Effects of exercise on insulin distribution and action in testosterone-treated oophorectomized female rats

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Niklasson, Maria, Peter Daneryd, Peter Lönroth, and Agneta Holmäng. Effects of exercise on insulin distribution and action in testosterone-treated oophorectomized female rats. J Appl Physiol 88: 2116–2122, 2000.—Administration of testosterone (T) to oophorectomized (Ovx) female rats is followed by severe insulin resistance, localized to postreceptor cellular events in the muscle. In this study, intervention by exercise was introduced to examine whether circulatory adaptations are involved in insulin resistance. Two groups of Ovx rats were studied: one group was given T (Ovx+T); another group had free access to running wheels (Ovx+T+Ex). In addition, one control group (sham operated) was studied. Insulin sensitivity was measured with the euglycemic hyperinsulinemic clamp technique (submaximal) for 150 min. Muscle interstitial glucose and insulin concentrations were measured by microdialysis. The measurements showed that, in Ovx+T rats, the onset of insulin action was significantly (P < 0.05) slower during the first 95 min of the clamp compared with that in Ovx+T+Ex and controls. Muscle interstitial concentrations of insulin but not glucose were lower in both Ovx+T and Ovx+T+Ex rats than in controls throughout the clamp. It was concluded that physical exercise prevented the slow onset of insulin action in Ovx+T rats without changing the distribution time of muscle interstitial insulin. The results indicate that hyperandrogenicity is characterized by delayed muscle insulin action. Physical exercise reverses these defects without any beneficial effect on muscle interstitial insulin concentrations.

testosterone; insulin resistance; microdialysis; skeletal muscle

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HYPERANDROGENIC CONDITIONS in women are often associated with severe insulin resistance (8, 28, 33, 37). In Swedish women selected at random, a low plasma level of sex hormone-binding globulin (SHBG) was found to be statistically associated with insulin resistance (9, 24) and with a strong risk for the development of non-insulin-dependent diabetes mellitus. In addition, a low SHBG predicts the development of hypertension and mortality from myocardial infarction in women (21, 22). There is no consensus on whether insulin resistance is the primary factor by inhibiting SHBG production from the liver, or whether androgens primarily cause insulin resistance (30, 36). However, administration of testosterone to normal, transsexual women (35) or to female rats (11, 14, 39) is followed by severe insulin resistance, strongly suggesting that hyperandrogenicity in women may be followed by insulin resistance and associated diseases.

Because of the potential importance of hyperandrogenicity as a disease-promoting factor in women, underlying mechanisms have previously been explored in a female rat model (11, 14, 39). Administration of testosterone after oophorectomy is followed by elevated insulin concentrations and by severely decreased insulin sensitivity localized to insulin-stimulated glucose transport, glycogen synthesis, and glycogen synthase in muscle (11, 14, 39). A defect in insulin-induced translocation of GLUT-4 to the plasma membrane and decreased expression of glycogen synthase in skeletal muscles seem to be responsible for the decrease in insulin sensitivity, whereas the activities of the insulin receptor and of tyrosine kinase are maintained (39). These perturbations were found to be paralleled by a decrease in capillary density in muscle, as measured with conventional histochemical methods (14). Lymph (45) and microdialysis (17) measurements have demonstrated an endothelial barrier to the delivery of insulin to the interstitial fluid; therefore, the number of capillaries in the muscle may be considered to be important for the time kinetics of the interstitial insulin concentration and effect.

Exercise is known to stimulate glucose transport in skeletal muscle independently of insulin (34) and also to increase the insulin sensitivity of the glucose transport process (38, 40). Insulin and exercise are similar to the extent that both result in increased glucose transport across the plasma membrane. Glucose transport capacity increases in trained muscles through an increase in the concentration of GLUT-4 (7).

Repeated bouts of exercise are known to be followed by increased muscular capillarization in normal individuals (1). The increased capillary density may favor the extraction of glucose in the muscle and reduces the delivery distance of insulin to its site of action in the muscle (23). As revealed by a shift to the right of the dose-effect curve of insulin (3), insulin insensitivity results in a delay in the insulin effect during the induction of an insulin infusion (32). Previous investiga-
tions in the oophorectomized plus testosterone treatment (Ovx+T) rat model have demonstrated that the effect of insulin on the uptake of glucose by muscle is markedly delayed as the result of a combination of muscle postreceptor defects and a time lag in the equilibration of the insulin concentration over the capillary wall (11, 14, 39). Because exercise may increase insulin sensitivity as well as muscle capillarization, it is possible that exercise shortens the time before the onset of the insulin effect.

The aim of this study was to use microdialysis measurements of insulin to study the effect of exercise and to differentiate between the effects on insulin delivery to the interstitial fluid and the effects at the postreceptor level. To meet this aim, we investigated the effects of Ovx+T on insulin sensitivity in female rats and examined whether the reduction in insulin sensitivity and the delayed insulin effect could be reversed by exercise. The euglycemic hyperinsulinemic clamp method was used simultaneously with the microdialysis technique.

MATERIALS AND METHODS

A total of 30 female Sprague-Dawley rats (B&K Universal, Sollentuna, Sweden) weighing 173 ± 2 g before treatment were used. They were fed with commercial rat chow containing 18.5% protein, 4.0% fat, 55.7% carbohydrates, and a sufficient supply of vitamins and minerals (Lactamin, Stockholm, Sweden), along with tap water ad libitum. The light cycle was 12:12 h, and the room temperature was maintained at 23°C. The study was approved by the Animal Ethics Committee of Göteborg University.

Study procedure. The rats were randomly divided into three study groups. The first group was the Ovx+T exercise group (Ovx+T+Ex, n = 10). These rats were Ovx and treated with intramuscular injections of 2 mg of testosterone enanthate in sesame oil (Testoviron Depot, Schering, Berlin, Germany) every second week. The first injection was given immediately after the oophorectomy, with three additional injections over the following 6 wk. The rats were then housed in individual cages with free access to a freely moving, nonmotorized running wheel with a wire bottom and a diameter of 33 cm (UNO Roestvaststaal, Arnhem, Holland) (4). Running distances were recorded every fourth day. The wheels were locked 24 h before the clamp experiments. The second group was the Ovx+T group (n = 10). These rats were treated identically to the rats in the exercise group, with oophorectomy and intramuscular injections of testosterone. They were housed in individual standard cages with approximately the same area and volume as those of the exercising group, but they did not have access to exercise. Body weight and food intake were recorded every fourth day. The third group was the control (C) group (n = 10). These rats were sham operated and treated with intramuscular injections of sesame oil (0.1 ml) every second week. The first injection was given immediately after the sham operation, with three additional injections over the following 6 wk. These animals were kept in cages as above without access to exercise.

After 5 wk of treatment, fasting tail samples were collected from all three groups and analyzed for testosterone, insulin, and glucose. The rats were anesthetized with diethyl ether, and an osmotic minipump (Alza, Palo Alto, CA) that continuously infused [14C]inulin (0.1 mCi/rat, pump rate 8 µl/h; NEN, Boston, MA) was implanted subcutaneously in the dorsal neck region 24 h before the clamp study was initiated.

Euglycemic hyperinsulinemic clamp. The euglycemic clamp technique described in detail (14). In brief, the animals (Ovx+T+Ex, Ovx+T, and C rats) were anesthetized in the morning with 170 mg/kg body wt thiobutabarbitual sodium salt (Inactin, RBI, Natick, MA) injected intraperitoneally. Catheters were then inserted in the left carotid artery for blood sampling and in the right jugular vein for infusion of insulin and glucose. Body temperature was maintained at 37°C with a heating blanket and a rectal probe. Measurements then started 30 min after the operation. Insulin (40 U/ml, Human Actrapid Novo, Copenhagen, Denmark) was infused to obtain a submaximal insulin concentration (5 mU·kg⁻¹·min⁻¹) for 150 min. Euglycemia was maintained by infusion of 10% glucose solution in physiological saline. The infusion speed was guided by glucose concentration measurements in 30-µl blood samples at regular intervals (every 5 min during the first 40 min; then every 10 min). A plasma glucose level of ~7 mM was chosen to match postprandial glucose concentrations determined just before the clamp. Insulin concentrations were determined in 250-µl blood samples taken after 0, 40, 95, and 150 min of infusion. The plasma insulin concentrations in the Ovx+T+Ex, Ovx+T, and C rats at 0 min were 28 ± 3, 29 ± 5, and 26 ± 4 mU/l (not significant). Less than 2 ml of blood were used for these determinations, and the loss was compensated for by the infusion volumes. At the completion of the clamp, the rats were killed with intravenous injections of KCl, and the muscles of the lower hindlimb and the parametrial and retroperitoneal adipose tissues were dissected out and weighed.

Microdialysis. Microdialysis was performed in the medial femoral muscle in both legs during the clamp, as previously described (25). Two 15-mm microdialysis catheters (30 mol wt cutoff; BAS, Indianapolis, IN) were perfused with isotonic saline containing 1% bovine albumin at the rate of 1 µl/min. The catheters were inserted just before the clamp was started (time = 0 min). After 40 min of equilibration, the dialysate was collected at 55-min intervals (40–95 and 95–150 min) for measurement of inulin, insulin, and glucose.

Calculations. The interstitial glucose concentration was calculated from the in vivo probe recovery according to the internal reference calibration technique (26). The perfusate was prepared with [3H]glucose (0.05 µCi/ml), and the loss over the membrane was taken as an estimate of recovery (dialysate concentration/interstitial concentration) (26). The experiments revealed a 55.4 ± 5.8% in vivo dialysate recovery of interstitial glucose (n = 14). The insulin concentration in the interstitial fluid was calculated by means of an external reference with the use of [14C]inulin infused subcutaneously for 24 h (see Study procedure). The recoveries of both [14C]inulin and insulin in dialysates obtained in vivo were compared, and the interstitial concentration of [14C]inulin was assumed to be the same in plasma. To characterize the different diffusion properties and to correct for differences in binding of the compounds to the catheter, identical experiments were performed in which [14C]inulin and insulin were dialysed in plasma at 37°C in vitro. Results from seven such in vitro experiments demonstrated that the relative recoveries of [14C]inulin and insulin in microdialysates were 0.22 ± 0.01 and 0.03 ± 0.01, respectively. The corresponding [14C]inulin recovery in experiments performed in vivo was 0.22 ± 0.04. The interstitial insulin concentration was then calculated in
RESULTS

There were no significant differences in body weights in the three groups before treatment. Ovx+T and Ovx+T+Ex rats gained weight more rapidly than the C rats did; their body weight was significantly higher after 12 days (200 ± 3, 216 ± 3, and 217 ± 7 g for C, Ovx+T, and Ovx+T+Ex, respectively, P < 0.05). This weight difference persisted, and there was also a tendency for the Ovx+T group to gain more weight than the exercise group did (Table 1). Food intake was 5.8 ± 0.2 (C), 6.5 ± 0.2 (Ovx+T; P < 0.05 vs. C), and 8.1 ± 0.3 g·100 g body wt⁻¹·day⁻¹ (Ovx+T+Ex; P < 0.001 vs. C, P < 0.001 vs. Ovx+T; ANOVA). The wet weights of the plantaris (P < 0.05) and the soleus muscles were significantly higher in the exercise group than in the other two groups (P < 0.001). Among the fat depots, the parametrial and retroperitoneal adipose tissue of the exercise group weighed significantly less than that in the other two groups (P < 0.001). The parametrial adipose tissue mass in the Ovx+T group was significantly greater than that in the exercise group but was significantly smaller than that in the C group (P < 0.001). In the Ovx+T group, the retroperitoneal adipose tissue weight was significantly greater than that in the other groups (P < 0.001) (Table 2).

In animals subjected to physical exercise, the total running distance recorded was 331,532 ± 40,145 m (7.879 ± 1,443 m/day) (n = 10).

Table 3 shows the fasting plasma values after 5 wk of treatment. There were no significant group differences in fasting glucose concentrations. The Ovx+T group showed higher fasting plasma insulin concentrations than the other two groups did (P < 0.05-0.01). The plasma insulin concentrations were significantly lower after exercise compared with C (P < 0.05) and Ovx+T (P < 0.01) rats. As an index of treatment, both groups of Ovx+T rats showed significantly higher levels of testosterone than the C rats did (P < 0.001).

Euglycemic hyperinsulinemic clamp. Figure 1 shows the glucose infusion rate during the euglycemic hyperinsulinemic clamp at submaximal insulin concentrations (5 mU·kg⁻¹·min⁻¹) for 150 min. The Ovx+T rats had a significantly lower glucose infusion rate during the first 95 min of the clamp than the two other groups did (P < 0.05). At 150 min, this difference had disappeared, and there were no longer any significant differences among the three groups during the rest of the clamp.

Figure 2A shows that there were no significant differences among the three groups in plasma insulin levels during the whole clamping period (40–150 min). The Ovx+T rats, both with and without exercise, had significantly lower interstitial insulin levels during the whole clamping period than the C rats did, as measured in medial femoral muscles (P < 0.01) (Fig. 2C). The C rats had a significantly higher interstitial level of insulin between 95 and 150 min than between 40 and 95 min of the clamping period (P < 0.01). Because of a nonphysiologically high interstitial insulin concentration measured in one C rat between 95 and 150 min, the interstitial concentration tended to be slightly higher numerically (16 ± 19 mU/l.) than in plasma without reaching statistical significance (Fig. 2). Between 40 and 95 min, the arterial-interstitial concentration ([a-i]) differences for insulin were 10 ± 13 (not significant), 41 ± 14 (P < 0.05), and 38 ± 8 mU/l (P < 0.05), and between 95 and 150 min, they were nonsignificant in all animal groups.

Plasma glucose concentrations reached a steady state at 7 mmol/l after 40 min and were the same in all three groups throughout the insulin clamp (Fig. 2B). Figure 2D shows that there were no significant differences among the three groups in interstitial glucose concent-
the uptake of glucose by muscles in insulin resistance has led to the idea that insulin transport is a saturable process (41). Moreover, in human muscle the gradient seems independent of the concentration of glucose in interstitial fluid is lower than in arterial plasma (12), whereas the concentration of glucose in interstitial fluid is lower than in arterial plasma (12). At supraphysiological concentrations of insulin, the concentration of insulin in interstitial fluid is lower than in plasma, indicating either that transcapillary insulin transport is saturable or that insulin elimination is concentration dependent (12). However, even though an insulin concentration gradient may exist, evidence for a saturable transport of insulin has not been achieved in animal studies on hindlimb lymph representing the interstitial fluid (42). In human muscle, insulin (41) and glucose (13, 29) concentrations are lower in interstitial fluid than in plasma, even when physiological insulin concentrations are in the low range. Hence, blood flow and transcapillary transport of insulin and/or glucose may be considered rate limiting for the insulin effect in human subjects (29, 41). Therefore, we recently evaluated an external reference technique for intramuscular measurements in the rat and in humans using the continuous infusion of insulin as a reference (12). It should be noted here, however, that the technique is sensitive enough to readily measure low-molecular-weight substances such as glucose and lactate but not peptide hormones such as insulin at low physiological concentrations (26). Consequently, in the present study, data on interstitial insulin levels could not be obtained before steady-state plasma insulin concentrations were reached because of the detection limits of the analysis method presently employed. The present results were achieved under prevailing supraphysiological plasma concentrations of insulin during steady-state plasma insulin clamping conditions; therefore, tentative changes in interstitial fluid concentrations of insulin at the earlier clamping period could not be elucidated.

In the normal-to-high physiological range of insulin concentration, measured in the lean Zucker rat, the muscle interstitial insulin concentration is the same as in plasma (12), whereas the concentration of glucose in interstitial fluid is lower than in arterial plasma (12).

Table 3. Plasma concentrations of glucose, insulin, and testosterone after 5 wk of treatment in fasting Ovx+T+Ex, Ovx+T, and control groups

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Glucose, mmol/l</th>
<th>Insulin, mU/l</th>
<th>Testosterone, mg/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>3.8 ± 0.3</td>
<td>58 ± 0.2**‖</td>
<td>0.69 ± 0.4*§</td>
</tr>
<tr>
<td>Ovx+T</td>
<td>10</td>
<td>3.3 ± 0.3</td>
<td>85 ± 0.5**‖</td>
<td>1.1 ± 0.2*§</td>
</tr>
<tr>
<td>Ovx+T+Ex</td>
<td>10</td>
<td>3.4 ± 0.3</td>
<td>4.8 ± 0.2*</td>
<td>13.3 ± 1.3‡</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of rats. † P < 0.05, ‡ P < 0.001 Ovx+T vs. control; * P < 0.05, ** P < 0.001 Ovx+T vs. Ovx+T+Ex, † P < 0.001, Ovx+T+Ex vs. control. The increase in interstitial levels of insulin during insulin infusion depends on the rate of transcapillary insulin delivery and the cellular insulin clearance. An increased insulin clearance, which is receptor mediated, implies an increase in receptor density. The insulin receptor number was measured in Ovx+T rats in a recent study and was found unchanged compared with that in C rats (39). Therefore, it may be hypothesized that lower interstitial insulin concentrations in Ovx+T rats might be due to altered capillary transport capacity. Microdialysis measurements allow highly precise estimates of the interstitial concentration of any substance, provided that the microdialysis sampling catheter is calibrated in situ (26). Low-molecular-weight substances such as glucose (26), lactate (19), and glycerol (18) may be readily measured by using equilibration (26) or stop-flow (10) techniques for calibration. In contrast, peptides such as insulin that are prone to binding to plastic materials cannot be measured using conventional or standard calibration (17, 41). Therefore, we recently evaluated an external reference technique for intramuscular measurements in the rat and in humans using the continuous infusion of insulin as a reference (12). It should be noted here, however, that the technique is sensitive enough to readily measure low-molecular-weight substances such as glucose and lactate but not peptide hormones such as insulin at low physiological concentrations (26). Consequently, in the present study, data on interstitial insulin levels could not be obtained before steady-state plasma insulin concentrations were reached because of the detection limits of the analysis method presently employed. The present results were achieved under prevailing supraphysiological plasma concentrations of insulin during steady-state plasma insulin clamping conditions; therefore, tentative changes in interstitial fluid concentrations of insulin at the earlier clamping period could not be elucidated.
lin sensitivity correlates with muscle blood flow (2, 16), the causal relationship is not yet clear (13). Most studies in humans designed to determine this relationship have been performed during steady-state conditions, and the time kinetics of the insulin effect have been studied less often. Microdialysis sampling (17), as well as measurements of lymph (45), has demonstrated that changes in interstitial insulin concentrations do not occur until ~30 min after a sudden increase in the concentration of plasma insulin. In the present study, we used long (40-min) sampling intervals; thus time kinetics were not followed closely. However, it should be noted that the dialysis membrane presently used registers 100% of the change in ambient insulin concentrations within 20 min (not shown). Therefore, a transient group difference in interstitial insulin concentrations registered at one sampling period represents at least a 20-min difference in the equilibration of insulin over the capillary wall. The Ovx+T rats had lower concentrations of interstitial insulin that never reached the level of plasma insulin within the 150-min sampling period. This is in contrast to the glucose disposal rates in Ovx+T rats showing normal insulin action already at 150 min. In the present study, it was thus confirmed that insulin action and the increase of the insulin concentration in the interstitial fluid were delayed in Ovx+T rats (31). We propose that this latter defect may be attributed to the decrease in capillary density (14) and the resulting restricted blood flow, as well as to the longer diffusion distance between capillaries and muscle cells previously demonstrated (23). It is important to note in this context, however, that the [a-i] difference was small and that a postreceptor defect leading to a rightward shift of the dose-effect curve of insulin should, by itself, lead to a delay in the onset of the insulin effect.

**Fig. 1.** Glucose infusion rate during a hyperinsulinemic euglycemic clamp at submaximal insulin concentrations (5 mU·kg⁻¹·min⁻¹) for 150 min in control rats (open bars), oophorectomized, testosterone-treated rats (Ovx+T; hatched bars), and oophorectomized, testosterone-treated, and exercised rats (Ovx+T+Ex; solid bars). Data are expressed as means ± SE (n = 10 rats). *P < 0.05, Ovx+T vs. control and Ovx+T+Ex. Student’s t-test was used for paired observations and ANOVA.

**Fig. 2.** A: plasma insulin concentrations determined from mean values of plasma samples taken after 40, 95, and 150 min of a hyperinsulinemic euglycemic clamp (5 mU·kg⁻¹·min⁻¹) in control (open bars), Ovx+T (hatched bars), and Ovx+T+Ex rats (solid bars). B: plasma glucose concentrations determined from mean values of plasma samples taken every 5 min. C: interstitial insulin concentrations in medial femoral muscles. Starting after 40 min of the clamp, samples of interstitial fluid were collected every 55 min for measurement of interstitial insulin. **P < 0.01, control vs. Ovx+T and Ovx+T+Ex rats; ††P < 0.01, control rats after 40–95 min vs. after 95–150 min. D: interstitial glucose concentrations. Data are expressed as means ± SE (n = 10). Student’s t-test was used for paired observations and ANOVA.
in the beginning of an insulin infusion. Postreceptor defects in insulin signaling and action, including defects in translocation of GLUT-4 transporter proteins to the plasma membrane and altered activation of glycogen synthase, were previously reported in studies of the plasma membrane and altered activation of glyco
defects in translocation of GLUT-4 transporter proteins to
in the beginning of an insulin infusion. Postreceptor
levels.
levels.

Physical exercise in Ovx+T rats prevented the develop-
ment of fasting hyperinsulinemia and delayed insu-
lin action; however, the muscle interstitial insulin
concentration was lower than in C rats throughout the
clamp. Thus, despite the expected effect of physical
exercise to increase the number of capillaries in muscles,
insulin transcapillary transport capacity was not im-
proved enough to normalize the interstitial insulin
centration. The present data suggest that the effects
of hyperinsulinemia and decreased insulin sensitivity
induced by Ovx+T could be significantly improved by
physical exercise by shortening the time of onset
of insulin action through action on a receptor/postrecep-
tor step in the muscle cells. Physical exercise leads to
enhanced insulin effects through action on multiple
postreceptor steps (5), including GLUT-4 (5) and glyco-
gen synthase (38, 40), and also enhances the percent-
age of insulin-sensitive slow-twitch muscle fibers (1).

In the present study, Ovx+T resulted in elevated
body weight as the result of increased amounts of
retroperitoneal fat. The effect of enlargement of the
abdominal fat depot on insulin sensitivity was previ-
ously demonstrated in obese women (20) with low
plasma levels of SHBG. Physical exercise effectively
increased muscle weight and prevented the shift in
adipose tissue distribution seen after Ovx+T. Based on
the data obtained in this rat model, this opens the
possibility that physical exercise may decrease the risk
for insulin resistance and delayed insulin action in
obesity in combination with hyperandrogenicity and
altered fat distribution (27, 36).

In summary, the present data obtained in the rat
show that Ovx+T results in a delay in the onset of
insulin action, and physical exercise prevented this
time shift. The extra time needed to equilibrate insulin
over the capillary wall seen in Ovx+T rats was not
affected by physical exercise. The data support the view
that transcapillary delivery of glucose and insulin is
rate limiting for the insulin effect (12). Furthermore,
the data are in agreement with the view that muscle
blood flow plays a minor role in the effect of insulin on
glucose uptake in resting insulin-sensitive (29) and
insulin-resistant muscle (13); however, it should be
noted that these data were obtained from resting
animals and that transcapillary diffusion of insulin and

glucose may be more critically dependent on the regula-
tion of blood flow during exercise (6).

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