SAS institute, Cary, N.C., USA) was used for both statistical analyses. p < 0.05 was considered statistically significant.

**Results**

Table 1 shows the bioindexes associated with MS in Wistar rats given plain water (C group) or sucrose water (SW group) to drink for 20 weeks. Indexes associated with obesity, including body weight, the Lee index, and relative visceral fat weight, were all significantly increased by the administration of sucrose water. Insulin resistance
was evidenced in the SW group by the significant increase in serum levels of insulin and the impaired glucose-lowering effect during OGTT and ITT (the AUC<sub>glu</sub> values for the OGTT and ITT were significantly higher in the SW group than in the C group). In addition, hypertriglyceridemia and hypertension were observed in the SW group. An increase in serum leptin levels and caloric intake (88 ± 15 vs. 108 ± 19 kcal/day, C vs. SW; p < 0.05) was also observed, implying that leptin resistance developed in sucrose water-treated rats. The TNF-α protein levels and cell size in epididymal fat were also measured and it was found that both were significantly increased in the SW group (4.5 ± 2.4 vs. 8.8 ± 4.0 ng/mg protein for TNF-α and 93 ± 40 vs. 152 ± 17 μm for adipocyte diameter, C vs. SW; both p < 0.05).

To test whether de novo lipogenesis was upregulated in sucrose-fed rats, FAS and ACC enzyme activity and mRNA levels for FAS, ACC, SCD1 and their transcriptional regulators, SREBP-1c and ChREBP, were measured. As expected, the SW group had significantly higher enzyme activities and mRNA levels for these lipogenic genes than did the C group (table 2).

Furthermore, the SW group showed a significant increase in nuclear levels of ChREBP and SREBP-1c compared to the C group (fig. 1b). The cytosolic and nuclear fractions obtained from rat liver were verified by positive staining for β-actin or histone, respectively (fig. 1a), and by negative staining for the other marker (data not shown). For PTP-1B protein levels in insulin-responsive tissues, sucrose water caused a significant increase in liver and muscle, but a significant decrease was seen in epididymal fat (fig. 2).

**Discussion**

In the present study, giving Wistar rats sucrose water to drink elicited a full array of MS as previously reported [3–8]. As expected, being a strain responsive to sucrose water-induced metabolic derangement, Wistar rats subjected to sucrose water drinking show an increase in de novo lipogenesis accompanied by transactivations of SREBP-1c and ChREBP in the liver. The increase in PTP-1B in liver and muscle might be attributed to the upregulation of de novo lipogenesis and the pathology of systemic insulin resistance. However, downregulated PTP-1B protein levels in adipose tissue were seen in these rats with sucrose water-induced MS. The Wistar rat is a strain not genetically susceptible to obesity or diabetes. Therefore, the model used in the present study is an environmentally acquired MS model which simulates the habitual consumption of sucrose-sweetened beverages commonly seen in modern human life and successfully produces a situation with excess energy intake and an inadequate nutritional status, which are the dietary factors attributed to the epidemic of MS [29, 30].

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**Table 1.** Bioindexes associated with MS in Wistar rats given plain water (C group) or sucrose water (SW group) to drink

<table>
<thead>
<tr>
<th></th>
<th>C group</th>
<th>SW group</th>
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<tbody>
<tr>
<td>Body weight, g</td>
<td>469 ± 32</td>
<td>714 ± 87***</td>
</tr>
<tr>
<td>Lee index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>325.05 ± 11.85</td>
<td>341.91 ± 11.22*</td>
</tr>
<tr>
<td>Relative visceral fat weight&lt;sup&gt;b&lt;/sup&gt;, %</td>
<td>2.95 ± 0.87</td>
<td>7.76 ± 1.68***</td>
</tr>
<tr>
<td>Serum leptin, μg/l</td>
<td>1.16 ± 0.57</td>
<td>6.03 ± 2.43***</td>
</tr>
<tr>
<td>Serum TG, mM</td>
<td>1.31 ± 0.29</td>
<td>2.06 ± 0.77*</td>
</tr>
<tr>
<td>Serum cholesterol, mM</td>
<td>1.33 ± 0.49</td>
<td>1.65 ± 0.35</td>
</tr>
<tr>
<td>Serum insulin, pM</td>
<td>0.54 ± 0.14</td>
<td>1.28 ± 0.70*</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;glu&lt;/sub&gt; for the OGTT&lt;sup&gt;c&lt;/sup&gt;, mmol · min/l</td>
<td>686 ± 67</td>
<td>807 ± 89*</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;glu&lt;/sub&gt; for the ITT&lt;sup&gt;c&lt;/sup&gt;, mmol · min/l</td>
<td>468 ± 29</td>
<td>679 ± 26*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>90 ± 43</td>
<td>128 ± 27*</td>
</tr>
</tbody>
</table>

The values are means ± SD (n = 8). The significance of differences between groups was analyzed using Student’s t test.

* p < 0.05; ** p < 0.01; *** p < 0.0001.

<sup>a</sup> Body weight (g)³⁄₂/nasoanal length (cm) × 1,000.

<sup>b</sup> Visceral fat weight (sum of the epididymal and retroperitoneal fats)/body weight × 100.

<sup>c</sup> AUC<sub>glu</sub> over the 2 or 1 h of the OGTT or ITT, respectively.

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**Table 2.** ACC and FAS enzyme activity and mRNA levels of lipogenic genes in Wistar rats given plain water (C group) or sucrose water (SW group) to drink

<table>
<thead>
<tr>
<th></th>
<th>C group</th>
<th>SW group</th>
</tr>
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<tbody>
<tr>
<td>Enzyme activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACC, U/mg protein</td>
<td>1.83 ± 1.39</td>
<td>3.68 ± 2.63***</td>
</tr>
<tr>
<td>FAS, U/mg protein</td>
<td>0.05 ± 0.02</td>
<td>0.30 ± 0.06***</td>
</tr>
<tr>
<td>mRNA levels (relative to the C group)</td>
<td></td>
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<tr>
<td>ACC1</td>
<td>1.03 ± 0.31</td>
<td>1.60 ± 0.77*</td>
</tr>
<tr>
<td>FAS</td>
<td>1.04 ± 0.35</td>
<td>2.27 ± 1.00*</td>
</tr>
<tr>
<td>SCD1</td>
<td>1.00 ± 0.37</td>
<td>1.85 ± 0.70*</td>
</tr>
<tr>
<td>SREBP-1c</td>
<td>1.07 ± 0.39</td>
<td>3.12 ± 0.68***</td>
</tr>
<tr>
<td>ChREBP</td>
<td>1.02 ± 0.22</td>
<td>2.52 ± 0.74**</td>
</tr>
</tbody>
</table>

The values are means ± SD (n = 8). The significance of differences between groups was analyzed using Student’s t test.

* p < 0.05; ** p < 0.01; *** p < 0.0001.
Although the transcriptional induction and translocation of SREBP-1c and ChREBP by glucose/fructose and insulin have been well studied in hepatocyte cell cultures [10, 11, 31, 32], different inducing effects of simple sugars on hepatic SREBP-1c have been observed in vivo due to the genetic diversity of the animals used. We have previously shown that Wistar rats are more responsive to a sucrose water regimen than are C57BL/6J mice in terms of eliciting a full array of MS [8]. The induction effects on SREBP-1c might contribute to the susceptibility of animals to simple sugar-induced metabolic derangement. C57BL/6J mice are considered to be resistant to sucrose treatment in terms of the development of obesity and insulin resistance [33, 34]. A fructose-rich diet also fails to induce liver steatosis in C57BL/6J and DBA mice [12]. This failure has been attributed to a single nucleotide polymorphism in the SREBP gene in these mice which prevents the increase in liver SREBP-1c mRNA levels in response to a high-fructose diet [12]. Therefore, it might be advisable for human subjects carrying the genetic polymorphism on the SREBP-1c promoter, which is responsive to sugar induction, to restrain the consumption of sugar-sweetened beverages.

SREBP-1c acts in synergy with ChREBP to upregulate lipogenic gene expression in response to carbohydrate feeding. The genes transcriptionally regulated by both factors include those coding for an array of enzymes participating in lipogenesis (FAS, ACC-1, SCD, and S14) and glycolysis (glucokinase and L-type pyruvate kinase) [10, 11]. Insulin has been reported to increase the mRNA levels of SREBP-1c and its proteolytic cleavage for nuclear import [35]. In addition, glucose has been documented to transactivate SREBP-1c in an insulin-independent manner [36, 37]. ChREBP gene expression in the mouse hepatocyte is stimulated by glucose and insulin [11, 38], and the nuclear transport of the dephosphorylated form of the protein involves PP2A activation by glucose metabolites [32].
de novo lipogenesis in the liver of sucrose water-treated rats was demonstrated by a significant increase in nuclear levels of SREBP-1c and ChREBP as well as mRNA levels of their target genes and the enzymatic activity of the corresponding proteins. We believe that hepatic SREBP-1c and ChREBP were initially transacti vated by glucose/fructose (from sucrose) and insulin in serum, which were present at persistently high levels due to sucrose administration. However, an alternative mechanism is required to explain the continued high expression of lipogenic genes under conditions of chronic hyperinsulinemia and insulin resistance. By activating PP2A, PTP-1B enhances SREBP-1c mRNA expressions through activation of the Spl site [17] and increases the nuclear import of ChREBP [11]. In the present study, increased PTP-1B protein levels were observed in the liver and muscle, but not in the adipose tissue, of rats chronically exposed to sucrose water to drink.

PTP-1B has been implicated as a tissue-specific regulator of insulin sensitivity. Overexpression of PTP-1B by adenovirus infection in Fao hepatoma and L6 myocyte cells results in liver resistance and inflammation, and TNF-α protein levels were observed in the liver and muscle, but not in the adipose tissue, of rats chronically exposed to sucrose water to drink. Zabolotny et al. [18] reported that high-fat feeding of mice resulted in increased PTP-1B protein levels in adipose, liver, muscle, and the arcuate nucleus of the hypothalamus. PTP-1B overexpression in adipose, liver, and muscle. Mice lacking a functional PTP-1B gene exhibit an increased insulin sensitivity in the liver and skeletal muscle, but not in fat tissue [14]. When PTP-1B expression in adipose tissue of ob/ob mice was suppressed by antisense oligonucleotide treatment, insulin sensitivity measured by protein kinase B phosphorylation was not improved [40]. The role of PTP-1B in adipose tissue is not as clear as in liver and muscle. Zabolotny et al. [18] reported that high-fat feeding of mice results in increased PTP-1B protein levels in adipose, liver, muscle, and the arcuate nucleus of the hypothalamus. PTP-1B overexpression in adipose tissue of high-fat fed mice coincides with obesity-mediated inflammation, and TNF-α was shown to activate the PTP-1B promoter through the nuclear factor κB pathway [18]. In the present study, TNF-α protein levels and cell size in epididymal fat were significantly increased in the SW group. However, PTP-1B protein levels decreased, instead of increasing, in the adipose tissue of sucrose-fed rats.

In the present study, overexpression of PTP-1B in the liver contributed not only to the upregulation of de novo lipogenesis and insulin resistance but also possibly to hypertriglyceridemia in sucrose-fed rats. PTP-1B overexpression contributes to VLDL-apoB overproduction by reducing apoB degradation since the increase in PTP-1B in the liver of fructose-fed hamsters coincides with the marked suppression of ER-60, a cysteine protease involved in intracellular apoB degradation [41]. Thus, in sucrose-fed rats, due to the increased synthesis and output of TG in the liver, TG overflow to other tissues and contribute to the accumulation of adipose fat. This might explain the lack of PTP-1B induction in adipose tissue seen in this study since de novo lipogenesis in the adipose tissue of sucrose-fed rats, which is suppressed, is not responsible for augmenting fat deposition.

The increase in SCD1 gene expression might also contribute to the upregulation of de novo lipogenesis in sucrose-fed rats. The importance of SCD1, also known as Δ9 desaturase, in carbohydrate-induced adiposity and hepatic steatosis is demonstrated by the fact that sucrose- or fructose-induced lipogenic gene expression is abolished in mice deficient in SCD1 but is preserved in mice deficient in SREBP-1c [42, 43]. An SREBP-1c-independent regulation of fructose-induced lipogenesis is postulated which involves a direct transactivation of the SCD1 gene by dietary factors and the enzyme product, C18:1, acting as a stimulator of lipogenic gene expression [42, 43]. The sucrose water-mediated induction of SCD1 mRNA observed in the present study (table 2) might also explain the finding of El Hafidi et al. [3], who attributed the sucrose water-induced high blood pressure to an increase in Δ9-desaturase activity and a decrease in Δ5-desaturase activity in the liver. Since an increase in oleic acid and a decrease in arachidonic acid in the phospholipids of liver microsomes in sucrose-fed rats was seen in their study, the observed disordering of the membrane and prostaglandin synthesis defect are thought to be involved in the elevation of blood pressure [3].

In conclusion, this study investigated the underlying molecular mechanism of sucrose water-induced MS in Wistar rats. As expected, in response to sucrose-containing drinking water, Wistar rats, a species responsive to sucrose-induced MS, showed a significant increase in gene expression and nuclear levels of hepatic SREBP-1c and ChREBP and consequent increases in lipogenic gene expression. The increase in PTP-1B protein levels in the liver and muscle of sucrose water-treated rats is in accordance with the upregulation of de novo lipogenesis in the liver and the pathology of systemic insulin resistance.

Acknowledgement

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Disclosure Statement

There is no conflict of interest that should be declared for this paper.
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