Combined effects of hyperaminoacidemia and oxandrolone on skeletal muscle protein synthesis

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Sheffield-Moore, Melinda, Robert R. Wolfe, Dennis C. Gore, Steven E. Wolf, Dennis M. Ferrer, and Arny A. Ferrando. Combined effects of hyperaminoacidemia and oxandrolone on skeletal muscle protein synthesis. Am. J. Physiol. Endocrinol. Metab. 278:E273–E279, 2000.—We investigated whether the normal anabolic effects of acute hyperaminoacidemia were maintained after 5 days of oxandrolone (Oxandrin, Ox)-induced anabolism. Five healthy men [22 ± 3 (SD) yr] were studied before and after 5 days of oral Ox (15 mg/day). In each study, a 5-h basal period was followed by a 3-h primed-continuous infusion of a commercial amino acid mixture (10% Travasol). Stable isotopic data from blood and muscle sampling were analyzed using a three-compartment model to calculate muscle protein synthesis and breakdown. Model-derived muscle protein synthesis increased after amino acid infusion in both the control [basal control (BC) vs. control + amino acids (C+AA); P < 0.001] and Ox study [basal Ox (BOx) vs. Ox + amino acids (Ox+AA); P < 0.01], whereas protein breakdown was unchanged. Fractional synthetic rates of muscle protein increased 94% (BC vs. C+AA; P = 0.01) and 53% (BOx vs. Ox+AA; P < 0.01), respectively. We conclude that the normal anabolic effects of acute hyperaminoacidemia are maintained in skeletal muscle undergoing oxandrolone-induced anabolism.

IN MOST CASES, THE MAINTENANCE of chronic protein homeostasis after injury, chronic illness, or trauma has been managed by providing nutritional support alone. However, results of prospective clinical trials using nutritional support as an adjunct therapy to primary treatment of cancer (9) and burns (14) indicate that muscle catabolism persists despite aggressive nutritional therapy. The difficulty in maintaining adequate nutritional status and lean muscle mass by simply providing nutrients to patients has led to the study of pharmacological agents such as oxandrolone (Oxandrin, Ox). Ox is a synthetic analog of testosterone currently used as an adjunctive approach to promote weight gain in patients after surgery, chronic infections, and severe trauma. Although anabolic agents such as Ox offer clinicians viable alternative to managing disease- or trauma-associated protein loss, few studies have directly measured protein synthesis and protein breakdown after androgen therapy.

In a companion study (15), we recently showed that Ox, given at a moderate dose of 15 mg/day for 5 days, increased the fractional synthetic rate (FSR) of skeletal muscle protein in normal healthy males by 44% in the postabsorptive state, with no change in fractional breakdown rate. Furthermore, a recent study from our laboratory showed that 5 days after a single intramuscular injection of testosterone enanthate (200 mg), FSR and model-derived protein synthesis increased twofold, with no change in fractional breakdown rate (11). Although these studies support the use of Ox or testosterone as anabolic hormones, the response during the postabsorptive state represents only part of the day. It is thus pertinent to assess whether the normal anabolic response to amino acids is retained after stimulation of the basal rate of muscle FSR by an anabolic hormone.

Data from our laboratory in normal resting males showed that amino acid infusion (10% Travasol) increased protein synthesis by ~150% after an overnight fast (8). More recently, Volpi et al. (17) showed that exogenous amino acids stimulate net muscle protein synthesis in the postabsorptive elderly patient. Furthermore, orally ingested amino acids also stimulate net muscle protein synthesis (16, 18). These data, along with studies in animals (19) and humans (2, 3, 12), indicate that amino acid availability is an essential component in regulating muscle protein metabolism. However, this may no longer be the case when the basal rate of protein synthesis has been elevated by administration of an anabolic hormone (i.e., oxandrolone). Therefore, using an established protein kinetic model (5, 7), we investigated whether the normal stimulatory effect of amino acids on muscle protein synthesis is maintained in skeletal muscle after Ox-induced anabolism.

METHODS

Subjects

Five healthy males [22 ± 3 (SD) yr; 76 ± 15 kg; 176 ± 5 cm] were studied in the postabsorptive state and after amino acid infusion both before and after taking Ox for 5 days. All subjects gave informed, written consent according to the guidelines established by the Institutional Review Board at the University of Texas Medical Branch at Galveston. Subjects were given a thorough medical screening, and eligibility

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Experimental Protocol

Studies were performed at the General Clinical Research Center (GCRC) at the University of Texas Medical Branch in Galveston. Subjects were admitted the night before each study and were fasted from 2200 until the completion of the 8-h study. At ~0630 the following morning (day 0), a 20-gauge polyethylene catheter (Insite-W, Becton-Dickinson, Sandy, UT) was inserted into the antecubital vein of one arm for purposes of infusion of amino acids. A second 20-gauge polyethylene catheter was placed in the contralateral wrist for purposes of blood sampling for measurement of systemic indocyanine green (ICG). A heating pad was placed around the arm and wrist to maintain a temperature of ~65°C during blood flow measurements.

Baseline blood samples were drawn at 0700 for the analysis of background amino acid enrichment, ICG concentration, and peak testosterone and oxandrolone concentrations. A primed (PD) continuous infusion of 99% pure labeled phenylalanine (Cambridge Isotope Laboratories, Andover, MA) was initiated 15 min before each 8-h infusion study. On the evening after the first infusion study (day 0 at 2100), all subjects began taking 15 mg of oxandrolone (BTG Pharmaceuticals, Iselin, NJ) orally each evening for 5 days. On day 3, subjects returned to the GCRC at 0700 for venous blood sampling to determine total testosterone and oxandrolone concentrations. This experimental protocol was repeated again on day 5.

Analytical Methods

Blood. Blood samples for the measurement of amino acid concentration and enrichment were collected as previously described (7). Briefly, a-v blood samples were collected in preweighed tubes containing 15% sulfosalicylic acid. A known internal standard was added to the blood samples (100 µl/ml of blood) for the measurement of blood amino acid concentrations. The composition of this standard mixture was 50.3 µmol/l of L-[ring−13C6]phenylalanine. After the tubes had been reweighed to determine final blood volume, the contents were centrifuged, and the supernatant was collected and stored at ~20°C until analysis. Blood amino acids were separated using cation exchange chromatography (21). The enrichments and the concentrations of phenylalanine in arterial and venous blood samples were determined on their tert-butyldimethylsilyl (t-BDMS) derivatives by use of gas chromatography-mass spectrometry (GC-MS) (21). The isotopic enrichment of free amino acids in blood was determined by GC-MS in electron impact mode with selected ion monitoring (model 5973, Hewlett-Packard, Palo Alto, CA). Finally, serum concentration of ICG was determined by means of a spectrophotometer at λ = 805 nm.

Muscle. Muscle samples were weighed and protein precipitated with 500 µl of 14% perchloric acid. A known internal standard solution (2 µl/mg of muscle tissue) was added to measure the intracellular concentrations of phenylalanine. The solution contained 2.4 µmol/l of L-[ring−13C6]phenylalanine. The supernatant was collected after homogenization of the tissue and centrifugation. This procedure was repeated three times. The amino acids in the pooled supernatant were then separated using cation exchange chromatography (21). The isotopic enrichment of the intracellular amino acids was determined on their t-BDMS derivatives (21) by GC-MS in electron impact mode. Intracellular enrichment was determined by correction for extracellular fluid on the basis of the chloride method (4). The remaining pellet was washed several times with 0.9% saline and again with absolute ethanol, dried at 50°C overnight, and hydrolyzed in 6 N HCl at 110°C for 24 h. The hydrolysate was then passed over a cation exchange column in the same manner as the blood was processed. Phenylalanine enrichment was measured by GC-MS (model 8000, MD 800, Fisons Instruments, Manchester, UK) in electron impact mode and the standard curve approach (13).

Amino Acids

<table>
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<th>Time (hr)</th>
<th>0</th>
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<td><strong>Arterio-venous Blood</strong></td>
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<td><strong>Leg Blood Flow</strong></td>
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Fig. 1. Stable isotope infusion protocol. ring-2H5-PHE, L-[ring-2H3]-phenylalanine.
Kinetic model. The mathematical derivation of the three-compartmental model of amino acid kinetics has been described in detail (7) and again in the companion study previously mentioned (15). However, we will briefly detail the kinetic parameters that make up the three-pool model of leg amino acid kinetics (Fig. 2). The assumptions and limitations of the kinetic model have also been described elsewhere (5, 8). However, it is important to note that the underlying assumptions of the kinetic model have also been described elsewhere (5, 8).

Calculations

Kinetic model. The mathematical derivation of the three-compartmental model of amino acid kinetics has been described in detail (7) and again in the companion study previously mentioned (15). However, we will briefly detail the kinetic parameters that make up the three-pool model of leg amino acid kinetics (Fig. 2). The assumptions and limitations of the kinetic model have also been described elsewhere (5, 8). However, it is important to note that the underlying assumptions of the kinetic model hold true even when the overall pool size of phenylalanine is increased after a primed, continuous infusion of amino acids. Because calculation of the model parameters depends on the maintenance of steady-state physiological conditions, we primed the amino acids and infused at a constant infusion rate. Finally, a-v sampling took place in the last hour of the 3-h amino acid infusion once blood amino acid concentrations and enrichments achieved steady state.

The protocol used in this study was designed to simultaneously assess both the kinetics of intracellular free amino acids and the FSR of muscle proteins by the incorporation of labeled phenylalanine. Enrichment data are expressed as tracer-to-trace ratio. The model enables the calculation of the rate of amino acid delivery by the femoral artery (F in) to the leg and also those amino acids leaving the leg via the femoral vein (F out). Therefore, intercompartmental movement of amino acids is considered to occur between the artery (A), vein (V), and muscle (M). Inward amino acid transport from A to M (F M,A) and outward amino acid transport from M to V (F V,M) occur via the femoral artery and vein, respectively. Thus inward (F in) and outward (F out) tissue transport was calculated as follows

\[ F_{\text{in}} = C_A \cdot BF \]  
\[ F_{\text{out}} = C_V \cdot BF \]  
\[ F_{M,A} = \frac{[\left(E_M - E_V\right)\left(E_A - E_M\right)] \cdot C_V + C_A \cdot BF}{EM} \]  
\[ F_{V,M} = \frac{[\left(E_M - E_V\right)\left(E_A - E_M\right)] \cdot C_V + C_V \cdot BF}{EV} \]

where \( C_A \) and \( C_V \) and \( E_A \) and \( E_V \) are amino acid concentrations and tracer enrichments in the femoral artery and vein, and \( E_M \) is enrichment in the muscle. BF represents leg blood flow. Amino acids that bypass the muscle via the femoral artery can be calculated by the following expression

\[ F_{V,A} = F_{\text{in}} - F_{M,A} = F_{\text{out}} - F_{V,M} \]

The model also enables the calculation of the rate of intracellular appearance (F M,O) of amino acids from protein breakdown and the rate of amino acid utilization (F O,M) for protein synthesis. Amino acid appearance and utilization are calculated by the following formulas, respectively

\[ F_{M,O} = F_{M,A} \cdot \left(\frac{E_A - E_M}{EM} - 1\right) \]  
\[ F_{O,M} = \left(C_A \cdot E_A - C_V \cdot E_V\right) \cdot BF/EM \]

The following expression represents the total rate of appearance (R A M) of the intracellular amino acids, which is a function of protein breakdown (F M,O) and inward tissue transport (F M,A)

\[ R_A = F_{M,O} + F_{M,A} \]

Protein synthesis efficiency. Using phenylalanine, we calculated the relative efficiency of protein synthesis as follows

\[ PSE = \frac{F_{O,M}}{F_{M,A} + F_{M,O}} \]

PSE is defined as the fraction of the intracellular amino acid rate of appearance that is incorporated into muscle proteins, taking into account that phenylalanine is not oxidized in the muscle. Therefore, F O,M represents the amount of amino acid incorporated in the muscle proteins.

FSR. Using the traditional precursor-product method, we determined the FSR of muscle proteins by measuring the rate of phenylalanine tracer incorporation into protein and the enrichment of the intracellular pool as the precursor

\[ \text{FSR} = \frac{\left(E_{p2} - E_{p1}\right)\left(E_M \cdot t\right)}{60 \cdot 100} \]

where \( E_{p1} \) and \( E_{p2} \) are the enrichments of the protein-bound \( L\)-(ring-\(^{2}H_3\)) phenylalanine at the 2- and 5-h and again at the 5- and 8-h sampling time points. Average intracellular \( L\)-(ring-\(^{2}H_3\)) phenylalanine enrichment is \( E_M \), and time in minutes is represented by \( t \). To express FSR in percent per hour (%/h), the expression is then multiplied by the factors 60 (min/h) and 100, respectively. The assumptions and limitations necessary for the traditional derivation have been outlined previously (20, 23).
Table 1. Effects of amino acid infusion on phenylalanine free amino acid enrichments in femoral artery, femoral vein, and muscle before and after oxandrolone administration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Phenylalanine Enrichments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Femoral Artery</td>
</tr>
<tr>
<td>Basal control</td>
<td>0.0640 ± 0.004</td>
</tr>
<tr>
<td>Control + amino acids</td>
<td>0.0398 ± 0.002*</td>
</tr>
<tr>
<td>Basal oxandrolone</td>
<td>0.0683 ± 0.002</td>
</tr>
<tr>
<td>Oxandrolone + amino acids</td>
<td>0.0404 ± 0.002*</td>
</tr>
</tbody>
</table>

Enrichment data (means ± SE) are expressed as a tracer-to-tracer ratio. Significant difference between phenylalanine free amino acid enrichments from basal state to amino acid infusion both before and after oxandrolone administration (*P < 0.05).

Statistical Analysis

Group comparisons were performed using a one-way ANOVA. Post hoc comparisons were accomplished using a one-tailed t-test with Bonferroni correction for multiple comparisons. Statistical significance was established at P < 0.05. Data are presented as means ± SE.

RESULTS

Steady-state blood amino acid concentrations and enrichments were maintained during each sampling hour (240–300 and 420–480 min) both before and after 5 days of Ox administration. All data identifying Ox's protein synthetic effect in the basal state, as well as its hormonal effects, have been presented elsewhere (15). Only data related to the response of skeletal muscle to amino acid infusion will be presented.

As depicted in Table 1, free amino acid enrichments in the femoral artery, vein, and muscle decreased significantly after amino acid infusion, whereas amino acid infusion significantly increased phenylalanine concentration in the femoral artery and vein (Table 2). Leg blood flow was unaffected during amino acid infusion alone [basal control (BC) vs. control + amino acids (C+AA), 4.3 ± 0.9 vs. 5.3 ± 0.8 ml·min⁻¹·100 ml leg⁻¹] or with amino acids and Ox combined [basal oxandrolone (BOx) vs. oxandrolone + amino acids (Ox+AA); 4.0 ± 0.8 vs. 3.7 ± 0.5 ml·min⁻¹·100 ml leg⁻¹]. FSR of muscle protein increased 94% (BC vs. C+AA; 0.0570 ± 0.004 vs. 0.1104 ± 0.013%/h, P = 0.01) and 53% (BOx vs. Ox+AA; 0.0820 ± 0.009 vs. 0.1252 ± 0.008%/h, P < 0.01; Fig. 3).

Table 3 depicts the model-derived parameters of leg muscle free amino acid kinetics of the five subjects in the control and Ox study after amino acid infusion. As expected, arterial delivery to the leg (Fᵢᵢ) increased significantly in the control and Ox study after amino acid infusion (P < 0.01). However, arterial delivery to the leg (Fᵢᵢ) was significantly less when amino acids were given after Ox treatment (P = 0.02). As a consequence, model-derived muscle protein synthesis (F₀₉) was unchanged from C+AA to Ox+AA. However, if synthesis was expressed relative to amino acid delivery to the leg (Fᵢᵢ), a combined effect of Ox and amino acids was seen compared with amino acids alone (P = 0.03; Fig. 4). The intracellular rate of appearance of phenylalanine (Fₐₐ), index of protein breakdown, was unaffected by either amino acid infusion or Ox. However, consistent with the direct incorporation data, the rate of intracellular utilization of phenylalanine for protein synthesis (F₀₉) increased significantly after amino acid infusion in both the control and Ox studies (BC vs. C+AA, P < 0.001; BOx and Ox+AA, P < 0.01; Table 3).

Amino acid infusion resulted in a shift in net balance from a net negative output to a net positive uptake both before and after Ox (Table 3). No difference was seen in net balance from C+AA to Ox+AA (45 ± 12 vs. 30 ± 8). Finally, protein synthesis efficiency remained unchangeable, with no significant differences observed between basal and Ox states.
and after oxandrolone administration.

Table 3. Effects of amino acid infusion on model-derived leg muscle amino acid kinetics before and after oxandrolone administration

<table>
<thead>
<tr>
<th>Kinetic Parameter</th>
<th>Basal Control</th>
<th>Control + Amino Acids</th>
<th>Basal Oxandrolone</th>
<th>Oxandrolone + Amino Acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial delivery (F_in)</td>
<td>263 ± 46</td>
<td>591 ± 83*</td>
<td>227 ± 42</td>
<td>401 ± 54§</td>
</tr>
<tr>
<td>Venous outflow (F_vo)</td>
<td>293 ± 46</td>
<td>545 ± 83*</td>
<td>228 ± 45</td>
<td>371 ± 55†</td>
</tr>
<tr>
<td>Inward transport (F_M,A)</td>
<td>144 ± 17</td>
<td>294 ± 59</td>
<td>124 ± 25</td>
<td>245 ± 55†</td>
</tr>
<tr>
<td>Outward transport (F_V,M)</td>
<td>175 ± 15</td>
<td>249 ± 64</td>
<td>125 ± 296</td>
<td>215 ± 58</td>
</tr>
<tr>
<td>Protein breakdown (F_M,O)</td>
<td>83 ± 8</td>
<td>81 ± 15</td>
<td>69 ± 8</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>Protein synthesis (F_O,M)</td>
<td>53 ± 3</td>
<td>127 ± 6*</td>
<td>68 ± 5†</td>
<td>111 ± 8†</td>
</tr>
<tr>
<td>Intracellular appearance (Rb_M)</td>
<td>228 ± 16</td>
<td>376 ± 61</td>
<td>193 ± 32</td>
<td>326 ± 64‡</td>
</tr>
<tr>
<td>Net balance (NB)</td>
<td>-30 ± 6</td>
<td>45 ± 12*</td>
<td>-1 ± 4</td>
<td>30 ± 8§</td>
</tr>
<tr>
<td>Protein synthesis (F_O,M/F_in) (Relative to arterial delivery)</td>
<td>0.22 ± 0.02</td>
<td>0.23 ± 0.03</td>
<td>0.35 ± 0.07</td>
<td>0.31 ± 0.06§</td>
</tr>
</tbody>
</table>

Data are means ± SE of 5 subjects expressed as nmol phenylalanine·min⁻¹·100 ml leg⁻¹. *Significantly different after amino acid infusion in control period (Basal Control vs. Control + Amino Acids), P < 0.05. †Significantly different after amino acid infusion following 5 days of oxandrolone administration (Basal Oxandrolone vs. Oxandrolone + Amino Acids), P < 0.05. ‡Significantly different after 5 days of oxandrolone administration (Basal Control vs. Basal Oxandrolone), P < 0.05. §Significantly different after amino acid infusion from control to oxandrolone (Control + Amino Acids vs. Oxandrolone + Amino Acids), P < 0.05.

DISCUSSION

We examined the response of muscle protein kinetics to an acute amino acid infusion before and after oxandrolone-induced anabolism. We demonstrated that both the model-derived value for muscle protein synthesis and the traditionally derived value of the FSR of muscle protein increased with infusion of amino acids both before and after oxandrolone-induced anabolism in young men. We did not, however, show a statistically significant increase in the FSR of muscle protein when comparing amino acids alone with the combination of oxandrolone and amino acids. However, when the model-derived measure of muscle protein synthesis (F_O,M) was expressed relative to arterial delivery (F_in), to the leg, the synthetic effect of amino acids was maintained, despite the ongoing anabolism of oxandrolone. The lower arterial delivery during oxandrolone and amino acids presumably reflected accelerated amino acid uptake in other tissues in addition to the muscle. Muscle anabolism during amino acid infusion occurred by stimulation of protein synthesis, because protein breakdown was unchanged. Moreover, protein synthetic efficiency was unchanged with amino acid infusion from control to oxandrolone, indicating that no greater fraction of the available intracellular amino acids was incorporated into muscle proteins.

We recently reported that 5 days of oxandrolone administration increased skeletal muscle anabolism by stimulation of protein synthesis, because protein breakdown was unchanged (15). Also, we reported a significant decrease in outward amino acid transport (F_V,M), along with a calculated increase in protein synthetic efficiency, together indicating increased intracellular reutilization of amino acids (15). These findings demonstrated the anabolic potential of oxandrolone in the skeletal muscle of normal fasted young men with only 5 days of administration. However, an individual is only postabsorptive for part of the day. The overall effectiveness of oxandrolone is thus dependent on the response during food intake as well. We, as well as others, have shown that increased availability of amino acids is a primary stimulus for muscle anabolism in the fed state. Data from our own studies in both young (8) and elderly (17) volunteers indicate that the stimulation of inward amino acid transport to the leg is the mechanism whereby the intravenous infusion of amino acids stimulates net muscle protein synthesis (8, 17). In agreement with our previous findings (8, 17), results from the present study indicate that protein synthesis efficiency did not change during amino acid infusion in the fasted state. In combination, these results identify amino acid availability as the rate-limiting factor in muscle protein synthesis in the fasted state. In contrast to the action of amino acids, anabolic hormones such as insulin (6), testosterone (11), and oxandrolone (15) increase the efficiency of protein synthesis while not affecting amino acid availability.

Several investigations have examined the in vivo response of skeletal muscle to insulin by utilizing the
arteriovenous balance method (1, 6, 10, 12, 22). From these results, we can deduce that, whereas insulin has the potential to stimulate muscle protein synthesis, this can only be reflected in an increased rate of synthesis if an adequate availability of amino acids is maintained. Thus systematically administered insulin can only stimulate muscle protein synthesis if amino acids are administered simultaneously. In contrast, the stimulation of muscle protein synthesis by oxandrolone does not require exogenous amino acids (15). Nonetheless, the current results indicate that exogenous amino acids stimulate muscle protein synthesis in subjects treated with oxandrolone. We can thus anticipate an overall anabolic effect of oxandrolone, because not only is protein synthesis increased in the postabsorptive state, but also the normal stimulatory effect of amino acids on muscle protein synthesis is maintained.

In the present study, amino acid infusion before and after oxandrolone administration significantly increased arterial delivery to the leg (Fi\textsubscript{a}) compared with basal (postabsorptive) arterial delivery. As a consequence, muscle protein synthesis was greatly improved in both cases. However, despite the considerable increase in arterial delivery with amino acids combined with oxandrolone, arterial delivery was significantly less than with amino acids alone. As a consequence, no further increase in muscle protein synthesis was realized. Thus, because delivery has an effect on protein synthesis, and delivery was reduced when amino acids were given to subjects who had been given oxandrolone, it is reasonable to examine protein synthesis relative to delivery. Therefore, by expressing synthesis relative to amino acid delivery to the leg, a combined effect of oxandrolone and amino acids was seen compared with amino acids alone. The retention of the anabolic effect of amino acids during oxandrolone treatment, coupled with the anabolic effect of oxandrolone alone on net muscle protein synthesis in the postabsorptive state, leads to the expectation of an overall anabolic effect of oxandrolone treatment on muscle protein.

The investigators thank the subjects who participated in this study. Also, many thanks to the nurses and staff of the University of Texas Medical Branch General Clinical Research Center (GCRC) for their assistance with this project, Lakshmi McRae for nursing support, Zhi Ping Dong for sample analysis, and BTG Pharmaceuticals for providing the study drug.

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