Increased muscular dehydroepiandrosterone levels are associated with improved hyperglycemia in obese rats

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Increased muscular dehydroepiandrosterone levels are associated with improved hyperglycemia in obese rats. Am J Physiol Endocrinol Metab 301: E274–E280, 2011. First published February 1, 2011; doi:10.1152/ajpendo.00564.2010.—This study was undertaken to assess the effects of dehydroepiandrosterone (DHEA) administration and exercise training on muscular DHEA and 5α-dihydrotestosterone (DHT) levels and hyperglycemia in diet-induced obese and hyperglycemic rats. After 14 wk of a high-sucrose diet, obese male Wistar rats were assigned randomly to one of three 6-wk regimens: control, DHEA treatment, or exercise training (running at 25 m/min for 1 h, 5 days/wk; n = 10 each group). Results indicate that either 6 wk of DHEA treatment or exercise training significantly attenuated serum insulin and fasting glucose levels compared with the control group. Plasma and muscle concentrations of DHEA and DHT and expression levels of 5α-reductase were significantly higher in the DHEA-treated and exercise-training groups. Moreover, both DHEA administration and exercise training upregulated GLUT4 translocation with concomitant increases in protein kinase B and protein kinase Cα phosphorylation. Muscle DHEA and DHT concentrations closely correlated with blood glucose levels (DHEA treatment: r = −0.68, P < 0.001; exercise training: r = −0.65, P < 0.001), serum insulin levels, and activation of the GLUT4-regulated signaling pathway. Thus, increased levels of muscle sex steroids may contribute to improved fasting glucose levels via upregulation of GLUT4-regulated signaling in diet-induced obesity and hyperglycemia.

EPIDEMILOGIC, EXPERIMENTAL, AND CLINICAL EVIDENCE has demonstrated that diet-induced obesity and weight gain are closely associated with increased risk of diabetes morbidity, including cardiovascular diseases, hypertension, and dyslipidemia (9). Obesity triples the diabetes morbidity that results from impaired glucose metabolism, such as decreased uptake and utilization in skeletal muscle (9, 10). These effects are mediated, in part, by impaired regulation of glucose transporter-4 (GLUT4); binding of insulin receptor substrate (IRS) is inhibited in skeletal muscle, which downregulates the activities of protein kinase B (Akt) and/or protein kinase Cα (PKCα) via phosphatidylinositol 3-kinase (PI 3-kinase) (14).

Dehydroepiandrosterone (DHEA) and its sulfate derivate (DHEA-S) are precursors of sex steroid hormones. DHEA is converted to testosterone and 5α-dihydrotestosterone (DHT) by 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD, and 5α-reductase. DHEA is most abundantly localized in blood before it is used by target tissues. Several reports have shown that short-term DHEA administration (2 wk) induces an acute decrease in blood glucose levels in type 2 diabetic mice (4–7). Recently, we used cultured muscle cells to demonstrate that DHEA induced local production of testosterone, whereas DHT increased the activation of the GLUT4-regulated signaling pathway (1, 25). Furthermore, using streptozotocin-induced diabetic rats, we showed that a single DHEA injection improved hyperglycemia via enhanced activity in the muscular Akt-PKCα/γ-GLUT4 pathway and increased levels of glucose metabolism-related enzymes such as hexokinase and phosphofructokinase (25, 26). Therefore, DHEA-induced improvements in blood glucose levels in type 2 diabetes and obesity may relate to activation of GLUT4-regulated signaling in skeletal muscle. The molecular mechanisms that govern the effects of long-term DHEA administration on muscular glucose metabolism in obesity and hyperglycemia, however, are still unclear.

Exercise training has also been shown effective in restoring glycemic control and reducing insulin resistance in type 2 diabetes. Increased insulin-mediated glucose transport in response to exercise appears to be related to increased GLUT4 translocation via activation of IRS-1 proteins, PI 3-kinase, Akt, and PKCα/γ (30). Recently, we reported that acute exercise induced an increase in muscle DHEA and DHT levels, which was accompanied by augmented expression of such steroidogenic enzymes as 5α-reductase and 17β-HSD (3). Accordingly, increased DHEA and DHT levels may contribute to exercise-induced enhancement of glucose metabolism signaling in skeletal muscle. Its still unclear, however, whether long-term exercise training increases muscular DHEA and DHT levels or whether such increases help to augment fasting blood glucose levels and glucose metabolism signaling in obesity and hyperglycemia.

Therefore, the purpose of this study was to investigate the relationships among fasting blood glucose and insulin levels, GLUT4 translocation and related signaling, and muscular DHEA and DHT levels after long-term DHEA administration or exercise training in rats with high-sucrose diet-induced obesity and hyperglycemia. In the present study, we used high-sucrose-induced obesity and hyperglycemic rats because these conditions are often caused in humans by long-term poor diet. We investigated the molecular underpinnings of DHEA- and exercise-induced improvements in blood glucose levels in these obese animals.

METHODS

Approval for the study was obtained from the Committee on Animal Care at the University of Tsukuba. Male Wistar rats (220–250 g, 10 wk old) were obtained (Charles River Japan, Kanagawa, Japan) and cared for according to the Guiding Principles for the Care and Use of Animals based on the Declaration of Helsinki. These Wistar rats were fed a high-sucrose diet (10% fructose). Wistar rats were assigned randomly to one of three 6-wk regimens: control, DHEA treatment, or exercise training (running at 25 m/min for 1 h, 5 days/wk; n = 10 each group). Results indicate that either 6 wk of DHEA treatment or exercise training significantly attenuated serum insulin and fasting glucose levels compared with the control group. Plasma and muscle concentrations of DHEA and DHT and expression levels of 5α-reductase were significantly higher in the DHEA-treated and exercise-training groups. Moreover, both DHEA administration and exercise training upregulated GLUT4 translocation with concomitant increases in protein kinase B and protein kinase Cα phosphorylation. Muscle DHEA and DHT concentrations closely correlated with blood glucose levels (DHEA treatment: r = −0.68, P < 0.001; exercise training: r = −0.65, P < 0.001), serum insulin levels, and activation of the GLUT4-regulated signaling pathway. Thus, increased levels of muscle sex steroids may contribute to improved fasting glucose levels via upregulation of GLUT4-regulated signaling in diet-induced obesity and hyperglycemia.

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rats were housed individually in an animal facility under controlled conditions (12:12-h light-dark cycle). To induce obesity and hyperglycemia, the rats were allowed water ad libitum and placed on a purified high-sucrose diet (68% of kcal from sucrose, 20% from protein, and 12% from fat) for 14 wk, which was based on a previous study with minor modifications (9, 17). After 14 wk, the obese animals were randomly assigned to one of three groups: control (n = 10), DHEA administration (n = 10), or exercise training (n = 10). DHEA was obtained from Wako Pure Chemical Industries. Blood samples were taken from the tail vein to obtain prefasting glucose levels. All animals continued the high-sucrose diet during the 6-wk experimental period. DHEA (1 mg/kg body wt) was dissolved in sesame oil and administered orally every day for 6 wk. In the control group, the same amount of vehicle (sesame oil) was administered orally every day. Body weight and dietary intake were measured every week during the experiment. Posttreatment experiments in trained rats were performed 48 h after the last exercise session. After all other measurements were completed, blood was again obtained from the tail vein to assess postfasting glucose levels. Additionally, the soleus and gastrocnemius muscles were quickly removed, weighed, rinsed in ice-cold saline, and frozen in liquid nitrogen.

**Exercise protocol.** Prior to the training period, the exercise training group was trained on a rodent treadmill at 10–15 m/min for 3 days. The rats then ran on the treadmill for 1 h at 25 m/min without incline 5 days/wk for 6 wk. The intensity of the exercise was kept constant during the training period.

**Immunoblot analysis.** Muscle specimens were homogenized in 20 mM Tris-HCl (pH 7.8), 300 mM NaCl, 2 mM ethylenediaminetetraacetic acid (EDTA), 2 mM diithothreitol (DTT), 2% nonidet P-40, 0.2% sodium dodecyl sulfate (SDS), 0.2% sodium deoxycholate, 0.5 mM phenylmethylsulfonyl fluoride, 60 μg/ml aprotinin, and 1 μg/ml leupeptin. Homogenates were rotated slowly for 30 min at 4°C and then centrifuged at 12,000 g for 15 min at 4°C. The protein concentration of the resulting supernatant was determined. Samples (50 μg protein) were denatured at 96°C for 7 min in Laemmli buffer. Western blot analysis was performed to detect phosphorylated Akt and PKC/α as well as GLUT4 protein expression (25, 26). Briefly, each sample was separated on a 10% SDS-polyacrylamide gel and transferred to a polyvinylidene difluoride membrane (Millipore, Billerica, MA). The immobilized polyclonal antibodies were raised by GE Healthcare Biosciences, Piscataway, NJ; Cell Signaling, Beverly, MA) for 1 h at room temperature. The membrane was then washed three times with PBS-T. Finally, GLUT4, phosphorylated Akt, total Akt, and phosphorylated PKC/α were detected using an enhanced chemiluminescence plus system (GE Healthcare Biosciences) and hyperfilm (GE Healthcare Biosciences).

**Preparation of cytosolic and plasma membrane protein fractions.** To assess GLUT4 translocation, two different membrane fractions were used on the basis of our previous studies (25, 26). Briefly, the cells were scraped in buffer A containing (in mM) 20 Tris (pH 7.4), 1 EDTA, 0.25 EGTA, 1 DTT, 50 NaF, 25 sodium pyrophosphate, and 40 β-glycerophosphate and 0.25 M sucrose. The resulting homogenates were centrifuged at 400 g for 15 min to remove debris. The supernatant was centrifuged again at 50,000 rpm for 1 h. The resulting pellet was homogenized in buffer A and used as the cytosol protein fraction. Proteins from different fractions were solubilized for 1 h at room temperature in buffer B containing 20 mM Tris (pH 7.4), 1 mM EDTA, 0.25 mM EGTA, 2% Triton X-100, 50 mM NaF, 25 μM sodium pyrophosphate, and 40 mM β-glycerophosphate. The homogenate was centrifuged briefly, and the supernatant was spun for 1 h at 50,000 rpm before it was used as the plasma membrane fraction. GLUT4 protein levels were measured in both the plasma cytosol and membrane fractions. Translocation was evaluated based on the difference in protein levels in the cytosol and membrane fractions (25, 26).

**Sandwich enzyme immunoassay.** The levels of DHEA, testosterone, and DHT in plasma and skeletal muscle extracts were determined using a sandwich enzyme immunoassay kit (Assay Designs, Ann Arbor, MI). The immobilized polyclonal antibodies were raised against DHEA, testosterone, and DHT, whereas the secondary HRP-coupled antibodies were monoclonal. Optical density at 450 nm was qualified using a microplate reader (BioLumin 960; Molecular Dynamics, Tokyo, Japan). Serum insulin concentrations were also measured using a sandwich enzyme immunoassay kit (Shibayagi, Gunma, Japan).

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**Table 1. Animal characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Lean (n = 10)</th>
<th>Obesity Control (n = 10)</th>
<th>DHEA Treated (n = 10)</th>
<th>Exercise Training (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>348 ± 12.1</td>
<td>712 ± 11.5</td>
<td>619 ± 11.8*</td>
<td>608 ± 12.3*</td>
</tr>
<tr>
<td>Muscle weight, g/body wt soleus</td>
<td>0.38 ± 0.01</td>
<td>0.32 ± 0.02</td>
<td>0.48 ± 0.04*</td>
<td>0.56 ± 0.02*†</td>
</tr>
<tr>
<td>CS activity, μmol/g/min</td>
<td>12.6 ± 1.5</td>
<td>11.2 ± 1.1</td>
<td>13.1 ± 1.4</td>
<td>19.3 ± 2.1*</td>
</tr>
<tr>
<td>Serum insulin, pmol/l</td>
<td>4.91 ± 1.38</td>
<td>8.92 ± 2.42</td>
<td>6.18 ± 2.51*</td>
<td>6.02 ± 2.53*</td>
</tr>
<tr>
<td>Prefasting glucose, mg/dl</td>
<td>84 ± 3.5</td>
<td>154 ± 11.5</td>
<td>159 ± 10.2</td>
<td>162 ± 8.7</td>
</tr>
<tr>
<td>Postfasting glucose, mg/dl</td>
<td>89 ± 2.1</td>
<td>148 ± 10.5</td>
<td>102 ± 9.5*</td>
<td>92 ± 7.8*</td>
</tr>
</tbody>
</table>

Values are means ± SE. DHEA, dehydroepiandrosterone; CS, citrate synthase. Prefasting glucose, fasting glucose before DHEA administration or exercise training; Postfasting glucose, fasting glucose after DHEA administration or exercise training. *P < 0.05 vs. obesity-control group; †P < 0.05 vs. obesity-DHEA group.
Table 2. Plasma sex steroid hormone concentrations

<table>
<thead>
<tr>
<th></th>
<th>Lean (n = 10)</th>
<th>Obesity Control (n = 10)</th>
<th>DHEA Treated (n = 10)</th>
<th>Exercise Training (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA</td>
<td>1.28 ± 0.21</td>
<td>0.71 ± 0.23</td>
<td>1.14 ± 0.31†‡</td>
<td>1.05 ± 0.27*</td>
</tr>
<tr>
<td>Testosterone</td>
<td>0.47 ± 0.08</td>
<td>0.11 ± 0.04</td>
<td>0.38 ± 0.05†‡</td>
<td>0.32 ± 0.06*</td>
</tr>
<tr>
<td>DHT</td>
<td>0.04 ± 0.005</td>
<td>0.018 ± 0.002</td>
<td>0.038 ± 0.004†‡</td>
<td>0.029 ± 0.007*</td>
</tr>
</tbody>
</table>

Values are means ± SE in ng/ml. DHT, dehydrotestosterone. *P < 0.05 vs. obesity-control group; †P < 0.05 vs. obesity-training group.

Japanese. All samples were assayed in duplicate. The coefficient of variation was 3.2 and r² = 0.967 in the present study.

Measurement of citrate synthase activity. Skeletal muscle tissues (50 mg) were homogenized in 10 volumes of 250 mM sucrose, 1 mM Tris-HCl (pH 7.4), and 130 mM NaCl on ice using a Teflon homogenizer. The homogenate was centrifuged at 9,000 g for 20 min at 0°C, and the pellet was resuspended in homogenate buffer and centrifuged at 600 g for 10 min at 0°C. The supernatant was centrifuged at 8,000 g for 15 min at 0°C, and the pellet was resuspended in 250 mM sucrose. To assess citrate synthase activity, which is a rate-limiting step enzyme in the tricarboxylic acid cycle, 50 μl of each sample was incubated for 2 min at 30°C in 900 μl of incubation mixture containing 100 mM Tris-HCl (pH 8.0), 1 mM 5,5'-dithio-bis [2-nitrobenzoic acid], and 10 mM acetyl-CoA. The reaction was initiated by adding 50 μl of 10 mM oxaloacetate, and the output was assessed spectrophotometrically at 412 nm for 3 min (11).

Statistical analysis. All values are expressed as means ± SE. Statistical evaluations were performed using two-way ANOVA. A post hoc comparison test was used to correct for multiple comparisons (Bonferroni test) when analyses revealed significant differences. For ANOVA, P < 0.01 was considered significant. Relationships between sex steroid hormone concentrations and serum insulin, blood glucose levels, and activation of glucose metabolism signaling were determined using Pearson correlation coefficients.

RESULTS

Animal characteristics. Both DHEA administration and exercise training significantly attenuated body weight compared with the control group (Table 1). Exercise training and DHEA administration did not modify caloric intake compared with obese-control. Average caloric intake during the 6 wk was 74.07 ± 0.74 kcal in the control group, 74.42 ± 0.78 kcal in the DHEA group, and 74.09 ± 0.76 kcal in the exercise group.

No significant differences were found among the groups before and during exercise or before and during DHEA administration (Fig. 1). Moreover, a marked increase in soleus muscle weight was observed in the DHEA-treated and exercise-training groups compared with the control group. Citrate synthase activity in soleus muscle was significantly higher in the exercise-training group than in the other groups. Serum insulin and fasting blood glucose levels were significantly lower in the DHEA-treated and exercise-training groups after 6 wk (Table 1). No significant differences were detected between the DHEA-treated and exercise-training groups, however.

Sex steroid hormone levels and expression of 5α-reductase. Plasma DHEA, testosterone, and DHT levels were significantly higher in the DHEA-treated group than in the control and exercise-training groups. Furthermore, sex steroid hormone levels were higher in the exercise-training group than in the control group, whereas no significant difference was observed between the DHEA-treated and exercise-training groups (Table 2). Compared with the control group, intramuscular DHEA and DHT levels were significantly higher in both the DHEA-treated and exercise-training groups and were similar to levels observed in a healthy lean group of animals (Fig. 2, A and B). Similar results were obtained for the expression of 5α-reductase (Fig. 3), although again there was no significant difference between the DHEA-treated and exercise-training groups.

Akt and PKCζ/λ phosphorylation. Akt phosphorylation was significantly lower in obese-control animals. On the other hand, Akt phosphorylation levels in the DHEA-treated and exercise-training groups were similar to those detected in the healthy lean group (Fig. 4A). Additionally, PKCζ/λ phosphory-
which was evaluated by assessing the difference between A). GLUT4 translocation,pared with the control group (Fig. 5
DHEA-treated and exercise-training intervention groups com-
membrane levels of GLUT4 were significantly higher in the
ences in Akt and PKC /
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bottom
/h9251
bottom
/h9261
changes in Akt and PKC

Relationship between sex steroid hormones and glucose metabolism indexes. Significant correlations were detected be-
tween muscular DHEA and DHT levels and fasting glucose levels (DHEA treatment: \( r = -0.68, r = -0.71, P < 0.001 \); exercise training: \( r = -0.65, r = -0.67, P < 0.001 \); serum insulin levels (DHEA treatment: \( r = -0.66, r = -0.68, P < 0.001 \); exercise training: \( r = -0.73, r = -0.77, P < 0.001 \); Akt phosphorylation (DHEA: \( r = 0.68, r = 0.71, P < 0.001 \); exercise training: \( r = 0.61, r = 0.63, P < 0.001 \); PKC\(/\alpha\) (DHEA treatment: \( r = 0.62, r = 0.65, P < 0.001 \); exercise training: \( r = 0.59, r = 0.62, P < 0.001 \); and GLUT4 translocation (DHEA treatment: \( r = 0.72, r = 0.69, P < 0.001 \); exercise training: \( r = 0.74, r = 0.77, P < 0.001 \).

Looking at parameter correlations among all the groups, muscular DHEA and DHT levels in both the DHEA-treated and exercise-training groups significantly correlated with fasting blood glucose levels, serum insulin levels, Akt phosphorylation, PKC\(/\alpha\) phosphorylation, and GLUT4 translocation (Fig. 6). The slopes of the regression lines for the DHEA-treated and exercise-training intervention groups did not differ significantly.

DISCUSSION

The present study demonstrated that long-term DHEA ad-
administration or exercise training induced significant increases in plasma and muscle DHEA, DHT, and 5\(\alpha\)-reductase levels. Additionally, a significant increase in activation of muscular GLUT4-regulated signaling and decreases in fasting insulin and blood glucose levels were observed in the intervention groups. Interestingly, DHEA and DHT levels significantly

cytosolic and membrane GLUT4 protein levels, was signifi-
cantly enhanced in the DHEA-treated and exercise-training groups (Fig. 5B). Moreover, there was no significant difference in GLUT4 translocation between the intervention groups, which produced results similar to those obtained for healthy lean animals.

GLUT4 expression and translocation. Both cytosolic and membrane levels of GLUT4 were significantly higher in the DHEA-treated and exercise-training intervention groups compared with the control group (Fig. 5A). GLUT4 translocation, which was evaluated by assessing the difference between

![Image](https://via.placeholder.com/150)

**Fig. 3.** Effects of DHEA administration or exercise training on protein expression of 5\(\alpha\)-reductase type 1 in gastrocnemius muscle. Representative immunoblotting images for 5\(\alpha\)-reductase type 1 protein are shown in top. Bottom: statistical analyses of the 5\(\alpha\)-reductase type 1 protein. Blot pictures for each group are shown in duplicate. Data are means ± SE. *P < 0.01 vs. obese-control group.

![Image](https://via.placeholder.com/150)

**Fig. 4.** Effects of DHEA administration or exercise training on Akt and PKC\(/\alpha\) phosphorylation in gastrocnemius muscle. A: representative immunoblotting images for phosphorylated (p-)Akt and total Akt protein are shown in top. Bottom: statistical analyses for levels of phosphorylated Akt protein to total Akt protein. Degree of Akt phosphorylation in skeletal muscle was calculated by dividing the total Akt protein level by the phosphorylated Akt protein level. B: representative immunoblotting images for phosphorylated PKC\(/\alpha\) protein are shown in top. Bottom: statistical analyses for levels of phosphorylated PKC\(/\alpha\) expression. Blot pictures for each group are shown in duplicate. Data are means ± SE. *P < 0.01 vs. obese-control group.
correlated with fasting blood glucose and insulin levels, Akt and PKC phosphorylation, and GLUT4 translocation in the exercise-training group. Of note, no significant differences were observed between DHEA administration and exercise training. These results suggest that both long-term oral administration of DHEA and exercise training restore glucose metabolism through an upregulation of GLUT4-regulated signaling in obese and hyperglycemic rats.

Previous studies showed that DHEA administration induced an acute decrease in blood glucose level in mouse models of type 2 diabetes (4–7), although the underlying molecular mechanism was unclear. In the present study of obese rats with hyperglycemia, DHEA administration activated GLUT4-regulated signaling with increased muscular DHEA and DHT levels. We recently used streptozotocin-induced diabetic rats to demonstrate that a single DHEA injection improved hyperglycemia with increased glycolytic enzyme activity via upregulation of muscular GLUT4-regulated signaling; these improvements were abolished by injection of a 5α-reductase inhibitor (26). Thus, changes in muscular DHEA and DHT levels that are related to enhanced glucose uptake and utilization via the Akt-PKC/GLUT4 signaling pathway may contribute to DHEA-induced improvements in hyperglycemia. In fact, DHEA/DHT levels and fasting glucose/insulin levels were negatively correlated. Therefore, in addition to insulin, which is known to decrease blood glucose levels and enhance glucose metabolism, DHEA may also function as a hormone that regulates blood glucose via the GLUT4-regulated signaling.

We also found that long-term exercise training increased resting levels of muscle DHEA and GLUT4-regulated signaling with a concomitant restoration of fasting glucose and insulin levels. Recently, we reported that acute exercise caused an increase in muscle DHEA and DHT as well as protein expression of 3β-HSD, 17β-HSD, and 5α-reductase, which convert DHEA and testosterone to DHT (2, 3). In our obese rats, long-term exercise training elevated basal muscular DHEA and DHT levels together with 5α-reductase protein levels. Thus, it appears that basal muscular steroidogenesis was enhanced by chronic exercise. However, obesity is characterized by lower production of androgens by gonads. DHEA, testosterone, and DHT are produced and synthesized in various tissues, however. Although both acute and chronic exercise training as well as DHEA administration increased muscular level of sex steroid hormones, the mechanism of such increases in muscular sex steroid hormones is still unclear.

![Fig. 5. Effects of DHEA administration or exercise training on GLUT4 protein expression and translocation in gastrocnemius muscle. A: representative immunoblotting images for GLUT4 proteins in cytosol and membrane are depicted in top. Bottom: statistical analyses of GLUT4 protein expression levels assessed using densitometry. B: level of GLUT4 translocation was calculated by assessing the difference in GLUT4 protein levels between cytosol and membrane fractions. Blot pictures for each group are shown in duplicate. Data are means ± SE. *P < 0.01 vs. obese-control group.](image)
Exercise training in rats increased GLUT4-regulated signaling, including IRS-1-associated PI 3-kinase, Akt, and PKC activity, and enhanced glucose uptake in the skeletal muscle via increased GLUT4 translocation (15). Obese individuals with type 2 diabetes generally demonstrate impaired activation of this signaling pathway (28). In the present study, exercise training improved hyperglycemia in obese rats. Therefore, exercise training is likely beneficial for patients with insulin resistance, in part because of its effects on GLUT4 translocation in skeletal muscle (10).

Patients with metabolic syndrome generally show lower DHEA and DHEA-S levels (4, 22–24), which mirrors the reduced muscle DHEA and DHT concentrations and 5α-reductase protein expression that we observed in obese rats. Decreased DHEA levels in obesity and type 2 diabetes may result from insulin-induced inhibition of adrenal 17,20-lyase activity, a key enzymatic step in adrenal androgen synthesis (14). The expressions of four steroidogenic enzymes, 3β-HSD, 17β-HSD, 5α-reductase, and P450 aromatase, have been detected in skeletal muscle; these enzymes synthesize testosterone, DHT, and estrogen from DHEA (1, 25). Thus, DHEA administration and exercise may promote testosterone and DHT synthesis from circulating DHEA-S. We found that chronic DHEA administration also improved fasting glucose and serum insulin levels via Akt-PKC/β-GLUT4 signaling; the achieved levels matched those observed in the exercise-training group or healthy lean animals without changing daily caloric intake. In the present study, we measured daily caloric intake, and DHEA did not significantly increase food intake compared with the obesity-control group. Moreover, contrary to the significant increase in citrate synthase activity seen in training group, no such change was observed by DHEA administration, indicating no vigorous physical activity by the DHEA group. However, we did not assess energy expenditure directly. Furthermore, correlations were not significantly different between DHEA administration and exercise training. Increasing basal DHEA and DHT levels using long-term DHEA administration might be beneficial for the treatment of hyperinsulinemia and hyperglycemia. According to Villareal et al. (29), DHEA administration for elderly people was beneficial for improve insulin sensitivity and body composition. In contrast, there are several studies that DHEA administration for the elderly found no effects in body composition or fasting level of insulin and glucose (13, 21). Thus, the study of DHEA administration for humans is not convincing.

In conclusion, results of this study demonstrated that 6 wk of DHEA treatment or exercise training increased basal levels of sex steroid hormones and produced beneficial effects on muscle glucose metabolism-related signaling in obese rats. Furthermore, improvements in blood glucose and insulin levels may be associated with DHEA and DHT concentrations in skeletal muscle.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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