Effect of voluntary exercise on peripheral tissue glucocorticoid receptor content and the expression and activity of 11β-HSD1 in the Syrian hamster

Agnes E. Coutinho, Jonathan E. Campbell, Sergiu Fediuc, and Michael C. Riddell
Department of Kinesiology and Health Science, York University, Toronto, Ontario, Canada

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Coutinho, Agnes E., Jonathan E. Campbell, Sergiu Fediuc, and Michael C. Riddell. Effect of voluntary exercise on peripheral tissue glucocorticoid receptor content and the expression and activity of 11β-HSD1 in the Syrian hamster. J Appl Physiol 100: 1483–1488, 2006. First published December 15, 2005; doi:10.1152/japplphysiol.01236.2005.—Recent findings indicate that elevated levels of glucocorticoids (GC), governed by the expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) and GC receptors (GR), in visceral adipose tissue and skeletal muscle lead to increased insulin resistance and the metabolic syndrome. Paradoxically, evidence indicates that aerobic exercise attenuates the development of the metabolic syndrome even though it stimulates acute increases in circulating GC levels. To investigate the hypothesis that training alters peripheral GC action to maintain insulin sensitivity, young male hamsters were randomly divided into sedentary (S) and trained (T) groups (n = 8 in each). The T group had 24-h access to running wheels over 4 wk of study. In muscle, T hamsters had lower 11β-HSD1 protein expression (19.2 ± 1.40 vs. 22.2 ± 0.96 optical density, P < 0.05), similar 11β-HSD1 enzyme activity (0.9 ± 0.27% vs. 1.1 ± 0.26), and lower GR protein expression (9.7 ± 1.86 vs. 15.1 ± 1.78 optical density, P < 0.01) than S hamsters. In liver, 11β-HSD1 protein expression tended to be lower in T compared with S (19.2 ± 0.56 vs. 21.4 ± 1.05, P = 0.07), whereas both enzyme activity and GR protein expression were similar. In contrast, visceral adipose tissue contained ~2.7-fold higher 11β-HSD1 enzyme activity in T compared with S (12.9 ± 3.3 vs. 4.8 ± 1.5% conversion, P < 0.05) but was considerably smaller in mass (0.24 ± 0.02 vs. 0.71 ± 0.06 g). Thus the intracellular adaptation of GC regulators to exercise is tissue specific, resulting in decreases in GC action in skeletal muscle and increases in GC action in visceral fat. These adaptations may have important implications in explaining the protective effects of aerobic exercise on insulin resistance and other symptoms of the metabolic syndrome.

Tissue exposure to glucocorticoids (GC) is regulated by several factors including circulating concentrations of the hormone, the activity of the prereceptor enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD), and the expression of the GC receptor (GR). In peripheral tissues, 11β-HSD-type 1 (11β-HSD1) isoenzyme increases local exposure to GC by converting the biologically inactive cortisone [11-dehydrocortico-sterone (11-DHC) in rodents] to active cortisol (corticosterone in rodents) and has been shown to dramatically modulate GC action in endothelial cells, liver, adipose tissue, and skeletal muscle (21). Chronic exposure to high circulating GC has been linked to the development of obesity (17), insulin resistance, and diabetes mellitus (2, 6), possibly by promoting whole body insulin resistance and increased rates of glucose-neogenesis (1). Selectively overexpressing 11β-HSD1 in the visceral adipose tissue of mice, to levels observed in obese humans, also leads to hyperglycemia, hyperinsulinemia, and increased levels of plasma free fatty acids and triglycerides (i.e., the metabolic syndrome), despite normal circulating GC concentrations (12). Moreover, elevations in 11β-HSD1 expression in skeletal muscle of insulin-resistant men strongly correlates with various markers of the metabolic syndrome (26). Together, these findings suggest that insulin resistance and the metabolic syndrome result from either an increase in circulating GC levels or changes in tissue regulatory mechanisms in GC activity.

Exercise is a common form of metabolic stress that is a powerful stimulus to the hypothalamo-pituitary adrenal (HPA) axis (18). As a result, increases in circulating GC concentrations help mobilize energy stores and protect the organism from an overreaction of the immune system in the face of exercise-induced muscle damage (20). Although training is generally not thought to cause chronic elevations in GCs, our laboratory has recently shown (15) that central adaptations occur in the HPA axis with regular endurance exercise, including transient decreases in GR gene expression in the hypothalamus and pituitary gland, which coincide with temporary increases in hypothalamic corticotrophin-releasing hormone gene expression and short-term elevations in basal pituitary adrenal activity. Despite repeated acute elevations in circulating GC (15), which would be expected to induce peripheral insulin resistance and enhance hepatic glucose-neogenesis, endurance exercise clearly has a protective effect on the development of insulin resistance (18). We speculate, therefore, that there are tissue-specific adaptations in peripheral GC target tissues in response to regular exercise that maintain insulin sensitivity in the face of repeated exposure to elevations in circulating GC. Specifically, we tested the hypothesis that regular endurance exercise lowers skeletal muscle, liver, and adipose tissue 11β-HSD1 activity and GR expression to help protect the organism from the deleterious effects of repeated elevations in GC. This hypothesis was tested by using the Syrian golden hamster, an animal model that is known to exercise voluntarily, causing large changes in diurnal HPA activity (3). In this investigation we are the first to report the effects of volitional exercise training on the activity and expression of 11β-HSD1 and GR concentrations in the main GC target tissues.

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METHODS

Research Design

Sixteen 24-day old, male Syrian golden hamsters (Mesocricetus auratus, Charles River, Montreal, QC, Canada) with an initial weight of 46.6 ± 0.83 g (mean ± SE) were housed individually in clear cages and kept in a temperature (23–25°C) and humidity (40–60%) controlled room. Hamsters were randomly divided into sedentary (S, n = 8) and trained (T, n = 8) groups. The T group had 24-h access to running wheels over 4 wk of study. Both groups were allowed to acclimatize to daily human handling and to a 12-h light-dark cycle for 1 wk before the start of a 4-wk experimental protocol (see below) and were given access to food (Purina Chow no. 5001) and water ad libitum. The experimental protocol was approved by York University Animal Care Committee before the start of the experiment.

Data collection. Running activity levels for T hamsters were monitored daily by recording the distance run per day using a cycloometer counter. Food consumption and body weight were monitored daily for both groups. Blood samples for each animal were taken via saphenous vein puncture on the last day of every week at 1300 for analysis of blood glucose and cortisone (Cort) levels throughout the 4-wk training period. Blood glucose was measured from the first drop of blood by use of a standard glucose meter (Glucometer Elite XL, via saphenous vein puncture on the last day of every week at 1300 for further analysis of plasma Cort concentrations.

Euthanization. The animals were euthanized by decapitation under terminal CO2 anesthesia. The use of this euthanization method has been previously shown to reduce acute distress before death in rodents (22). Approximately 3 ml of whole blood were removed through an external cardiac puncture, while the animal was anesthetized before decapitation. Whole blood was collected into a 3-ml tube with no preservative added, allowed to clot, and centrifuged for serum collection at 4°C for 5 min at 2,000 rpm and frozen until further analysis of plasma Cort concentrations.

Plasma hormone determination. Plasma Cort concentration was determined with a commercially available RIA kit (ICN Biomedicals, Costa Mesa, CA). Frozen samples were thawed, centrifuged, and brought to room temperature before predilution with the supplied steroid diluent at a ratio of 1:200. 125I-Cort derivative (200 μl) was added to all samples and standards, followed with the same amount of anti-corticosterone. After incubation and the addition of the provided reagents, the supernatant was aspirated and the remaining pellet was counted for radioactivity by using a gamma-counter. The interassay coefficient of variation is between 6.5 and 7.2% and the intra-assay coefficient of variation is 4.8–20.7%, as calculated from reference plasma.

11β-HSD1 and GR expression. Expression of 11β-HSD1 and GR was analyzed by Western blotting in skeletal muscle and in liver only. Unfortunately, insufficient visceral adipose tissue was available for successful optimization of 11β-HSD1 and GR protein expression in this tissue. For muscle and liver, tissues were homogenized on ice in lysis buffer (135 mM NaCl, 1 mM MgCl2, 2.7 mM KCl, 20 mM Tris-base, 0.5 mM Na3VO4, 10 mM NaF, 0.2 mM PMSF, 10 μg/ml leupeptin, 1% Triton, 10% glycerol), quantified for protein concentration by the Bradford method, and frozen for subsequent analysis. Acrylamide gels were prepared by using the Bio-Rad electrophoresis equipment: 12% for 11β-HSD1 and 8% for the GR analysis. A volume equivalent to 25 μg of protein was loaded into each well. The gels were run at 120 V for 1 to 1 1/2 h and transferred onto a nitrocellulose membrane (Hybond ECL, Amersham International) at 1.2 V for 1 h. Membranes were blocked for 1 h in 5% milk (TBBS) before application of primary antibodies.

For analysis of 11β-HSD1, primary antibody (Alpha Diagnostic International, San Antonio, TX) was in applied in 1:1,500 ratio. For analysis of GR, primary antibody (H-300, Santa Cruz Biotechnology, Santa Cruz, CA) was in applied in 1:1,000 ratio. Secondary antibody (peroxidase-labeled anti-rabbit, Amersham Science) was applied in 1:5,000 ratio. Enhanced chemiluminescence detection (ECL Western Blotting Analysis System, Amersham Science) and film (Bioflex, InterScience) were used to visualize the bands in the dark room.

After the analysis of both 11β-HSD1 and GR, the membranes were stripped and reprobed with mouse monoclonal primary antibody for GAPDH (Cedarlane Laboratories, Hornby, ON, Canada) in 1:5,000 ratio, used as a loading control for all membranes. Secondary antibody (peroxidase-labeled anti-mouse, Amersham Science) was used in 1:5,000 ratio.

11β-HSD1 activity assay. 11β-HSD1 activity was assessed in various tissues (muscle, fat, and liver) as previously described (9). Briefly, tissues were homogenized on ice in homogenizing buffer, estimated for total protein concentration of each sample by the Bradford method, and further diluted in C buffer (10% glycerol, 300 mM NaCl, and 1 mM EDTA) at ~0.2 mg/ml protein. Duplicate aliquots of samples were then incubated with 25 nM [3H]Cort (specific activity ~84 Ci/mmol, Amersham International) and 2 μM 11β-HSD1-specific NADP cofactor (Sigma-Aldrich, Oakville, Canada, ON, Canada) at 37°C. Steroids were then extracted by using ethyl acetate, dried down at 50°C, and separated by thin-layer chromatography. Cort and 11-dehydrocortisol (11-DHC) bands were visualized under fluorescent light (254 nm), scraped into scintillation vials with liquid scintillant (Cocktail T, BDH), and counted in a β-counter. Activity was determined by conversion of [3H]Cort to [3H]11-DHC.

Cytochrome c-oxidase activity assay. Cytochrome c oxidase (COX) activity in quadriceps muscle was determined as previously described (8). Because no visible muscle fiber-type differentiation is observed in hamsters (13), the entire quadriceps muscle was pounded under liquid N2 conditions and stored frozen (~80°C) until analysis. For the analysis, 100 μl of an extraction buffer (100 mM Na-K-phosphate, 2 mM EDTA, pH 7.2) were added to 15–20 mg of powdered muscle sample stored in a 1.5-ml Eppendorf tube placed on ice. Subsequently, the volume of extracted buffer required to dilute the sample 20-fold was determined and added to these tubes. Tubes were then mixed for 15 min and sonicated on ice twice for 8–10 s each time. A test solution was produced by dissolving 20 mg of horse heart cytochrome c (Sigma, C-2506) in 1 ml of 10 mM KPO4 buffer in an opaque scintillation vial mixed with 40 μl of fresh dithionite stock solution (10 mg/ml sodium dithionite-10 mM KPO4). When prepared, 980 μl of test solution were pipetted into cuvettes and incubated at 30°C for room temperature for 30 min. After another washing, 100 μl of sheath fluid were added and the plate was immediately read on the Luminex 100. The intra-assay coefficient of variation is between 3.8 and 10.6%, and the interassay coefficient of variation is 4.8–20.7%, as calculated from reference plasma.
10 min. Cuvettes containing incubated test solution were placed into a spectrophotometer (Beckman DU-64), and 20 μl of muscle extract were then added and quickly mixed by stirring with a plastic stir stick. The kinetics program of the spectrophotometer was initiated immediately, and the change in absorbance was recorded for 5 min. The enzyme activity was determined as the maximal rate of oxidation of fully reduced cytochrome c, as measured by changes in absorbance at 550 nm in and expressed in micromoles per minute per gram of tissue.

**Statistical Analysis**

Scion Image software (Scion, Frederick, MD) was used to measure the optical density of all Western blotting protocols. Mixed ANOVA was used to analyze food consumption, weekly blood glucose, and weekly plasma Cort levels. A one-way ANOVA was used for analysis of running distance. All other results were analyzed by an independent, by-groups t-test. Statistical analysis was completed by using Statistica 6.0 statistical software with P ≤ 0.05 as the criterion for statistical significance. All data are expressed as means ± SE.

**RESULTS**

**Running Distance and Food Consumption**

Weekly average distance run by the hamsters in the T group increased from 14.7 ± 0.6 km/day for week 1 to 20.3 ± 0.8 km/day by week 4. At the start of the study, food consumption was comparable for all animals. However, by the end of the first week, food consumption was higher (P < 0.01) in T (9.1 ± 0.3 g/day) than in S (8.0 ± 0.2 g/day) animals. This pattern continued until the end of the study (Table 1).

**Body Mass and Organ Mass**

Both groups gained weight throughout the 4-wk training period and there was no difference at any time point between T and S animals. However, despite similar body mass, body composition differed between the two groups. The right visceral fat pad was larger (P < 0.01) in S (0.71 ± 0.06 g) than in T (0.24 ± 0.02 g) and a trend (P = 0.07) for a larger plantaris muscle was seen for the T (0.03 ± 0.005 g) compared with the S (0.02 ± 0.002 g) animals. There was no difference noted in adrenal mass between the two groups (Table 1).

**Blood Glucose and Plasma Insulin Levels**

No difference in nonfasted blood glucose concentration was found over the 4-wk training period between T and S hamsters (4.6 ± 0.1 vs. 4.8 ± 0.1 mmol/l, respectively, for data pooled across weeks). Additionally, plasma insulin concentration was comparable between T and S hamsters (284.0 ± 50.6 vs. 291.6 ± 49.7 pM, respectively) at the end of the study.

**Plasma Cort Levels**

For the first 3 wk of the study, basal plasma Cort levels were similar for both groups, however, by week 4 hormone levels were lower (P < 0.01) in T (13.0 ± 0.4 mg/ml) than S (16.4 ± 0.8 mg/ml) animals (Table 1).

**11β-HSD1 and GR Protein Expression**

Western blot analyses showed lower (P < 0.05) gastrocne-mius 11β-HSD1 expression in T than in S animals, and a trend was noted for a lower (P = 0.07) liver 11β-HSD1 expression in T than in S animals (Fig. 1). Gastrocnius GR expression was also lower (P < 0.05) in T than in S, whereas no difference was found in liver GR expression between the two groups.

**COX Activity**

Plantaris muscle COX activity was ~2.3-fold higher (P < 0.01) in T than in S after 4 wk of wheel running (Table 1).

**DISCUSSION**

Despite repeated acute elevations in HPA activity, regular aerobic exercise increases insulin sensitivity and promotes

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Table 1. Training effects on running distance, body mass, food intake, plasma corticosterone, and peripheral tissue protein expression of 11β-HSD1 and GR

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Terminal</th>
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</thead>
<tbody>
<tr>
<td>Running distance, km/day</td>
<td>T</td>
<td>14.7±0.6</td>
<td>17.6±1.5</td>
<td>20.9±0.9</td>
<td>20.3±0.8</td>
<td></td>
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<tr>
<td>Body mass, g</td>
<td>T</td>
<td>70.9±1.71</td>
<td>80.3±2.09</td>
<td>86.2±2.81</td>
<td>92.4±2.44</td>
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<tr>
<td></td>
<td>S</td>
<td>72.3±1.21</td>
<td>79.0±1.43</td>
<td>85.3±1.60</td>
<td>91.0±1.64</td>
<td></td>
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<tr>
<td>Food consumption, g</td>
<td>T</td>
<td>9.1±0.3</td>
<td>9.7±0.3</td>
<td>9.3±0.3</td>
<td>9.6±0.2</td>
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<tr>
<td></td>
<td>S</td>
<td>8.0±0.2</td>
<td>7.9±0.3</td>
<td>6.5±0.2</td>
<td>6.4±0.1</td>
<td></td>
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<tr>
<td>Plasma corticosterone, ng/ml</td>
<td>T</td>
<td>16.3±0.44</td>
<td>13.8±0.57</td>
<td>13.4±0.46</td>
<td>13.0±0.36†</td>
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<tr>
<td></td>
<td>S</td>
<td>16.4±0.43</td>
<td>13.5±0.93</td>
<td>13.9±0.44</td>
<td>16.4±0.83</td>
<td></td>
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<tr>
<td>Blood glucose concentration, mM</td>
<td>T</td>
<td>4.7±0.14</td>
<td>4.5±0.24</td>
<td>4.7±0.13</td>
<td>4.6±0.12</td>
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<tr>
<td></td>
<td>S</td>
<td>4.8±0.18</td>
<td>4.8±0.24</td>
<td>4.6±0.16</td>
<td>4.8±0.20</td>
<td></td>
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<tr>
<td>Right visceral fat mass, g</td>
<td>T</td>
<td>0.24±0.02*</td>
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<td></td>
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<tr>
<td></td>
<td>S</td>
<td>0.71±0.06</td>
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<tr>
<td>Right plantaris mass, g</td>
<td>T</td>
<td>0.03±0.005</td>
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<td></td>
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<tr>
<td></td>
<td>S</td>
<td>0.02±0.002</td>
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<tr>
<td>Cytochrome c oxidase activity, μmol·min⁻¹·g⁻¹</td>
<td>T</td>
<td>2.5±0.3‡</td>
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<td></td>
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<tr>
<td></td>
<td>S</td>
<td>1.1±0.2</td>
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</table>

Values are means ± SE. 11β-HSD1, 11β-hydroxysteroid dehydrogenase type 1; GR, gluocorticoid receptor; T, trained group; S, sedentary group. *P < 0.05 vs. sedentary; †P < 0.01 vs. sedentary.
overall improvements in symptoms of the metabolic syndrome in both humans and in rodent models of the disease (18). This is somewhat surprising because elevations in circulating GC concentrations are clearly associated with increased obesity, insulin resistance, and the development of the metabolic syndrome (2). In this study, we show that there are no elevations in circulating basal GC levels and tissue-specific alterations in GC exposure, through changes in GR, 11β-HSD1 protein expression, and 11β-HSD1 activity, in response to regular exercise. The low circulating basal GC levels and the changes in the regulators of GC action, which we observed in skeletal muscle, liver, and visceral adipose tissue would be expected to alter GC exposure in these insulin sensitive tissues.

A significant portion of GCs entering tissue is biologically inactive and therefore does not bind to GR (7). 11β-HSD1 is responsible for intracellular reactivation of inert GC, and its overexpression has recently been linked with visceral adipose tissue accumulation and the metabolic syndrome (12), increases in hepatic gluconeogenesis (11), and insulin resistance in skeletal muscle (26). We have recently shown central changes in HPA axis activity that cause a transient upregulation in circulating GC levels with training and a subsequent restoration in basal activity (15). In this study, we show that there are also peripheral changes in HPA activity with voluntary exercise training. Skeletal muscle responds to endurance training by lowering 11β-HSD1 and GR protein levels (Figs. 1 and 2), which would be expected to lower intracellular GC action. GCs are known to have antagonistic effects on the insulin activity in muscle (1, 24), which is the primary organ for glucose disposal in both the resting and exercising conditions. A reduced GC action, as we have observed here, and an increase in insulin action via changes to the insulin signaling pathway (19) would be expected to increase overall glucose disposal in this important target tissue. We also measured the enzyme activity of 11β-HSD1 and found that that in vitro activity in the muscle was not significantly different between T and S hamsters (Fig. 2). This finding suggests that, despite a significant decrease in enzyme protein in the muscle of the trained hamsters, this small difference may not have a strong enough physiological impact on the in vitro activity of the enzyme. Unfortunately, a true direct comparison cannot be made between the two muscle measurements because the assay was performed on the quadriceps, whereas the protein measurement was performed in the gastrocnemius muscle.

In hepatic tissue, we observed a tendency for 11β-HSD1 protein expression to be lower and GR expression to be unchanged with 4 wk of endurance training (Fig. 1). We also found no difference in in vitro liver enzyme activity between T and S groups (Fig. 2). The role of elevations in 11β-HSD1 activity in the development of insulin resistance in the liver has been demonstrated in transgenic mice selectively overexpressing the enzyme (16). These mice exhibit modest insulin resistance and an attenuated version of the metabolic syndrome but without the onset of obesity. The relevance of the trend for a small reduction in hepatic 11β-HSD1 protein expression in our study is unknown, but it may confer some protection against elevations in GC exposure.

In contrast to the first two tissues and counter to our hypothesis, we observed a dramatically higher 11β-HSD1 enzyme activity in the visceral adipose tissue of the trained compared with the sedentary hamsters (Fig. 2). This finding is surprising because an increase in GC action in adipose tissue has been linked to the development of central obesity, hyper-

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**Fig. 1.** Liver and gastrocnemius muscle (Gastroc) 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1; A) and glucocorticoid receptor (GR; B) protein expression in trained (T) and sedentary (S) hamsters. Representative blots for the relevant protein and GAPDH loading controls are also shown. Values are means ± SE. *P ≤ 0.05; **P ≤ 0.001; &P ≤ 0.07.

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**Fig. 2.** 11β-HSD1 activity, expressed as conversion of cortisone to 11-dehydrcorticosterone, in quadriceps, liver, and visceral fat tissues. Values are means ± SE. *P < 0.05
insulinemia, hyperglycemia, hyperlipidemia, and hypertension (12). Unfortunately, owing to technical difficulties (i.e., inability to optimize protein expression analysis with the small amount of visceral fat removed, particularly in the T group), we were unable to measure adipose 11β-HSD1 and GR protein expression in these animals. In a separate analysis in older hamsters, we have recently confirmed that regular exercise also increases perirenal fat 11β-HSD1 and GR protein expression despite causing a dramatic reduction in visceral fat mass (5). Similar to our observation for trained animals, caloric restriction causing weight loss in humans has recently been shown to increase subcutaneous (buttocks) adipose tissue 11β-HSD1 activity (24). Together, these results suggest that in visceral fat there is a shift in the set point of 11β-HSD1 activity toward the generation of cortisol when fat mass is lost. The physiological significance of this shift is unclear but may be related to a greater mobilization of free fatty acids from stored triglycerides during a negative energy balance. The enzyme is more highly expressed in omental compared with subcutaneous preadipocytes (4), and some believe that 11β-HSD1 acts to limit preadipocyte proliferation and promote adipocyte differentiation (25). It may also be that the organism responds to weight loss, either through exercise or dietary restriction, by increasing 11β-HSD1 activity in an attempt to promote adipose tissue mass restoration. This response might explain why fat mass gain is so rapid after the cessation of regular exercise (10). It has been postulated that adipose tissue 11β-HSD1 activity decreases with the development of obesity in nondiabetic individuals, perhaps as a compensatory mechanism to help maintain insulin sensitivity (24), and it may be that this adaptation is not required with the introduction of exercise and/or diet-induced weight loss. Indeed, high-fat feeding in mice induces a marked fall, rather than an increase, in adipose 11β-HSD1, again suggesting a novel physiological adaptation mechanism to maintain insulin sensitivity with high-fat feeding (14). Clearly, future investigations should determine the physiological relevance of increased adipose tissue 11β-HSD1 activity that is associated with caloric restriction and/or regular exercise.

Another novel finding of this study is that after 4 wk of endurance training plasma Cort levels are slightly but significantly lower in trained compared with untrained hamsters, suggesting an attenuation in the basal pituitary-adrenal activity despite an increase in running wheel behavior (Table 1). Importantly, neither group exhibited basal hypercortisolism, indicating that our protocol and the method of blood collection did not constitute a significant stress to the hamsters. Our results are in agreement with other reports of normal basal (i.e., morning) circulating GC levels in wheel-running rodents (23) yet are in conflict with others that show an elevation (3) in plasma Cort levels with training. It is likely that the varied findings may be indicative of interspecies variations and differences in serum collection as well as exercise protocol methods that are used in different studies.

In summary, data from this study reveal that voluntary wheel running in hamsters induces changes in factors that are responsible for determining tissue exposure to GCs. These changes are tissue specific and act to decrease GC action in muscle and liver but increase action in visceral fat.

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