Eccentric exercise induces transient insulin resistance in healthy individuals

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KIRWAN, J. P., R. C. HICKNER, K. E. YARASHESKI, W. M. KOHRT, B. V. WIETHOP, AND J. O. HOLLOSZY. Eccentric exercise induces transient insulin resistance in healthy individuals. J. Appl. Physiol. 72(6): 2197–2202, 1992.—Euglycemic-hyperinsulinemic clamps were performed on six healthy untrained individuals to determine whether exercise that induces muscle damage also results in insulin resistance. Clamps were performed 48 h after bouts of predominantly 1) eccentric exercise [30 min, downhill running, −17% grade, 60 ± 2% maximal O2 consumption (VO2 max)], 2) concentric exercise (30 min, cycle ergometry, 60 ± 2% VO2 max), or 3) without prior exercise. During the clamps, euglycemia was maintained at 90 mg/dl while insulin was infused at 30 mU·m−2·min−1 for 120 min. Hepatic glucose output (HGO) was determined using [6,6-2H]glucose. Eccentric exercise caused marked muscle soreness and significantly elevated creatine kinase levels (273 ± 73, 92 ± 27, 87 ± 25 IU/l for the eccentric, concentric, and control conditions, respectively) 48 h after exercise. Insulin-mediated glucose disposal rate was significantly impaired (P < 0.05) during the clamp performed after eccentric exercise (3.47 ± 0.51 mg·kg−1·min−1) compared with the clamps performed after concentric exercise (5.55 ± 0.94 mg·kg−1·min−1) or control conditions (5.48 ± 1.0 mg·kg−1·min−1). HGO was not significantly different among conditions (0.77 ± 0.26, 0.65 ± 0.27, and 0.66 ± 0.64 mg·kg−1·min−1 for the eccentric, concentric, and control clamps, respectively). The insulin resistance observed after eccentric exercise could not be attributed to altered plasma cortisol, glucagon, or catecholamine concentrations. Likewise, no differences were observed in serum free fatty acids, glycerol, lactate, β-hydroxybutyrate, or alanine. These results show that exercise that results in muscle damage, as reflected in muscle soreness and enzyme leakage, is followed by a period of insulin resistance.

Methods

Subjects. Six healthy untrained individuals (3 males, 3 females) volunteered to participate in this study after signing an informed consent in accordance with the University Guidelines for the Protection of Human Subjects. This study was approved by the Human Studies Committee of Washington University School of Medicine. Selected physical characteristics are shown in Table 1. All subjects had a normal response to a 75-g oral glucose tolerance test.

Exercise. Maximal O2 consumption (VO2 max) was determined by use of an incremental treadmill protocol. Gas volumes were measured by a dry gas meter (Parker-Cowan). O2 (Applied Electrochemistry S-3A) and CO2 (Beckman LB-2) concentrations were determined by use of a semiautomated on-line system. Heart rate was monitored by electrocardiogram with a modified V5 lead. Skinfold measurements were obtained for estimation of percent body fat, as described by Jackson and Pollock (15).

The eccentric exercise bout consisted of 30 min of downhill running on a treadmill declined at −17%. The subjects ran at an intensity designed to elicit ~60% VO2 max. Expired air was collected using a Daniels valve and meteorological balloons at 10-min intervals during exercise, and O2 consumption (VO2) was measured with a mass spectrophotometer (Perkin-Elmer MGA 1100). Ventilation was determined using a Collins gasometer.
TABLE 1. Subject characteristics

| Age, yr | 29.0±2.0 |
| Height, cm | 168.6±2.7 |
| Weight, kg | 71.0±5.1 |
| BMI, kg/m² | 24.8±1.3 |
| Body fat, % | 20.8±3.9 |
| VO₂ max, ml·kg⁻¹·min⁻¹ | 46.1±5.2 |

Values are means ± SE of 6 subjs. BMI, body mass index; VO₂ max, maxi-
mal O₂ consumption.

The concentric exercise bout consisted of 30 min of

cycling on an electronically braked cycle ergometer

(Lode, Groningen, Holland) at an intensity similar to

that for the downhill run, i.e., ~60% VO₂ max. VO₂ was

measured at 10-min intervals, as described for the cen-

tric exercise bout.

Euglycemic-hyperinsulinemic clamps. Three euglyce-

mic-hyperinsulinemic clamps were performed on each

subject in a counterbalanced design. The clamps were

performed 48 h after 1) downhill running, 2) cycling, or

3) a period of no exercise. Clamps were performed 1 wk

apart, with the exception that when the downhill running

clamp was performed, a 3-wk interval separated the tests

to allow recovery from the muscle damage resulting from

eccentric exercise.

On the morning of the clamp, the subjects reported to

the Clinical Research Center of the Washington Uni-

ersity Medical Center at 0700 h after an overnight fast. The

clamps were performed according to the procedures de-

scribed by De Fronzo et al. (8). A polyethylene catheter

was inserted into a dorsal hand vein that was warmed in a

heated box (75°C) for sampling of arterialized blood (23).

A second catheter was placed in an antecubital vein for

infusion of insulin, glucose (20% dextrose), [6,6-²H]-

glucose, and potassium chloride.

To measure hepatic glucose output (HGO), a [6,6-

²H]glucose (96% Tracer Technology, Somerville, MA)

prime (18 µmol/kg) was given at the beginning of a 2-h

equilibrium period, followed by a constant in-

fusion (0.22 µmol·kg⁻¹·min⁻¹), which was maintained

throughout baseline and the 2-h euglycemic clamp pe-

riod. After tracer equilibration a primed-continuous in-

fusion rate (µg·kg⁻¹·min⁻¹) of regular porcine insulin

(Sfjbh-Novio, Princeton, NJ) was begun and was main-

tained throughout the clamp. Blood samples for glucose

kinetics were collected before the tracer infusion and at

10-min intervals during the last 30 min of the baseline

period and the last 40 min of the hyperinsulinemic clamp

period. Plasma glucose levels were clamped at 90 mg/dl

during hyperinsulinemia by use of a variable glucose in-

fusion. Blood samples for plasma glucose and insulin
determination were drawn at 5- and 15-min intervals,

respectively, during the clamp. Blood samples for addi-
tional hormone, metabolite, and substrate measure-
ments were obtained before and at 110 min of the eugly-
cemic clamp.

Blood analysis. Plasma glucose concentration was

measured immediately by the glucose oxidase method

(Beckman Instruments, Fullerton, CA). Blood samples

for hormone, substrate, and metabolite measurements

were kept chilled on ice (except for serum free fatty acids

(FFA)], centrifuged at 4°C, and stored at −80°C for sub-

sequent analysis. Samples for insulin were assayed in
duplicate by a double-antibody radioimmunoassay (27).

Blood samples for epinephrine and norepinephrine deter-

mination were collected in tubes containing reduced glu-
thione and ethylene glycol-hist(β-aminoethoxy ether)-

N,N,N'-N'-tetraacetic acid. The samples were assayed

by a single isotopic derivative (radioenzymatic) method

(33). Blood samples for cortisol (10) and glucagon (9)

were dispensed into tubes containing aprotinin (FBA

Pharmaceuticals, New York, NY). Blood lactate (22),
glycerol (30), β-hydroxybutyrate (30), and alanine (5)

were determined enzymatically from perchloric acid

extracts. Serum FFA were determined using an enzymatic

colorimetric procedure (NEFA C kit, Wako Chemicals,

Dallas, TX).

Blood samples for [6,6-²H]glucose determination were

centrifuged, and the plasma (200 µl) was deproteinized

with 300 µl of cold acetone. After further centrifugation,

the supernatant was removed and evaporated and the

tenpentacetate derivative of glucose was formed by addi-
tion of 100 µl of acetic anhydride-pyridine (1:1). Glucose

was separated at 180°C on a 3% OV column, and its²H

isotopic abundance was measured by positive ion-chemi-
nical ionization mass spectrometry by use of selective ion

monitoring of mass-to-charge ratios of 333 and 331.

Calculations and statistics. Glucose appearance rate

(Ra) was calculated from plasma [6,6-²H]glucose enrich-

ments and rate of tracer infusion by use of the equation

[Ra = [(APE influsate/APE plasma glucose)-1] · F],

where APE is atoms percent excess, described previously

by Jahanor (16).

In this case, F represents the iso-

topic infusion rate (µg·kg⁻¹·min⁻¹). HGO was cal-

culated as Ra minus the glucose infusion rate. Glucose disposal

rates were calculated as glucose infusion rate plus HGO.

Differences among the experimental conditions were

examined by repeated-measures analysis of variance.

Specific mean differences were identified by a Newman-

Keuls post hoc test. All values are expressed as means ±

SE. The acceptable level for statistical significance

was 0.05.

RESULTS

Exercise. Exercise intensity was determined from

VO₂ measurements obtained during each bout. Downhill run-

ning elicited a VO₂ of 26.9 ± 4.2 ml·kg⁻¹·min⁻¹ or 60 ±

2% of VO₂ max, whereas the cycle ergometry elicited a VO₂

of 26.8 ± 4.0 ml·kg⁻¹·min⁻¹ or 60 ± 2% of VO₂ max. These

values were not significantly different. The eccentric ex-

ercise trial resulted in marked muscle soreness in the

quadriceps, gluteal, and lower leg muscles. The soreness

was progressive and appeared to peak 48-72 h after exer-

cise. No soreness was reported after the concentric exer-

cise trial.

Euglycemic-hyperinsulinemic clamps. Fasting plasma

SERUM GLYCEMIC LEVELS: CLINICAL AND EXPERIMENTAL STUDIES

1928

VO₂ max, maximal O₂ consumption.
ECCENTRIC EXERCISE INDUCES INSULIN RESISTANCE

CONTROL CONCENTRIC ECCENTRIC

FIG. 1. Plasma creatine kinase levels 48 h after eccentric and concentric exercise and under control conditions with no exercise. *Significantly different from concentric and control, P < 0.05.

TABLE 1. Effects of exercise on basal Ra and effect of exercise and hyperinsulinemia on HGO during euglycemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Basal Ra, mg·kg⁻¹·min⁻¹</th>
<th>Control</th>
<th>Concentric Exercise</th>
<th>Eccentric Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.20±0.19</td>
<td>1.99±0.24</td>
<td>2.33±0.13</td>
</tr>
<tr>
<td>HGO, mg·kg⁻¹·min⁻¹</td>
<td></td>
<td>0.66±0.64</td>
<td>0.65±0.27</td>
<td>0.77±0.26</td>
</tr>
</tbody>
</table>

Values are means ± SE of 6 subjs. Ra, glucose appearance rate; HGO, hepatic glucose output.

1.2 μU/ml for the control, concentric, and eccentric exercise trials, respectively) levels were similar among trials. Basal glucose Ra was also similar for the three clamps (Table 2).

During the euglycemic clamps, plasma glucose was maintained at 88 ± 0.3, 88 ± 1.0, and 89 ± 0.7 mg/dl for the eccentric exercise, concentric exercise, and control trials, respectively. Coefficients of variation for plasma glucose were 2.0 ± 0.3, 3.7 ± 0.3, and 2.6 ± 0.4% for eccentric exercise, concentric exercise, and control trials, respectively. Plasma insulin levels during the clamps were 32 ± 0.01, 38 ± 0.04, and 35 ± 0.01 μl/ml for eccentric exercise, concentric exercise, and control trials, respectively, and no significant differences were observed among trials.

During the final 30 min of the clamps, glucose disposal rates (Fig. 2) were significantly reduced after eccentric exercise (3.47 ± 0.51 mg·kg⁻¹·min⁻¹) compared with the concentric exercise (5.55 ± 0.94 mg·kg⁻¹·min⁻¹) and control trials (5.48 ± 1.0 mg·kg⁻¹·min⁻¹). Thirty minutes of moderate-intensity cycling exercise had no effect on glucose disposal measurements obtained 48 h after the exercise bout. HGO during hyperinsulinemia appeared to be elevated slightly during clamps performed after the exercise bouts; however, these differences were not significantly different (Table 2).

Metabolites and hormones. Resting concentrations of lactate, FFA, glycerol, β-hydroxybutyrate, and alanine were not different among trials (Table 3). During the hyperinsulinemic-euglycemic clamp, FFA levels were significantly depressed (P < 0.05) for all three trials and were not different among the trials. Lactate levels were increased during all three clamps, but the increase was statistically significant only during the control trial. Lactate concentrations during hyperinsulinemia were not significantly different among trials. Changes in glycerol, β-hydroxybutyrate, and alanine were not statistically significant.

Resting catecholamine, glucagon, and cortisol levels were not different among trials (Table 1). The insulin infusions led to a small increase in both norepinephrine and epinephrine. These increases were not significant and were not different among the trials. Both glucagon and cortisol were unchanged during the clamps, and no differences were found for either hormone when the response was compared among trials.
TABLE 4. Effects of exercise and hyperinsulinemia on concentration of plasma hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Control</th>
<th>Concentric Exercise</th>
<th>Eccentric Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Clamp</td>
<td>Basal</td>
</tr>
<tr>
<td>Cortisol, mg/dl</td>
<td>8.6</td>
<td>8.8</td>
<td>9.9</td>
</tr>
<tr>
<td>±1.7</td>
<td>±1.1</td>
<td>±2.7</td>
<td>±2.4</td>
</tr>
<tr>
<td>Epinephrine, pg/ml</td>
<td>39.8</td>
<td>45.3</td>
<td>37.7</td>
</tr>
<tr>
<td>±6.2</td>
<td>±9.4</td>
<td>±7.6</td>
<td>±5.4</td>
</tr>
<tr>
<td>Norepinephrine, pg/ml</td>
<td>166.8</td>
<td>182.8</td>
<td>163.5</td>
</tr>
<tr>
<td>±10.6</td>
<td>±12.8</td>
<td>±17.6</td>
<td>±15.4</td>
</tr>
<tr>
<td>Glucagon, ng/ml</td>
<td>108.4</td>
<td>112.2</td>
<td>114.5</td>
</tr>
<tr>
<td>±15.4</td>
<td>±16.8</td>
<td>±18.1</td>
<td>±12.2</td>
</tr>
</tbody>
</table>

Values are means ± SE of 6 subjs.

DISCUSSION

The principal finding in this study was that exercise induces muscle trauma and soreness results in a marked decrease (37%) in insulin-mediated whole body glucose disposal. This degree of insulin resistance 48 h after exercise is quite remarkable. The effect was independent of any measurable alteration in metabolite concentrations or the hormonal milieu, as evidenced by the data reported in Tables 3 and 4.

We previously showed that an acute bout of exhausting treadmill running caused an increased insulin response during a hyperglycemic clamp (19). The exhausting bout of treadmill running caused some muscle soreness and elevated CK levels. Although the hyperglycemic clamp does not permit a clear-cut conclusion regarding insulin action, the findings suggested that exercise of this nature may cause insulin resistance. The euglycemic-hyperinsulinemic clamp procedure used in the present study provides more specific information on the action of insulin by controlling the glycemic and insulimetric stimuli for glucose disposal. Thus, the reduced rate of glucose disposal after eccentric exercise provides more conclusive evidence that exercise of this nature leads to insulin resistance.

These data also show that relatively short-duration moderate-intensity cycling exercise had no measurable effect (either positive or negative) on insulin action at submaximal insulin levels 48 h after the exercise bout. These data do not agree with previous conclusions by Mikines et al. (24) regarding the duration of the effect of the last bout of exercise on insulin sensitivity. However, the length of the exercise bout in the two studies was considerably different (30 vs. 60 min), and this may have contributed to the contradictory conclusions. The fact that concentric exercise did not negatively affect glucose uptake suggests that it is the eccentric nature of the exercise that leads to insulin resistance.

Eccentric exercise involves lengthening of the muscle fibers as tension is developed and has been shown to produce pronounced and delayed muscle trauma (11, 14, 31). A number of investigators (11, 17, 28) showed ultrastructural changes in skeletal muscle after eccentric exercise, including evidence of disrupted sarcomeres, Z-band streaming, necrotic fibers, increased lysosomal activity, and infiltration of damaged fibers by macrophages, and/or mononuclear cells. Elevated CK levels and muscle soreness are routinely used as clinical indicators of muscle damage (34). The occurrence of muscle soreness and elevated CK levels after eccentric, but not concentric, exercise indicates that the eccentric exercise did cause muscle trauma. Thus, damage to skeletal muscle resulting from eccentric exercise appears to have contributed to the insulin resistance observed in this study. This conclusion is supported by our observation (unpublished data) that insulin-resistant individuals do not have elevated CK levels and do not generally complain of muscle soreness.

The observation of insulin resistance after trauma is not new (4, 13). This phenomenon, termed “stress diabetes,” is associated with decreased glucose disposal and elevated plasma glucose concentrations arising from reduced insulin action (4). Inadequate suppression of HGO at submaximal insulin concentrations contributes to the high plasma glucose concentrations. Elevated counter-regulatory hormones, including cortisol, glucagon, epinephrine, and norepinephrine, have been reported to mediate the response (1). The degree of trauma and muscle damage associated with this phenomenon is considerably greater than that after exercise. In the present study, slightly less hepatic suppression was present after eccentric exercise. However, differences in HGO were not statistically significant, and so we cannot say that hepatic insulin resistance was present. The relatively small sample size may have contributed to the absence of statistical significance; however, a power calculation indicated that 47 subjects would be required to avoid making a type II error. It is unrealistic in this type of study to include such a large number of subjects. Furthermore, because all subjects showed the same trend in HGO, we believe that the data reflect the physiological response to the treatment under the conditions of the study. None of the counter-regulatory hormones measured was elevated at rest or during the clamp performed after eccentric exercise. Thus, although inhibition of insulin action at the level of the peripheral tissue as a result of elevated counter-regulatory hormones cannot be ruled out, it does not appear that the hormones measured were responsible for the impaired glucose disposal.

Decreased insulin binding to skeletal muscle and interference with glucose transporter translocation in the plasma membrane are among the factors that may help explain the decreased glucose uptake after exercise-induced muscle trauma. However, the magnitude of the decrease in whole body glucose disposal (37%) relative to the localized muscle trauma appears too great to be entirely accounted for by actual damage to the muscle cells. Some systemic factor released as a result of the exercise-induced muscle trauma could possibly also play a role in inducing the insulin resistance. Previous reports of a circulating inhibitor of insulin action suggest that this factor may be involved in uncoupling the ability of insulin to stimulate glucose transport at a point beyond the binding of insulin to the insulin receptor on the plasma membrane (26).

It has been suggested that the enhanced insulin action associated with exercise may be due to an increase in muscle glycogen storage capacity and facilitates replacement of glycogen depleted during exercise (3). Although
prolonged or exhausting exercise is generally followed by
glycogen supercompensation in the active muscles (7),
this is not always the case, especially when the exercise
induces muscle damage. O’Reily et al. [29] showed that
muscle glycogen repletion is inhibited for up to 10 days
after eccentric exercise. Costill et al. [6] also found signif-
ically impaired glycogen resynthesis in muscle 72 h after
eccentric exercise. They suggested that inflammatory
cells compete with muscle for the available glucose and,
thus, less glucose is available for storage. Our data do not
support this suggestion but, instead, suggest that less
glycogen is available for storage because of impaired glu-
cose uptake by the muscle.

In conclusion, we have shown that exercise that
involves primarily eccentric work results in marked tran-
sient insulin resistance that is evident 48 h after the
exercise bout. Thus, in clinical trials, it is not advisable to
evaluate the effectiveness of exercise in promoting en-
hanced insulin action if the exercise protocol results in
muscle trauma or soreness. In addition, failure to re-
synthesize glycogen stores for several days after eccen-
tric exercise may be due to impaired insulin-mediated
uptake by skeletal muscle.

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