Functional impact of high protein intake on healthy elderly people

Stephane Walrand, Kevin R. Short, Maureen L. Bigelow, Andrew J. Sweatt, Susan M. Hutson, and K. Sreekumaran Nair

Endocrinology Research Unit, Mayo Clinic School of Medicine, Rochester, Minnesota; and Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Submitted 24 June 2008; accepted in final form 11 August 2008

Walrand S, Short KR, Bigelow ML, Sweatt AJ, Hutson SM, Nair KS. Functional impact of high protein intake on healthy elderly people. Am J Physiol Endocrinol Metab 295: E921–E928, 2008. First published August 12, 2008; doi:10.1152/ajpendo.90536.2008.—Decline in muscle mass, protein synthesis, and mitochondrial function occurs with age, and amino acids are reported to enhance both muscle protein synthesis and mitochondrial function. It is unclear whether increasing dietary protein intake corrects postabsorptive muscle changes in aging. We determined whether a 10-day diet of high [HP; 3.0 g protein·kg fat-free mass (FFM)−1·day−1] vs. usual protein intake (UP; 1.5 g protein·kg FFM−1·day−1) favorably affects mitochondrial function, protein metabolism, and nitrogen balance or adversely affects insulin sensitivity and glomerular filtration rate (GFR) in 10 healthy younger (24 ± 1 yr) and 9 older (70 ± 2 yr) participants in a randomized crossover study. Net daily nitrogen balance increased equally in young and older participants, but postabsorptive catabolic state also increased, as indicated by higher whole body protein turnover and leucine oxidation with no change in protein synthesis. Maximal muscle mitochondrial ATP production rate was lower in older people, with no change occurring in diet. GFR was lower in older people, and response to HP was significantly different between the two groups, with a significant increase occurring only in younger people, thus widening the differences in GFR between the young and older participants. In conclusion, a short-term high-protein diet increased net daily nitrogen balance but increased the postabsorptive use of protein as a fuel. HP did not enhance protein synthesis or muscle mitochondrial function in either young or older participants. Additionally, widening differences in GFR between young and older patients is a potential cause of concern in using HP diet in older people.

dietary protein; protein metabolism; mitochondrial function; kidney function; aging

AGE IS ASSOCIATED WITH A PROGRESSIVE DECLINE in body protein content, as reflected by declining fat-free mass (FFM) (33). The reduction in FFM is attributed mainly to loss of skeletal muscle, i.e., sarcopenia, and is associated with reduced muscle strength and exercise endurance as well as predisposition to many metabolic disorders (33). The disabilities related to sarcopenia and associated disorders are not fully assessed but result in substantial health care costs (25).

One of the potential mechanisms contributing to sarcopenia is reduced muscle protein synthesis, which was shown to decline by 3.5% per decade (49). Aging is also associated with reductions in the skeletal muscle mitochondrial ATP production and the abundance of mitochondrial DNA and transcripts of genes that encode mitochondrial proteins (44, 47). Reduced ability to produce ATP, the key chemical form of energy for cellular functions, could potentially contribute to the vitality of the aging population and may contribute to the overall reduction in many muscle functions (33). The reduced ability to maintain muscle proteins may result from decreased sensitivity of muscle to efficiently use exogenous amino acids for protein anabolism. It has been reported (56) that skeletal muscle protein synthesis increases in elderly people following administration of amino acids by either intravenous or oral routes (55). Moreover, amino acids play a key role in translational regulation of protein synthesis (54). Administration of insulin and amino acids can enhance mitochondrial biogenesis and ATP production (51). Collectively, these data demonstrate that acute administration of amino acids increases net protein balance in skeletal muscle of older people by enhancing protein synthesis and may improve mitochondrial function. However, it remains to be determined whether increasing dietary protein over a longer period improves postabsorptive muscle protein synthesis and muscle mitochondrial function, in which case such an approach has potential in treating/preventing age-related muscle changes.

We addressed the hypothesis that increased protein intake improves whole body and muscle protein synthesis and enhances muscle mitochondrial function in healthy younger and older people. To test this hypothesis, we examined the effect of 10-day “usual” or “high” protein diets on whole body and skeletal muscle protein metabolism and muscle mitochondrial function. We also measured insulin sensitivity and glomerular filtration rate (GFR) to address concerns that a high-protein diet may adversely affect insulin action and kidney function.

MATERIALS AND METHODS

Subjects. Ten younger and 10 older participants were enrolled in the study between November 2003 and September 2004. Nineteen participants completed the study, and one older person withdrew for unknown reasons. Data and analyses presented are for the 10 younger and nine older people who completed the study (Table 1). Participants were recruited from the local community through advertisements and were paid for their participation. All were healthy based on history, physical examination, and laboratory tests. Exclusion criteria included body mass index ≥32 kg/m², smoking, pregnancy, regular exercise for more than 30 min twice/wk during the past 3 mo that could impact the study outcomes, and medications including β-blockers, steroids, and any medication affecting metabolism or muscle, endocrine, cardiovascular, or digestive function.

Study protocol. The study was approved by the Institutional Review Board of the Mayo Clinic, and written, informed consent was obtained before participation. A randomized crossover design was used to compare the effects of 10 days of usual protein (UP) to 10...
days of high dietary protein (HP). Participants received both diets in a random order. The same measurements were performed at the end of both dietary periods, and the two study phases were separated by 2–8 wk. A single-blind design was used; i.e., participants were not told whether they were in the UP or HP phases. Since protein turnover and energy expenditure are more closely related to FFM than body mass, the diets were prescribed on the basis of FFM, with 1.5 g·kg FFM\(^{-1}\)·day\(^{-1}\) for the UP diet and 3.0 g·kg FFM\(^{-1}\)·day\(^{-1}\) for the HP diet. The UP diet was based on the average protein intake of the US population (http://www.cdc.gov/nchs/nhanes.htm) (57), whereas the HP diet had twice the protein content of UP (Table 2). Dietary energy from protein as a percentage of calories was 11 (younger) and 12% (older) in the UP diets and 21 (younger) and 24% (older) of calories in the HP diets, respectively. Carbohydrate content of both diets was kept constant at 50% of calories, whereas the fat content was adjusted to keep the diets isocaloric. All food was prepared in the Metabolic Kitchen at the Clinical Research Unit of the Mayo Clinic Center for Translational Science Activities (CTSA) during the 10-day dietary periods. Calorie (energy) intake was based on resting metabolic rate and physical activity levels to maintain body weight. Participants were weighed daily, and total dietary energy intake was adjusted to ensure weight maintenance. Compliance to the diet was checked by measuring 24-h urinary nitrogen and protein oxidation rate at the end of each 10-day dietary period. Body composition was measured at beginning of the study using dual-energy X-ray absorptiometry (DPX-IQ; Lunar) (26). This measurement was not repeated after each test since it was considered unlikely that a significant change in body composition would be detected with only 10 days of dietary intervention. Subjects were admitted on the evening of day 8, and testing including collection of 24-h urine was performed on days 9–11; other tests were performed following an overnight fast.

**Methods.** GFR was measured on day 9 of each experimental period using nonradioabeled iothalamate meglumine (Conray 60%), as pre-

Table 1. **Subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Younger (n = 5 Women/5 Men)</th>
<th>Older (n = 4 Women/5 Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>24.3±1.2</td>
<td>70.0±1.8*</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>69.5±5.3</td>
<td>77.8±2.8</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>23.3±1.0</td>
<td>27.2±0.9*</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>48.5±4.1</td>
<td>45.7±4.1</td>
</tr>
<tr>
<td>Body fat, %mass</td>
<td>17.4±0.5</td>
<td>27.1±0.8*</td>
</tr>
</tbody>
</table>

*Values are means ± SE. BMI, body mass index; FFM, fat-free mass. \(^*P<0.05\) vs. younger participants.

Insulin sensitivity was measured on day 10 using an intravenous glucose tolerance test after an overnight fast, as described previously (4, 53). The glucose dose was 0.3 g/kg body wt, and the insulin dose was 0.03 IU/kg body wt. The minimal model was used to calculate insulin sensitivity (4). Glucose was measured with a Beckman Glucose Analyzer (Beckman Instruments, Porterville, CA). Insulin and human growth hormone were measured with two-site immunoenz-

Table 2. **Energy and protein intake and substrate oxidation rate**

<table>
<thead>
<tr>
<th></th>
<th>UP</th>
<th></th>
<th>Older</th>
<th>HP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake</td>
<td>kcal/day</td>
<td>kcal·kg BW(^{-1})·day(^{-1})</td>
<td>kcal·kg FFM(^{-1})·day(^{-1})</td>
<td>kcal/kg BW(^{-1})·day(^{-1})</td>
<td>kcal·kg FFM(^{-1})·day(^{-1})</td>
</tr>
<tr>
<td>kcal/day</td>
<td>2,615±155</td>
<td>38.4±2.17</td>
<td>55.2±1.8</td>
<td>72.7±2.6</td>
<td>1.40±0.03</td>
</tr>
<tr>
<td>kcal·kg BW(^{-1})·day(^{-1})</td>
<td>2,626±148</td>
<td>38.2±1.2</td>
<td>55.4±2.1</td>
<td>146.5±12.9*</td>
<td>2.08±0.07*</td>
</tr>
<tr>
<td>kcal·kg FFM(^{-1})·day(^{-1})</td>
<td>2,314±105</td>
<td>29.8±1.0*</td>
<td>51.2±1.7</td>
<td>68.6±4.6</td>
<td>0.89±0.05</td>
</tr>
<tr>
<td>Protein intake</td>
<td>148 2,314</td>
<td>12.9*</td>
<td>68.6*</td>
<td>137.1±9.5*</td>
<td>1.79±0.10*</td>
</tr>
<tr>
<td>%Total energy</td>
<td>2,147 3,174</td>
<td>12.9*</td>
<td>68.6*</td>
<td>137.1±9.5*</td>
<td>1.79±0.10*</td>
</tr>
<tr>
<td>Substrate oxidation, mg·kg FFM(^{-1})·min(^{-1})</td>
<td>1.03±0.07</td>
<td>1.44±0.08*</td>
<td>1.17±0.06</td>
<td>1.41±0.05*</td>
<td>1.03±0.07</td>
</tr>
<tr>
<td>Protein</td>
<td>2.04±0.23</td>
<td>1.76±0.46</td>
<td>1.57±0.38</td>
<td>1.30±0.30</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>1.29±0.12</td>
<td>1.24±0.13</td>
<td>1.41±0.20</td>
<td>1.28±0.16</td>
<td></td>
</tr>
</tbody>
</table>

Data are means ± SE. UP, usual-protein diet; HP, high-protein diet; BW, body weight. \(^*P<0.05\) vs. UP; \(^*P<0.05\) vs. younger participants (same diet).
younger and older groups and between dietary phases.

Substrate oxidation rate. Carbohydrate and lipid oxidation rates were calculated by indirect calorimetry, as reported previously (17). Leucine oxidation rate was converted to the corresponding estimate of whole body protein oxidation using the conversion constant (24 h/day)/(590 μmol leucine/g protein) to yield grams of oxidized protein per day. These values matched closely with protein oxidation on the basis of urinary nitrogen (r = 0.92, P < 0.01) but were less variable.

Muscle biochemistry. Skeletal muscle branched-chain aminotransferase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD) protein expression and activities were measured as described previously (1, 15). Skeletal mitochondrial ATP production rate was measured with a bioluminescent technique after mitochondrial isolation from fresh tissue, and activity of citrate synthase was measured as described previously (47).

Statistical analysis. Data are presented as means ± SE, and statistical analysis was performed using StatView program 4.02 (Abacus Concepts, Berkley, CA). A repeated-measures analysis of variance was used to discriminate among the effects of age and diet. An a posteriori Fisher test was applied as appropriate to locate pairwise differences among means, i.e., categorical variables, after adjustments for multiple comparisons were made (Bonferroni adjustment). Student’s t-test was also used to compare subject characteristics. P < 0.05 was considered as significant. Preliminary data on the whole body Leu flux and oxidation, muscle protein FSR, and mitochondrial ATP production rate (47, 48, 51) were used to estimate whole body Leu flux and oxidation, muscle protein FSR, and mitochondrial ATP production rate (47, 48, 51) were used to estimate whole body protein oxidation using the conversion constant (24 h/day)/(590 μmol leucine/g protein) to yield grams of oxidized protein per day. These values matched closely with protein oxidation on the basis of urinary nitrogen (r = 0.92, P < 0.01) but were less variable.

Muscle biochemistry. Skeletal muscle branched-chain aminotransferase (BCAT) and branched-chain α-keto acid dehydrogenase (BCKD) protein expression and activities were measured as described previously (1, 15). Skeletal mitochondrial ATP production rate was measured with a bioluminescent technique after mitochondrial isolation from fresh tissue, and activity of citrate synthase was measured as described previously (47).

Statistical analysis. Data are presented as means ± SE, and statistical analysis was performed using StatView program 4.02 (Abacus Concepts, Berkley, CA). A repeated-measures analysis of variance was used to discriminate among the effects of age and diet. An a posteriori Fisher test was applied as appropriate to locate pairwise differences among means, i.e., categorical variables, after adjustments for multiple comparisons were made (Bonferroni adjustment). Student’s t-test was also used to compare subject characteristics. P < 0.05 was considered as significant. Preliminary data on the whole body Leu flux and oxidation, muscle protein FSR, and mitochondrial ATP production rate (47, 48, 51) were used to estimate sample size. Nine or 10 subjects per group were expected to provide 80% power to detect 20–30% differences in these variables between younger and older groups and between dietary phases.

RESULTS

Protein intake and substrate oxidation. By design, dietary protein intake was doubled during the HP vs. UP diet (Table 2). The HP diet resulted in a similar increase in protein oxidation in both age groups, from 1.03 ± 0.07 to 1.44 ± 0.08 mg·kg FFM⁻¹·min⁻¹ in younger and from 1.11 ± 0.06 to 1.41 ± 0.05 mg·kg FFM⁻¹·min⁻¹ in older participants, but did not significantly change oxidation rates of either carbohydrate or fat. There were no differences in fuel oxidation with age on either diet.

Insulin sensitivity and hormone profile. Insulin sensitivity and the acute insulin response to glucose did not vary with age or diet (Table 3). Likewise, fasting glucose and insulin and growth hormone concentrations did not vary with diet, although growth hormone changed with age (P < 0.05).

Table 3. Insulin sensitivity and hormone profile

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UP</td>
<td>HP</td>
</tr>
<tr>
<td>S0, 10⁻⁵ ml·min⁻¹·pmol⁻¹·g⁻¹</td>
<td>7.5 ± 1.4</td>
<td>9.5 ± 1.8</td>
</tr>
<tr>
<td>AIRg,m U/l·min⁻¹</td>
<td>445 ± 103</td>
<td>418 ± 62</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>5.1 ± 0.2</td>
<td>5.0 ± 0.2</td>
</tr>
<tr>
<td>Fasting insulin, μU/ml</td>
<td>6.3 ± 1.2</td>
<td>6.5 ± 1.0</td>
</tr>
<tr>
<td>Growth hormone, ng/ml</td>
<td>1.4 ± 0.6</td>
<td>1.4 ± 0.7</td>
</tr>
</tbody>
</table>

Data are means ± SE. S0, insulin sensitivity; AIRg,m, acute insulin response to glucose. There were no significant differences due to age or diet.

Whole body and muscle protein metabolism. The flux rates of both lysine and leucine, indexes of whole body protein degradation, increased significantly in both younger and older participants on the HP diet (Fig. 1). Lysine flux was significantly (10%) lower in older vs. younger people while on the HP diet only, but no other age differences in flux rates were evident. The recovery fraction of 13CO2 was 13% lower in older vs. younger people, i.e., 75% in younger and 65% in older people. Thus, for calculations of leucine oxidation, recovery factors of 0.75 for younger participants and 0.65 for older participants were used. Compared with the UP diet, leucine oxidation increased on the HP in both groups, from 27.4 ± 1.8 to 38.2 ± 2.1 μmol·kg FFM⁻¹·min⁻¹ in younger participants and from 31.2 ± 1.5 to 37.3 ± 1.3 mg·kg FFM⁻¹·min⁻¹ in older participants, with younger participants showing greater increase (39%) than older (20%) participants. When expressed as a percentage of leucine flux, however, the increase in leucine oxidation on the HP diet was only significant in younger people. Compared with younger people, older people had higher leucine oxidation relative to leucine flux on the UP diet (21.5 ± 1.2 vs. 27.3 ± 1.3%), with a similar trend (P = 0.068) on the HP diet (28.2 ± 1.3 vs. 31.7 ± 1.6%). Nonoxidative leucine disposal, an index of whole body protein synthesis rate, was not significantly affected by diet, and there was no significant age effect. Nitrogen balance also did not differ with age but did increase nearly twofold on the HP diet in both groups from 2.77 ± 0.11 to 5.42 ± 0.45 g·kg FFM⁻¹·day⁻¹ in younger participants and from 2.48 ± 0.12 to 5.32 ± 0.18 g·kg FFM⁻¹·day⁻¹ in older participants. There were no significant differences in muscle protein synthesis with either age or diet.

Amino acid and KIC concentrations and muscle BCAT and BCKD. Fasting plasma total concentrations, nonessential and essential amino acid concentrations, and the concentrations of leucine and lysine were not affected by age or dietary treatment (Table 4). However, BCAA concentration increased 25% on the HP diet in younger but not older people, resulting in a difference between groups only during the HP diet. KIC concentration also increased on the HP diet only in younger (12%) but not older people.

The skeletal muscle concentration of lysine was higher in older vs. younger people during the UP but not the HP diet. Muscle lysine increased 47% in the younger group but was not affected by diet in the older group. Muscle leucine did not differ with either age or diet. There were also no differences with age or dietary treatment in the activity or protein expression of BCAT or the basal or total activity of BCKD.

GFR. GFR was significantly lower in older participants during both diets (older was only an average of 76.8% of younger participants during UP and 57.7% during HP; Fig. 2). Compared with the UP diet, GFR increased 17% [from 105.9 ± 3.6 to 127.8 ± 5.7 ml·min⁻¹·surface area (SA)⁻¹, P < 0.05] on the HP diet in the younger participants, whereas it tended to decline (9%) in the older group (from 81.3 ± 6.5 to 74.0 ± 6.3 ml·min⁻¹·SA⁻¹, P = 0.13), leading to a significance difference between groups in the adaptation response to the HP diet (P < 0.05). As a result, the age-related differences in GFR between younger and older participants increased (P < 0.05). GFR of older people was ~77% of younger people during UP diet and ~58% during HP diet.
Mitochondrial ATP production rate and citrate synthase activity. Muscle mitochondrial ATP production was significantly (35–40%) lower in older vs. younger people on either diet when measured using substrates that supply electrons primarily to complex I (glutamate + malate) or complex II (succinate + rotenone) of the electron transport chain (Table 5). Citrate synthase activity was also 16–21% lower in older people. Adjusted for the lower citrate synthase activity, which suggests lower mitochondrial content, ATP production was still significantly lower in older vs. younger people (19–27%). There were no effects of diet on these measurements in either age group.

DISCUSSION

The current study demonstrates that 10 days of a high-protein diet result in increased whole body protein turnover and...
Table 4. Amino acid concentrations and skeletal muscle BCAT and BCKD activity

<table>
<thead>
<tr>
<th></th>
<th>Younger (UP)</th>
<th>Younger (HP)</th>
<th>Older (UP)</th>
<th>Older (HP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma, μmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total amino acids</td>
<td>2,570±94</td>
<td>2,488±119</td>
<td>2,457±93</td>
<td>2,570±164</td>
</tr>
<tr>
<td>Nonessential amino acids</td>
<td>1,575±62</td>
<td>1,544±76</td>
<td>1,592±68</td>
<td>1,640±117</td>
</tr>
<tr>
<td>Essential amino acids</td>
<td>995±54</td>
<td>944±53</td>
<td>865±41</td>
<td>930±65</td>
</tr>
<tr>
<td>Branched-chain amino acids</td>
<td>415±27</td>
<td>521±42</td>
<td>390±40</td>
<td>416±23</td>
</tr>
<tr>
<td>Leucine</td>
<td>130±8</td>
<td>134±9</td>
<td>132±7</td>
<td>135±6</td>
</tr>
<tr>
<td>KIC</td>
<td>14.4±0.8</td>
<td>16.1±0.6</td>
<td>13.3±0.7</td>
<td>13.7±0.9</td>
</tr>
<tr>
<td>Lysine</td>
<td>208±8</td>
<td>227±13</td>
<td>253±21</td>
<td>236±16</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysine concentration, μmol/μg</td>
<td>0.55±0.04</td>
<td>0.81±0.09</td>
<td>0.74±0.06</td>
<td>0.72±0.08</td>
</tr>
<tr>
<td>Leucine concentration, μmol/μg</td>
<td>0.11±0.01</td>
<td>0.12±0.01</td>
<td>0.12±0.01</td>
<td>0.12±0.01</td>
</tr>
<tr>
<td>BCAT activity, nmol·min⁻¹·mg⁻¹</td>
<td>76±9</td>
<td>77±8</td>
<td>107±14</td>
<td>100±16</td>
</tr>
<tr>
<td>BCAT protein expression, AU</td>
<td>1.07±0.11</td>
<td>1.17±0.15</td>
<td>1.28±0.20</td>
<td>1.09±0.19</td>
</tr>
<tr>
<td>Basal BCKD activity, nmol·min⁻¹·mg⁻¹</td>
<td>147±23</td>
<td>139±20</td>
<td>116±18</td>
<td>123±11</td>
</tr>
<tr>
<td>Total BCKD activity, nmol·min⁻¹·mg⁻¹</td>
<td>414±36</td>
<td>368±48</td>
<td>339±39</td>
<td>352±39</td>
</tr>
<tr>
<td>%Active BCKD</td>
<td>36±5</td>
<td>37±2</td>
<td>33±2</td>
<td>37±4</td>
</tr>
</tbody>
</table>

Data are means ± SE. BCAT, branched-chain aminotransferase; BCKD, branched-chain α-keto acid dehydrogenase; AU, arbitrary units. *P < 0.05 vs. UP; †P < 0.05 vs. younger participants (same diet).

A high-protein diet did not have an adverse effect on insulin sensitivity, but it did have a potentially negative effect on glomerular filtration rate in older people. Although the younger group significantly increased GFR on the HP diet, older people did not demonstrate this adaptive response and even showed a tendency to decline.

Previous studies have shown that aging is associated with a decline in skeletal muscle mitochondrial capacity to produce ATP along with lower abundance of mitochondrial DNA and mRNA transcripts, mitochondrial protein synthesis, content of several mitochondrial proteins, and oxidative enzyme activity (44, 47, 48). Since ATP is the chemical energy needed for most biological functions, it is possible that this basic defect in mitochondria may contribute to overall decline in muscle functions with aging (33). Aerobic exercise training can stimulate muscle mitochondrial oxidative capacity (22, 50), mRNA abundance of the master regulator of energy metabolism, peroxisome proliferator-activated receptor-γ coactivator-1α (50), and muscle protein synthesis in older people (49), demonstrating that some of the age-related metabolic dysfunction is at least partially reversible. The objective of the current study was to determine whether it was possible to enhance muscle mitochondrial function and protein synthesis in older people by increasing protein intake. We hypothesized that a high-protein diet could stimulate muscle protein synthesis based on previous studies that showed that acute intake of amino acids increases muscle protein synthesis (55, 56) and, in combination with insulin, enhances muscle mitochondrial function (51) compared with these measurements taken in the fasting state. The current results showed that increased protein intake for 10 days did not stimulate these potentially reversible age-related muscle changes in younger or older people. There are many potential explanations for the current observations. Although the acute amino acid effects on muscle protein synthesis and mitochondrial function have been demonstrated previously, it is unclear whether there are dose-dependent effects. It is possible that the maximal benefit from dietary proteins and amino acids is already achieved with the UP diet, which reflects the average protein intake of the US population. Sec-

Fig. 2. Glomerular filtration rate (GFR). Data are means ± SE. GFR by renal clearance of iothalamate. Top: GFR measured during the adequate-protein diet (baseline). Bottom: change in GFR on the HP vs. the adequate-protein diet. *P < 0.05 vs. UP diet within age group; †P < 0.05 vs. younger participants on the same diet.
protein intake in elderly people may induce skeletal muscle splanchnic bed in the elderly people (8, 56). It has been proposed that a greater amount of leucine is catabolized in higher fraction of endogenously appearing leucine. It has been shown to occur following amino acid infusion. The results suggest that part of higher retention of amino acids following a meal is utilized as a fuel source in between meals. It remains to be determined whether there is a body protein store that could be used in time of need without having any functional consequences. On the basis of protein loss during weight reduction, Garrow (19) estimated that a 70-kg person could afford to lose 4.5 kg of protein without any serious functional impact. On the basis of measurements of protein synthesis and mitochondrial function, no beneficial effects are noted following the HP diet.

We measured the enzymes involved in leucine oxidation in skeletal muscle but observed no change in the complexes involved in leucine transamination (the first reversible step in leucine catabolism) and decarboxylation of KIC, the transamination product of leucine. Although leucine is transaminated mainly in skeletal muscle, it is possible that activity of BCKD in the liver may change with dietary protein intake since the liver is the main site of KIC decarboxylation (31, 32, 38). Animal studies have shown that total BCKD activity and mitochondrial function while on similar activity levels. Administration of amino acids has been shown to enhance exercise effect on muscle protein anabolism (5, 6), and studies in elderly people suggest that further research is needed to determine whether high protein intake may be required by elderly people to get the full benefit of a resistance exercise program. Further studies may address the question of whether benefits from an exercise program may be enhanced by higher protein intake in elderly people without any adverse effect on renal function (13).

In summary, high protein intake for 10 days increased net daily nitrogen balance in both younger and older people but had no beneficial effects on muscle protein synthesis and mitochondrial function while on similar activity levels. Administration of amino acids has been shown to enhance exercise effect on muscle protein anabolism (5, 6), and studies in elderly people suggest that further research is needed to determine whether high protein intake may be required by elderly people to get the full benefit of a resistance exercise program. Further studies may address the question of whether benefits from an exercise program may be enhanced by higher protein intake in elderly people without any adverse effect on renal function (13).
results of this study do not support the idea that older people who are already consuming adequate protein may benefit from high protein intake, and in fact, the current data allude to potential negative effects of high protein intake on older kidneys.

ACKNOWLEDGMENTS

We gratefully acknowledge the support of the Mayo CTSA Clinical Research Unit nursing, nutrition, and technical staff (Lavonne Oenning and Helen O’Connell) and the skillful technical assistance of the Metabolomic Core, Jane Kahl, Dawn Morse, Kate Klauss, and Jill Schimke.

GRANTS

This study was supported by National Institute on Aging Grant No. R01-AG-09531 and CTSA Grant No. UL1-RR-024150-01 from the National Center for Research Resources.

REFERENCES


