Acute effects of resistance exercise on muscle protein synthesis rate in young and elderly men and women

KEVIN E. YARASHESKI, JEFFREY J. ZACHWIEJA, AND DENNIS M. BIER

Metabolism Division, Washington University School of Medicine, St. Louis, Missouri 63110


—Muscle mass and function are improved in the elderly during resistance exercise training. These improvements must result from alterations in the rates of muscle protein synthesis and breakdown. We determined the rate of quadriceps muscle protein synthesis using the in vivo rate of incorporation of intravenously infused [13C]leucine into mixed-muscle protein in both young (24 yr) and elderly (63–66 yr) men and women before and at the end of 2 wk of resistance exercise training.

Before training, the fractional rate of muscle protein synthesis was lower in the elderly than in the young (0.030 ± 0.003 vs. 0.049 ± 0.004 %/h; P = 0.004) but increased (P < 0.03) to a comparable rate of muscle protein synthesis in both young (0.075 ± 0.009 %/h) and elderly subjects (0.076 ± 0.011 %/h) after 2 wk of exercise. In the elderly, muscle mass, 24-h urinary 3-methylhistidine and creatinine excretion, and whole body protein breakdown rates determined during the [13C]leucine infusion were not changed after 2 wk of exercise. These findings demonstrate that, during the initial phase of a resistance exercise training program, a marked increase in quadriceps muscle protein synthesis rate occurs in elderly and young adults without an increase in the rate of whole body protein breakdown. In the elderly, this was not accompanied by an increase in urinary 3-methylhistidine excretion, an index of myofibrillar protein breakdown.

Methods

Subjects. Six healthy elderly men and women and six healthy young men and women (Table 1) volunteered for this study, which was approved by the Human Studies Review Board at Washington University School of Medicine. Informed consent was obtained after the purpose and procedures were described.

Before enrollment, all subjects were screened for cardiovascular, metabolic, and neuromuscular disease and received a physical examination, including a medical history, blood chemistry profile (SMA-12), complete blood cell count, and urinalysis. In addition, the elderly subjects were required to pass a Bruce treadmill graded exercise test. None of the young women studied were taking birth control pills, and the phase of their menstrual cycle during which they were studied was not standardized. There is no evidence suggesting that the rate of human muscle protein synthesis is affected by the cycle phase.

These tests were followed by a 3-day meat-free controlled protein diet (elderly subjects only) for estimations of muscle protein breakdown and muscle mass by urinary excretion of 3-methylhistidine and creatinine. On the last day of the diet, the rates of skeletal muscle protein synthesis and whole body protein breakdown were determined in the overnight-fasted condition using an intravenous infusion of [13C]leucine (described below).

Exercise protocol. All subjects then completed 2 wk of daily supervised progressive resistance exercise consisting of moderate- to high-intensity (60–90% maximum strength) low-repetition (4–10) weight lifting performed for 2–4 sets/exercise ses-
Data for each young man and elderly woman are shown. Weight equipment (shoulder press for the elderly and squats) and upper body exercises (biceps curl, shoulder press, deltoid lifts, bench press, latissimus pulldown, arm cross) were performed predominantly on Nautilus machines but also included some free-weight equipment (shoulder press for the elderly and squats). Typically, the first 5 days (Monday-Friday) of exercise consisted of 2–3 sets/exercise, 8–10 repetitions/set at 60–75% of maximum strength (one-repetition maximum). The subjects did no resistive exercise on the weekends, and the second 5 days of exercise consisted of 3–4 sets/exercise, 4–8 repetitions/set at 75–90% of maximum strength. The subjects were instructed to lift the weight in 2 s and to lower the weight in 4 s, taking no less than 2 min and no more than 5 min of rest between exercise sets.

As expected, initial muscle strength was lowest in the elderly women, highest in the young men, and similar in the young men and elderly men (Table 2). Therefore, when exercise intensity was prescribed as a percentage of the maximum strength, the elderly women and men were lifting less absolute weight than the young women and men, respectively, but the relative exercise intensity (percentage of maximum strength lifted) was equivalent for all subjects during training. On the final day of exercise and within 3 h of the last exercise session for the lower body, the final measurement of muscle protein synthesis was initiated.

Whole body protein breakdown and skeletal muscle protein synthesis rates were studied in the young subjects first and provided preliminary information about the acute effects of resistance exercise on these processes. After these data were analyzed, it became clear that indexes of muscle mass and muscle protein breakdown would enhance interpretation of the data. Consequently, the subsequent experiments in the elderly included estimates of muscle mass and myofibrillar protein breakdown using 24-h urinary excretion measures of creatinine and 3-methylhistidine while the subjects consumed a meat-free diet.

### Table 1. Descriptive characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Subjects</th>
<th>Age, yr</th>
<th>Height, cm</th>
<th>Weight, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young women</td>
<td>4</td>
<td>24±1</td>
<td>167±3</td>
<td>65±6:2.7</td>
</tr>
<tr>
<td>Young men</td>
<td>2</td>
<td>24/24</td>
<td>185/175</td>
<td>83:4/71.0</td>
</tr>
<tr>
<td>Elderly women</td>
<td>2</td>
<td>60/73</td>
<td>165/162</td>
<td>67:9/58:8</td>
</tr>
<tr>
<td>Elderly men</td>
<td>4</td>
<td>63±1</td>
<td>172±2</td>
<td>79:3±2.7</td>
</tr>
</tbody>
</table>

Values are means ± SE for young women and elderly men. Individual data for each young man and elderly woman are shown.

**Table 2. Initial maximum voluntary strength of young and elderly subjects**

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Young Women</th>
<th>Young Men</th>
<th>Elderly Women</th>
<th>Elderly Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps curl</td>
<td>10±1.2</td>
<td>11±1.3</td>
<td>7±0.6</td>
<td>11±1.7</td>
</tr>
<tr>
<td>Shoulder press</td>
<td>7±0.2</td>
<td>10±1.4</td>
<td>5±0.1</td>
<td>11±1.4</td>
</tr>
<tr>
<td>Deltoids</td>
<td>7±8.2</td>
<td>13±11</td>
<td>5±4.7</td>
<td>8±4±1</td>
</tr>
<tr>
<td>Bench press</td>
<td>9±8.2</td>
<td>14±17</td>
<td>7±6.5</td>
<td>12±8±1</td>
</tr>
<tr>
<td>Arm press</td>
<td>6±6.0</td>
<td>10±9</td>
<td>4±5.5</td>
<td>7±2±1</td>
</tr>
<tr>
<td>Latissimus</td>
<td>9±1.1</td>
<td>12±12.5</td>
<td>5±6.5</td>
<td>11±2±1</td>
</tr>
<tr>
<td>Knee extension</td>
<td>18±2±4</td>
<td>22±19</td>
<td>14±11</td>
<td>16±4±3</td>
</tr>
<tr>
<td>Leg press</td>
<td>16±0.4</td>
<td>20±21</td>
<td>14±13</td>
<td>18±2±5</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>9±2±0.9</td>
<td>13±11</td>
<td>6±5.25</td>
<td>8±2±0.6</td>
</tr>
</tbody>
</table>

Values are means ± 5D. Values represent maximum no. of 4.5-kg weights lifted (one-repetition maximum). Elderly subjects were unable to lift minimum number of weights (2 × 4.5 kg) on shoulder press.

**Dietary control.** Dietary intakes were not measured in the young adults. In previous studies from our laboratory carried out with this population of young individuals (28), their dietary energy intake and composition were calculated by a research dietitian as follows: 160 ± 8 kJ (38 ± 2 kcal)·kg⁻¹·day⁻¹, 1.5 ± 0.1 g protein·kg⁻¹·day⁻¹, 15 ± 1% calories from protein, 51 ± 2% from carbohydrate, and 30 ± 1% from fat. To assure a comparable meatless protein intake in the elderly adults, they were interviewed by a research dietitian who assessed each subject’s typical food and caloric consumption patterns and designed a 3-day meat-free meal plan that consisted of 1.5 g protein·kg⁻¹·day⁻¹ and 126 150 kJ (30 36 kcal)·kg⁻¹·day⁻¹. These meals (3 daily and snacks) were prepared and served to each subject in the General Clinical Research Center. The subjects were instructed to eat no other food and to eat all of the food provided. Any small amount not consumed was weighed, and the daily intake record was corrected. During the exercise program the subjects returned to their typical eating habits but consumed the identical meal plan during the final 3 days of the exercise program before repeating the measurement of muscle protein synthesis and whole body protein breakdown.

**Muscle protein metabolism.** The elderly subjects collected all urine excreted during the 3-day meat-free diet into bottles provided and labeled with the date and time of collection. All urine collected during the same 24-h period after the bladder was emptied was mixed, the volume recorded, and an aliquot frozen (−20°C) for creatinine and 3-methylhistidine analyses. 3-Methylhistidine concentration was determined on an automated amino acid analyzer (high-pressure liquid chromatography with fluorescence detection) using lithium buffers and an ion-exchange column (Beckman Instruments, Palo Alto, CA). Urinary creatinine was determined colorimetrically using a commercially available automated analyzer (Kodak Ektachem 700XR). Skeletal muscle mass was estimated from creatinine excretion assuming 20 kg muscle mass·g creatinine excreted−¹ 24-h period−¹ (15). Urinary indexes of muscle mass and myofibrillar protein breakdown were calculated by averaging the analytical results from the last two of each subject’s three 24-h urine collections. The urinary creatinine measures verified that all urine produced during each 24-h period before and after exercise was collected.

On the evening of the 3rd day of the controlled meal plan, both before starting the exercise program (initial) and −3 h after the final exercise session (final), each subject was admitted to the General Clinical Research Center where, during an overnight fast (12–14 h), a primed (7.58 μmol/kg) constant intravenous infusion (7.58 μmol·kg⁻¹·h⁻¹) of either [1-¹³C]leucine or [1,2,1-¹³C₂]leucine (Tracer Technologies, Somerville, MA) was used to estimate the rate of whole body protein breakdown using the reciprocal pool approach (1) and to determine the fractional rate of muscle protein synthesis (4, 29). In blood samples taken before and at 30 min intervals during the last 4 h of the infusion, plasma α-ketoisocaproic acid was isolated, chemically derivatized, and analyzed using positive chemical ionization mass chromatography-mass spectrometry (24). The plasma [1-¹³C]-ketoisocaproic acid enrichment (atom %excess) was used to calculate the rate of whole body protein breakdown [systemic leucine rate of appearance in μmol·kg⁻¹·h⁻¹ (1)] and was used as the precursor pool enrichment for the calculation of the rate of muscle protein synthesis (22, 27). Muscle [¹³C]leucine content was measured in one muscle sample (−16–30 mg wet wt) removed from the vastus lateralis ~1.5–2 h after the [¹³C]leucine infusion began and in a second muscle sample removed from the contralateral vastus lateralis at the end of the infusion (28). Muscle [¹³C]leucine enrichment was measured in hydrolyzed mixed muscle protein as the n-acetyl n-propyl ester using
gas chromatography-combustion-isotope ratio mass spectrometry (29). As mentioned previously (29), \([1,2^{13}C_2]\)leucine was used in two young and one elderly subject to improve the sensitivity of the muscle leucine enrichment measure.

**Statistical analysis.** To determine whether changes in muscle protein metabolism occurred within a group, the initial and final measures were evaluated with a paired t test. To assess changes in muscle protein synthesis between the groups, delta scores (final - initial) and percent change scores were computed for each group and compared using Student’s t test. Means ± SE are reported.

**RESULTS**

The fractional rate of muscle protein synthesis increased in the young from 0.049 ± 0.004 to 0.075 ± 0.009 %/h \((P = 0.03)\) and in the elderly from 0.030 ± 0.003 to 0.076 ± 0.011 %/h \((P = 0.01; \text{Fig. 1})\). In the elderly, the absolute rate of muscle protein synthesis was estimated as the fractional rate of synthesis times muscle protein mass \([\text{assuming elderly skeletal muscle is 19% protein (i)}]\) and increased from 1.6 ± 0.3 to 3.7 ± 0.8 g protein/h \((P = 0.02)\) after 2 wk of resistance exercise. The initial fractional rate of muscle protein synthesis was lower \((P = 0.004)\) in the elderly than in the young, but, after 2 wk of exercise, the rate of muscle protein synthesis was identical in the two age groups (Fig. 1). The absolute increase (final - initial) in the rate of muscle protein synthesis in the elderly \((0.046 ± 0.009 \%)\) was not significantly greater \((P = 0.1)\) than the absolute increase in the young adults \((0.026 ± 0.008 \%)\). However, because the initial rate of muscle protein synthesis was lower (38%) in the elderly, when the increase in the elderly was expressed as a percent increment \((155 ± 24\%)\) above the initial value, this difference was significantly greater \((P = 0.01)\) than the percent increment in the young adults \((57 ± 20\%)\).

Finally, in these young and elderly men and women, there appeared to be no gender difference with respect to muscle protein synthesis rate (Fig. 1). This permitted us to group men and women to examine the effects of resistance exercise on muscle protein synthesis in the elderly and young, but the small number of subjects of each sex prohibits definite conclusions regarding gender differences.

In the elderly, the exercise regimen did not change the daily urinary excretion of 3-methylhistidine or creatinine; consequently, the ratio 3-methylhistidine/creatinine excretion was not altered (Table 3). As expected, muscle mass was not changed during this short exercise program; therefore, the increase in the absolute rate of muscle protein synthesis was due exclusively to an increase in the fractional rate of \([^{13}C]\)leucine incorporation into mixed muscle protein. In the absence of an increase in myofibrillar protein breakdown estimated by urinary 3-methylhistidine excretion, only 100–150 g new muscle protein would have accumulated in the elderly if the increment in the absolute rate of muscle protein synthesis was extrapolated over the duration of the exercise program. This change is below the detection limits of the creatinine excretion estimate of muscle mass.

In agreement with the urinary index of myofibrillar protein catabolism, whole body protein breakdown rate was not changed after 2 wk of resistance exercise in either the young or the elderly (Table 4). In addition, the rate of whole body protein breakdown \([\text{systemic leucine rate of appearance (1)}\] in \(\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}\) was lower in the elderly than in the young adults, both before \((P = 0.05)\) and after \((P = 0.03)\) the resistance exercise program. However, if the rate of whole body protein breakdown was expressed per unit lean mass \([\text{assuming fat-free mass is } \sim 63\text{ and } \sim 72\% \text{ of body mass in elderly women and men, respectively (10, 12), and } \sim 79\text{ and } \sim 83\% \text{ of body mass in young women and men, respectively (7, 10, 28)}]\), then the fasting whole body protein breakdown rates were not significantly different \((P = 0.12)\) between the elderly \((124 ± 3 \mu\text{mol} \cdot \text{kg} \cdot \text{fat-free mass}^{-1} \cdot \text{h}^{-1})\) and young subjects \((134 ± 5 \mu\text{mol} \cdot \text{kg} \cdot \text{fat-free mass}^{-1} \cdot \text{h}^{-1})\).

**DISCUSSION**

These findings demonstrate that the fractional rate of quadriceps muscle protein synthesis is reduced with ad-

![Fig. 1. Fractional vastus lateralis muscle protein synthesis rate measured in young (A) and elderly (B) men and women before and after 2 wk of resistance exercise training. Open symbols represent men, and filled symbols represent women. *\(P = 0.03\) vs. initial, \(\#P = 0.004\) vs. initial value for young subjects.](image-url)
protein turnover in the elderly. When expressed per unit of fat-free mass, the rate of whole body protein breakdown was similar between the young and the elderly, despite the fact that the elderly had less total body protein. This implies that advancing age does not alter the intrinsic rate at which body proteins degrade. Instead, on a per unit protein basis, the rate of whole body protein breakdown appears to be sustained with age, as has been previously reported (12, 13, 26), but the fractional rate of muscle protein synthesis declines. This may at least partially explain the reduction in muscle protein (7) that occurs with advancing age. These findings are consistent with the previous suggestion (26) that muscle protein turnover contributes less and other proteins contribute more to the rate of whole body protein turnover in the elderly.

Conversely, there is also some preliminary evidence suggesting that, on a per unit fat-free mass basis, whole body protein breakdown rate is slightly higher ($P = 0.073$) and, when expressed per unit of muscle mass, is significantly higher ($P < 0.05$) in the elderly than in young men matched for body mass index (3). Taken collectively, these observations suggest that the concept that aging decreases the rate of whole body protein metabolism and reduces dietary protein requirements needs to be reexamined.

In summary, these studies demonstrate directly for the first time that the skeletal muscle protein synthesizing pathways are activated in elderly and young men and women after 2 wk of resistance exercise. This was not accompanied by an increase in the rate of whole body protein breakdown, and, at least in the elderly, an index of myofibrillar protein breakdown was also not increased. These data suggest that, during the initial phase of a resistance exercise training program, the muscles of elderly men and women experience a rapid stimulation in the rate of muscle protein synthesis, which in absolute terms is similar in magnitude to the increase in muscle protein synthesis observed in young men and women. These findings help explain how muscles hypertrophy in response to resistance exercise and may influence estimates of dietary protein requirements in physically active elderly men and women.

Table 4. Whole body protein breakdown rate measured before and at end of 2 wk of resistance exercise in young and elderly men and women

<table>
<thead>
<tr>
<th>Group</th>
<th>Whole Body Protein Breakdown Rate, pmol·kg$^{-1}$·h$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>Young</td>
<td>110±7*</td>
</tr>
<tr>
<td>Elderly</td>
<td>87±5*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Whole body protein breakdown rate was determined using constant intravenous infusion of $[^{13}C]$leucine (see METHODS). * $P < 0.05$ vs. young subjects.

would counterbalance the large initial increment in muscle protein synthesis rate and reduce the rate of accumulation of muscle protein.

When expressed per unit of fat-free mass, the rate of whole body protein breakdown was similar between the young and the elderly, despite the fact that the elderly had less total body protein. This implies that advancing age does not alter the intrinsic rate at which body proteins degrade. Instead, on a per unit protein basis, the rate of whole body protein breakdown appears to be sustained with age, as has been previously reported (12, 13, 26), but the fractional rate of muscle protein synthesis declines. This may at least partially explain the reduction in muscle protein (7) that occurs with advancing age. These findings are consistent with the previous suggestion (26) that muscle protein turnover contributes less and other proteins contribute more to the rate of whole body protein turnover in the elderly.

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Address for reprint requests: K. E. Yarasheski, 660 S. Euclid Ave., Metabolism Division, Box 8127, Washington University School of Medicine, St. Louis, MO 63110.

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