Gender differences in the regulation of amino acid metabolism

Linda S. Lamont,1 Arthur J. McCullough,2 and Satish C. Kalhan2

1Exercise Science Program, University of Rhode Island, Kingston, Rhode Island 02881; and 2The Schwartz Center for Metabolism and Nutrition, Case Western Reserve University School of Medicine at MetroHealth Medical Center, Cleveland, Ohio 44109

Submitted 11 November 2002; accepted in final form 9 June 2003

Lamont, Linda S., Arthur J. McCullough, and Satish C. Kalhan. Gender differences in the regulation of amino acid metabolism. J Appl Physiol 95: 1259–1265, 2003. Exercising men, compared with women, have a greater increase in leucine oxidation but not lysine rate of appearance. The cause for this sexual dimorphism is unknown; however, an inhibition of β-adrenergic-receptor activity has previously been shown to mediate amino acid metabolism (Lamont LS, McCullough AJ, and Kalhan SC. Am J Physiol Endocrinol Metab 268: E910–E916, 1995; Lamont LS, Patel DG, and Kalhan SC. J Appl Physiol 67: 221–225, 1989). This study was a gender comparison of leucine and lysine kinetics during a β-adrenergic-receptor blockade (β1,β2-blockade) and a placebo control by using a double-blind crossover protocol. Subjects exercised at 50% of their trial-specific maximal O2 consumption (1 h) after 7 days of dietary control. During exercise with β-blockade, men had an increased nonprotein respiratory exchange ratio (P < 0.001), whereas women had an increased circulation of free fatty acids (P < 0.001). The genders also displayed distinct differences in exercise amino acid kinetics. The men, but not the women, increased leucine oxidation (P < 0.005) and lysine rate of appearance (P < 0.009) when exercising during β-adrenergic blockade. This study indicates that during β-blockade, exercising men increase their need for amino acids (and carbohydrate) to fuel energy needs, whereas women increase their mobilization of fat, thereby requiring less alternative fuels such as carbohydrate and amino acids. Gender-specific fuel preferences during exercise are regulated by β-adrenergic-receptor activity. Substrate availability during exercise appears to modulate the amino acid oxidation differences between genders.

\[ l-\text{[L-13C]} \text{leucine}; l-\text{[\alpha-15N]} \text{lysine}; \text{prolonged exercise}; \beta-\text{adrenergic blockade} \]

Many studies indicate that there are gender-specific fuel preferences during exercise, with differences being reported in the contribution of fat, carbohydrate, and amino acids to total body energy needs (3, 7, 9, 13–15, 17, 18, 21, 22). The regulatory mechanism(s) for these gender-based differences in exercise fuel preference remains unknown, but there are studies to indicate that substrate metabolism can be influence by the female sex hormones (23). With respect to amino acid metabolism, endurance exercise has been shown to cause a greater increase in leucine oxidation but not lysine rate of appearance in men compared with women (9, 14, 17). The cause for this gender difference in leucine oxidation has not been attributable to differences within skeletal muscle, such as percent activation of muscle branched-chain 2-oxoacid dehydrogenase (14). Rather, it appears to be a compensatory response to fuel availability. Women derive more of their exercise energy needs from fat, thereby requiring less alternative fuels, such as amino acids and carbohydrate (9). Whether this sexual dimorphism in whole body amino acid metabolism can be mediated by β-adrenergic-receptor activity has not been studied.

Men may typically have heightened β-adrenergic-receptor stimulation during exercise due to a greater circulating epinephrine and norepinephrine level that has been reported in some (7, 13, 21) but not all studies (15, 18). Despite these reports of gender differences in β-receptor stimulation during exercise, there are no comparative studies of β-adrenergic regulation of amino acid metabolism. However, previous human studies do indicate that whole body amino acid metabolism can be mediated with an inhibition of β-adrenergic-receptor activity (8, 10). Specifically, when subjects of both genders were exercised in the presence of a β-adrenergic-receptor blockade, there were dramatic increases in leucine oxidation and lysine rate of appearance (8). These previous studies did not compare or isolate specific gender responses (8, 10). Therefore, the purpose of this experiment was to determine whether there are gender differences in the β-adrenergic-receptor regulation of leucine and, for comparison purposes, lysine metabolism.

METHODS

Subjects. Eight healthy, nonsmoking, individuals were recruited for this experiment. A physician performed a physical examination on all subjects to confirm that there were no medical reasons for their exclusion from this study. All subjects had normal electrocardiograms and were without a family or personal history of diabetes mellitus. The menstrual cycle phase has been shown to alter leucine kinetics in women (11). Therefore, the female subjects were studied during the follicular phase of their menstrual cycle.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: L. S. Lamont, 25 West Independence Way, Suite J, Kingston, RI 02881 (E-mail: lla4983u@postoffice.uri.edu).
during the follicular phase of their menstrual cycle (days 1–13) to reduce any confounding effects of their cycle. The follicular phase was determined by counting days from the onset of menses along with the use of a monoclonal antibody self-test kit (Ovukit, Quidel San Diego, CA). Male and female subjects were matched according to their age, exercise habits, and maximal oxygen consumption \( \dot{V}_{O_2} \max \); women = 43 ± 5.4 mL·kg\(^{-1}\)·min\(^{-1} \) and men = 48 ± 6.0 mL·kg\(^{-1}\)·min\(^{-1} \) (NS) as well as body weight (see Table 2). Our human experimentation review board approved this project, and written, informed consent was obtained from each subject before participation.

**Dietary and pharmacological procedures.** A registered dietitian designed standardized 1-wk meal plans for all subjects using dietary exchange procedures (4). An exchange list for meal planning was given to each subject along with specific menu ideas. The subjects repeated this weekly meal plan twice: once while ingesting a placebo (twice a day) and once while ingesting a \( \beta_1,\beta_2 \)-adrenergic blocking agent (propranolol, 80 mg twice a day). Both pills were formulated to be the same color and size and were distributed in a random, double-blind manner. A drug washout period of a minimum of 1 wk was interspersed between trials. These meal plans were designed to be weight maintaining and employed standard metabolic equations to determine daily energy needs (2, 5). The specific Harris-Benedict equation used to determine resting energy expenditure was as follows: women = 655 + (9.6 × weight) + (1.8 × height) − (4.7 × age) and men = 66 + (13.7 × weight) + (5 × height) − (6.8 × age). Each subject was required to maintain a daily dietary logbook. The dietary macronutrient composition was controlled in both genders and was 58–60% carbohydrate, 30% fat, and 10–12% protein. Daily caloric intake was 1260 kcal for men and 1290 kcal for women. The subjects repeated this weekly meal plan three times, with 7 days interspersed between each trial.

\( \dot{V}_{O_2} \) max was determined on day 4 or 5 of each trial with the use of a graded, cycle ergometer protocol. Therefore, each subject was \( \dot{V}_{O_2} \) max tested twice to calculate a trial-specific submaximal workload for the subsequent infusion study. \( \dot{V}_{O_2} \max \) was assessed with a metabolic cart that was calibrated with a standard gas mixture (model 2900, Sensor Medics, Yorba Linda, CA). \( \dot{V}_{O_2} \max \) was assumed if there was a plateau in oxygen uptake (\( \dot{V}_{O_2} \)) and/or a respiratory exchange ratio (RER) that exceeded one at maximal exercise.

**Tracer infusion studies.** To avoid an acute exercise recovery effect on leucine or lysine kinetics, the subjects were instructed to refrain from physical activity for 2 days before each infusion. The subjects reported to the Clinical Research Center (Case Western Reserve University) in a postabsorptive state (−15 h) on the morning of day 7 for both trials. Before each infusion, an intravenous cannula was placed into a superficial vein in each hand. One cannula was used for the tracer infusions of L-[1-\( ^{13} \)C]leucine (99 atom % excess of \( ^{13} \)C), L-[\( ^{15} \)N]lysine (99 atom % excess of \( ^{15} \)N), and sodium bicarbonate Na\( ^{13} \)CO\(_3\) (99 atom % excess of \( ^{13} \)C) (Merck, Dorval, Canada). All tracers were tested for sterility and pyrogenicity before the infusion and were weighed, dissolved in normal saline, and filtered (Micropore filter, 0.22 \( \mu \)m). The second intravenous cannula was used for blood sample collections and was kept patent with a saline infusion (10 mL/h). This sampling site was warmed to obtain arterialized venous blood.

Primed doses of the isotopes were administered to reach an early isotopic steady-state and were 1.2 \( \mu \)mol/kg of Na\( ^{13} \)CO\(_3\), 4.0 \( \mu \)mol/kg of L-[1-\( ^{13} \)C]leucine, and 6.8 \( \mu \)mol/kg of L-[\( ^{15} \)N]lysine. These priming doses were followed by a constant-rate infusion of labeled leucine at 5.0 \( \mu \)mol·kg\(^{-1}\)·h\(^{-1} \) and of lysine at 7.0 \( \mu \)mol·kg\(^{-1}\)·h\(^{-1} \). A background amount of labeled water \( [H_2^{18}O, 99 \text{ atom } \% \text{ excess of } ^{18}O; \text{ MSD Isotopes}] \) was orally given to assess total body water.

**Tracer infusion during rest.** The first 3 h of each infusion protocol included a supine rest that was used to obtain an isotopic plateau for the determination of resting leucine and lysine kinetics (8, 9). During this rest period, the venous blood samples were withdrawn every 30 min. These blood samples were immediately centrifuged, and the plasma was stored at −70°C for later biochemical analyses. Breath samples were collected every 30 min by using a Hans-Rudolph, one-way non-rebreathing valve that was connected to a 5-liter anesthesia bag. An aliquot of each breath sample was trapped in an evacuated glass tube for the subsequent analysis of \( ^{13} \)CO\(_2\). \( ^{13} \)CO\(_2\) production (\( V_{CO_2} \)) and \( V_{O_2} \) were determined continuously throughout rest. Leucine and lysine kinetics were calculated by using an averaged isotopic enrichment value (180 min of rest).

**Tracer infusion during exercise.** After 3 h of supine rest, each subject began exercising at 50% of his or her trial-specific \( \dot{V}_{O_2} \max \) (workloads were specific for the placebo and \( \beta \)-blockade trial). A constant-load, pan-weight Monark cycle ergometer was used (Varberg, Sweden). Blood samples were withdrawn at 0, 15, 30, 45, 50, 55, and 60 min of exercise. Heart rates were determined during rest and throughout exercise at 20, 30, 40, 45, 50, and 60 min. \( V_{O_2} \) and \( V_{CO_2} \) were continuously monitored with a Hans-Rudolph adult face mask that was interfaced with the metabolic cart. Aliquots of breath samples were trapped in an evacuated glass tube at 0, 5, 12, 17, 35, 45, 55, and 57 min of exercise for the subsequent determination of \( ^{13} \)CO\(_2\) enrichment. With this steady-state exercise procedure, there was an isotopic plateau in plasma \( [L-\text{KIC}] \) enrichments for both groups.

**Analytic methods.** Plasma free fatty acid (FFA) concentrations were determined according to Laurell and Tebbling (12). Total plasma protein concentration was measured with a refractometer (model SPR-TZ, Atago). The percent increase in plasma protein concentration during exercise was used to correct FFA concentrations for fluid volume shifts (19). Total 24-h urine volumes were collected on day 6 of each experiment, and urinary urea nitrogen excretion was determined with a colorimetric assay (640A, Sigma Chemical).

The method of Adams (1) was used to perform plasma derivatizations, and the \( \alpha \)-propyl N-acetyl ester was used for derivatizations, and the \( \alpha \)-propyl N-acetyl ester was used for hydrolysis and derivatization to \( \alpha \)-ketoisocaproate (KIC).

### Table 1. \( \alpha-[^{13} \)C\]KIC enrichments for both groups

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>( \beta )-Blocked</td>
<td>Placebo</td>
<td>( \beta )-Blocked</td>
</tr>
<tr>
<td>Rest</td>
<td>120 min</td>
<td>2.90 ± 0.06</td>
<td>3.11 ± 0.29</td>
<td>2.61 ± 0.33</td>
</tr>
<tr>
<td></td>
<td>150 min</td>
<td>2.89 ± 0.03</td>
<td>3.05 ± 0.11</td>
<td>2.63 ± 0.65</td>
</tr>
<tr>
<td>Exercise</td>
<td>45 min</td>
<td>3.22 ± 0.32</td>
<td>3.00 ± 0.12</td>
<td>2.65 ± 0.40</td>
</tr>
<tr>
<td></td>
<td>50 min</td>
<td>3.04 ± 0.08</td>
<td>2.93 ± 0.18</td>
<td>2.68 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>55 min</td>
<td>2.92 ± 0.23</td>
<td>2.92 ± 0.23</td>
<td>2.76 ± 0.39</td>
</tr>
</tbody>
</table>

Values are as means ± SE given in mol % excess. KIC, ketoisocaproate.
the subsequent quantitative analyses (1). The analytic methods employed to determine the $[^{13}C]$leucine and expired $^{13}$CO$_2$ enrichments have been described elsewhere (8–10). Plasma $\alpha$-KIC and lysine enrichments were measured with a Hewlett-Packard model 5985A gas chromatograph-mass spectrometer with selective ion-monitoring software. Selected ion monitoring was performed at a mass-to-charge ratio of 273/274 for lysine and of 174/175 for $\alpha$-KIC. The expired CO$_2$ was separated from each breath sample by cryogenic distillation, and the $^{13}$CO$_2$- to $^{12}$CO$_2$ ratio was measured on an isotope ratio mass spectrometer (8–10).

Calculations. Leucine kinetic calculations were corrected for background enrichment of expired CO$_2$ as well as for bicarbonate retention. The background enrichment of expired $^{13}$CO$_2$ was measured before each infusion. This background enrichment was subtracted from the isotopic plateau to calculate leucine kinetics (10). $\beta$-Blockade had no measurable effect on the $^{13}$C enrichment of CO$_2$ ($[^{13}C]_{\text{placebo}} = 1.0871 \pm 0.0005$ vs. $[^{13}C]_{\text{blocker}} = 1.0878 \pm 0.0005$) ($n = 8$). Therefore, no correction was made to breath CO$_2$ because of $\beta$-blockade. Leucine oxidation was corrected for bicarbonate retention as previously described (8). Body composition measures were determined by using the H$_2$O$_{18}$ tracer dilution method (20). Total body water and fat-free mass (FFM) were calculated with this labeled-water technique. An isotopic plateau for expired C$^{18}$O$_2$ was achieved within 3 h (9, 20).

Data analyses. Steady-state tracer kinetic equations were used to calculate leucine and lysine kinetics. The reciprocal pool model was used for the leucine kinetic calculations. The statistical analyses for this study included the three-way analysis of variance (gender $\times$ treatment $\times$ time) for leucine and lysine metabolism, RER, and blood measures. Time was a repeated measure. Statistical techniques also included the two-way analysis of variance for VO$_2$max, resting heart rates, and urinary urea nitrogen (gender $\times$ treatment). When a significant main effect was found, pairwise comparisons were performed with a Newman-Keuls post hoc test. A probability value of $P < 0.05$ was considered statistically significant. The statistical power for these data at an $\alpha$ of 0.05 included leucine kinetics (0.81), lysine kinetics (0.98), indirect calorimetry (0.96), urinary urea nitrogen (0.95), and circulating free fatty acids (0.96). Values are means $\pm$ SE.

RESULTS

Subjects. Table 2 indicates that there was no difference between genders in age, body weight, or body mass index (BMI). There was no significant change in body weight due to the treatments or throughout the duration of the experiment (F $= NS$). As expected, the men had a larger FFM (F $= 0.007$), and the women had a larger percent body fat (F $= 0.05$). VO$_2$max did not change due to the administration of the $\beta$-blocking drug (womenplacebo $= 42.8 \pm 5.4$ and women$\beta$-blocked $= 36.0 \pm 4.2$; menplacebo $= 47.7 \pm 6.0$ and men$\beta$-blocked $= 43.4 \pm 3.7$ ml·kg$^{-1}$·min$^{-1}$; P $= NS$). All subjects exhibited a significant reduction in $\beta$-adrenergic stimulation during the $\beta$-blockade trial as demonstrated by the decrease in resting heart rate (menplacebo $= 65.7 \pm 2.45$ and men$\beta$-blocked $= 50.5 \pm 1.32$ beats/min; womenplacebo $= 65.5 \pm 6.3$ and women$\beta$-blocked $= 56.5 \pm 3.0$ beats/min; P $< 0.002$). When both groups exercised in the presence of a $\beta$-blockade, the heart rates were significantly lower at all exercise time points (P $< 0.001$).

Expired gas measurements during submaximal exercise. Figure 1 displays the mean nonprotein RER values for both trials and both genders. The RER was found to exhibit a significant gender (P $< 0.001$), a significant treatment (P $< 0.04$), and a significant exercise effect (P $< 0.01$). Therefore, the RER values were significantly greater in the men compared with the women and significantly increased as a result of $\beta$-blocker administration. In the men, the RER during exercise was increased from rest during the $\beta$-blockade trial (P $< 0.05$). There was no significant gender $\times$ exercise interaction for the RER (P $= NS$).

**Table 2. Physical characteristics of the female and male subjects**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>FFM, kg</th>
<th>BMI, kg/m²</th>
<th>Body Fat, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 4)</td>
<td>28.8 ± 4.1</td>
<td>76.0 ± 3.9</td>
<td>67.5 ± 2.9</td>
<td>24.7 ± 1.6</td>
<td>12.8 ± 1.6</td>
</tr>
<tr>
<td>Women (n = 4)</td>
<td>30.8 ± 3.9</td>
<td>58.4 ± 5.1</td>
<td>47.2 ± 4.2</td>
<td>20.9 ± 1.2</td>
<td>20.0 ± 2.3</td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>NS</td>
<td>0.007</td>
<td>NS</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SE; n, no. of subjects. FFM, fat-free mass; BMI, body mass index; NS, nonsignificant.
FFA and urinary urea nitrogen concentrations. There was a significant gender ($P < 0.001$) and treatment ($P < 0.03$) effect on FFA concentration. Figure 2 indicates that, during both trials, the FFA concentrations were greater in the women compared with the men ($P < 0.05$). Additionally, during the β-blockade trial, the women had a heightened FFA concentration compared with their placebo control trial ($P < 0.05$). There was no gender $\times$ treatment interaction effect for FFAs ($P = \text{NS}$).

Urinary urea nitrogen excretion displayed a significant treatment effect. There was a significant increase in urinary urea nitrogen excretion during the β-blockade trial (placebo = 0.12 ± 0.02 vs. β-blockade = 0.17 ± 0.02 g·kg body wt$^{-1}$·24 h$^{-1}$; $P < 0.005$). There was no gender difference in urinary urea nitrogen excretion ($P = \text{NS}$).

Leucine kinetics. The leucine rate of appearance data (whole body protein breakdown) is located in Table 3. We found no significant gender, treatment, or exercise effect for leucine rate of appearance ($P = \text{NS}$). However, there was a significant gender ($P < 0.005$), treatment ($P < 0.05$), and exercise effect ($P < 0.001$) for leucine oxidation (displayed in Fig. 3). There was also a significant gender $\times$ time interaction effect for this measure ($P < 0.04$). Hence, leucine oxidation was significantly greater in men compared with women and was greater in exercise compared with rest. Women showed no change in exercise leucine oxidation when placebo control was compared with β-blockade, but the men had a heightened exercise leucine oxidation when their β-blockade and control trials were compared ($P < 0.05$). In addition, leucine oxidation during the β-blockade exercise trial in the men was greater compared with the female β-blockade exercise trial ($P < 0.05$). Nonoxidative leucine disposal (protein synthesis) demonstrated no gender or treatment effects. However, there was a significant exercise effect ($P < 0.002$). Table 3 indicates that nonoxidative leucine disposal was significantly reduced during exercise compared with rest ($P < 0.05$).

Lysine kinetics. Figure 4 illustrates the lysine rate of appearance data for both genders during both trials. There was a significant gender effect ($P < 0.009$) and a gender $\times$ treatment interaction for lysine rate of appearance ($P < 0.001$). During resting conditions, the β-blocked women had a decrease in lysine rate of appearance ($P < 0.05$), but no change was observed in the

Table 3. Mean leucine rate of appearance and nonoxidative disposal

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β-Blocked</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Rest</td>
<td>152.53 ± 4.83</td>
<td>143.35 ± 10.02</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
<td>138.45 ± 5.45</td>
<td>142.09 ± 4.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonoxidative leucine disposal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-Blocked</td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>136.50 ± 4.13</td>
<td>127.34 ± 8.31</td>
<td>141.32 ± 11.44</td>
</tr>
<tr>
<td>Exercise</td>
<td>112.10 ± 4.39*</td>
<td>115.46 ± 6.98*</td>
<td>113.51 ± 13.78*</td>
</tr>
</tbody>
</table>

Values are means ± SE given in μmol·kg$^{-1}$·h$^{-1}$. *Significantly different from rest, $P < 0.05$. 

*J Appl Physiol* • VOL 95 • SEPTEMBER 2003 • www.jap.org
DISCUSSION

The purpose of this investigation was to determine whether there are gender differences in the regulation of amino acid metabolism during exercise. We compared the response of leucine and lysine kinetics during a β-adrenergic-receptor blockade and a placebo control in pair-matched men and women. These gender pairs were matched on age, aerobic fitness, exercise habits, and body weight. Our subjects were more lean and aerobically fit than average, two factors that are known to influence gender-specific fuel utilization during exercise (15). To eliminate confounding influences on exercise metabolism, the preexperimental diet of our subjects was controlled. A gender difference in the β-adrenergic regulation of whole body amino acid metabolism during moderate-intensity, long-term exercise was found. Specifically, when exercising during a β₁,β₂-adrenergic-receptor blockade, the men increased their whole body leucine oxidation and lysine rate of appearance, whereas women exhibited no change in leucine oxidation and decreased their lysine rate of appearance.

We previously reported that there were no gender differences in lysine rate of appearance during rest, exercise, or exercise recovery (9). The present study indicates, however, that gender and β-adrenergic activity interact in their regulation of lysine kinetics. During β-adrenergic blockade and rest, lysine rate of appearance decreases in women but remains unchanged in men, thereby explaining the gender × treatment interaction effect. When the subject exercises in the presence of a β-adrenergic blockade, the lysine rate of appearance increases in men but decreases in women, again explaining the gender × treatment interaction. The likely explanation for these findings is that the regulation of lysine kinetics occurs through an interaction between gender-specific sex hormones and β-adrenergic-receptor activity.

These distinct differences in lysine kinetics were accompanied by gender differences in leucine metabolism. Leucine rate of appearance or whole body protein breakdown remained unaffected by gender, β-blockade treatment, or exercise time. Nonoxidative leucine disposal showed a significant main effect for time. Hence, there was a significant decrease in protein synthesis rate in both genders due to exercise. As has previously been reported, we found that the genders differ in whole body leucine oxidation (9, 14, 17). These men, compared with women, had a greater rate of leucine oxidation during endurance exercise. Leucine oxidation further increased in these men but not women when they exercised in the presence of a β-blockade. Exercise in combination with β-adrenergic-receptor blockade has previously been shown to heighten leucine oxidation rate in humans when studied without regard to gender (8, 10). It was concluded that β-adrenergic stimulation downregulates whole body leucine oxidation and that both the β₁- and β₂-adrenoreceptors mediate this downregulation (8, 10). The present data indicate that in men, compared with women, there was heightened branched-chain amino acid sensitivity to β-adrenergic-receptor inhibition. Whereas men doubled their rate of leucine oxidation when exercising in the presence of a β-blockade, women showed no β-adrenergic effect. This gender dimorphism in leucine oxidation might indicate that there are differences in the regulation of branched-chain 2-oxoacid dehydrogenase. However, previous research has failed to show a gender difference in skeletal muscle activation of branched-chain 2-oxoacid dehydrogenase activation due to exercise (17). To our knowledge, a gender comparison of β-adrenergic-receptor sensitivity of branched-chain 2-oxoacid dehydrogenase activation has not been done. Alternatively, this increased whole body leucine oxidation in our β-blocked men may be a metabolic compensation for the lack of other primary fuel sources (16). Our laboratory previously postulated that increased exercise leucine oxidation during β-blockade might be due to a fuel-mediated effect on whole body metabolism (8, 10). That is, leucine oxidation will be heightened during β-blockade in response to a reduction in other fuel sources such as FFA and glucose (8, 10). Subsequently, another research group has found an increased use of alternative fuels when humans exercised during β-adrenoreceptor blockade (16). They reported a suppression of lipolysis and FFA availability and an increase in glucose rate of disposal (carbohydrate oxidation) when humans exercise in the presence of a β-blockade (16). Unfortunately, a gender comparison was not

![Fig. 4. Lysine rate of appearance for both genders during both trials. Values are means ± SE. **Significant main effect for gender, P = 0.009. * Significant gender × treatment interaction effect, P = 0.001.](image-url)
made in any of these experiments (8, 10, 16). The present study extends previous findings to indicate that men, but not women, have a reduction in lipolysis and hence fat oxidation during β-blockade, thereby increasing their need for alternative fuels such as carbohydrate and amino acids.

This study and others have reported a significant main effect of gender on exercise energy metabolism (3, 7, 9, 13-15, 17, 18, 21, 22). Both animal and human studies have linked gender differences in carbohydrate, fat, and amino acid metabolism during exercise to the female sex hormones (see Ref. 23 for review). It has been reported numerous times that the genders differ in their relative contribution of fat and carbohydrate to exercise energy needs (3, 7, 9, 13–15, 17, 18, 21, 22). Women have a greater reliance on fat, and men a greater reliance on carbohydrate, to fuel long-duration exercise when conducted at similar relative intensities. These data build on those previous studies to indicate that gender-specific fuel regulation can be mediated by β-adrenergic-receptor activity. Men increase their reliance on carbohydrate when exercising in the presence of a β-adrenergic blockade. On the other hand, women are able to increase circulating FFA and fat availability during similar conditions (exercise with β-blockade). Therefore, when β-adrenergic-receptor activity is inhibited, men and women will increase their reliance on their gender-specific preferred fuels (i.e., carbohydrate in men and fat in women). Mittendorfer et al. (15) recently reported that whole body lipolytic rate and plasma FFA availability and uptake are greater in exercising women compared with men. These researchers employed a different methodological approach than ours, however, and matched their subjects according to body fat (adiposity) (15). They speculated that there could be three possible explanations for the higher lipolytic rates in women: increased adipose tissue sensitivity to β-adrenergic stimulation, a decreased α-adrenergic stimulation, or a combination of these two mechanisms (15). Our data show that women have increased adipose tissue sensitivity to adrenergic-receptor stimulation. It should be noted, however, that there is evidence of α-adrenergic-receptor activity inhibiting lipolysis during exercise in men but not women (6). Therefore, sexual dimorphism in fat availability during exercise appears to be at least partially mediated by β-adrenergic-receptor activity.

The significance of this study is that, for the first time, indicates that gender-specific preferences for amino acid oxidation during exercise are regulated by β-adrenergic activity. It has been known that amino acids provide a small percentage of energy needs during exercise and that men oxidize more amino acids than women, and these data now indicate that amino acids become an important alternative fuel for men (but not women) during times of substrate deficits. Our data also indicate that women do not need to draw on amino acids as an alternative fuel during β-adrenergic blockade because of an enhanced lipolytic responsiveness.

In summary, there is a sexual dimorphism in the regulation of whole body amino acid metabolism during exercise. Leucine oxidation and lysine rate of appearance during exercise showed a heightened sensitivity to β-adrenergic-receptor blockade in men but not women. This gender dimorphism was probably a compensation for a reduction in primary fuel sources in the men, notably circulating FFA. Moreover, women display an enhanced lipolytic responsiveness to β-adrenergic blockade, thereby sparing alternative fuels. To conclude, gender-specific fuel preferences during exercise are regulated by β-adrenergic-receptor activity. Substrate availability during exercise appears to modulate the amino acid oxidation differences between genders.

DISCLOSURES

This study was supported by American Heart Association (Dallas, TX) Grant AHA 91007450 and by National Institutes of Health Grants GCRC RR-00080 and HD-11089.

REFERENCES

5. Harris JA and Benedict FG. A Biometric Study of Basal Metabolism in Man. Washington, DC: Carnegie Institute, 1919. (Publ. no. 279)


