Synthesis of hepatic secretory proteins in normal adults consuming a diet marginally adequate in protein

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Received 12 December 2000; accepted in final form 8 August 2001

Jackson, Alan A., Gary Phillips, Irene McClelland, and Farook Jahoor. Synthesis of hepatic secretory proteins in normal adults consuming a diet marginally adequate in protein. Am J Physiol Gastrointest Liver Physiol 281: G1179–G1187, 2001.—The plasma concentration and hepatic synthesis rates of albumin, transthyretin, very low-density lipoprotein apolipoprotein B-100 (VLDL-apoB-100), high-density lipoprotein apolipoprotein A-1, fibrinogen, α1-antitrypsin, and haptoglobin were measured in six normal adults before and after consuming a protein intake of 0.6 g·kg body wt⁻¹·day⁻¹ for 7 days. The synthesis of hepatic proteins was measured from the incorporation of [²H₅]-phenylalanine, following prime/continuous infusion, using plasma VLDL-apoB-100 isotopic enrichment to represent the precursor pool. Synthesis of albumin declined by 50% (P < 0.001) following the lower-protein diet, VLDL-apoB-100 de-
tions (21). A sterile solution of [2H5]phenylalanine (Cam- 
bridge Isotope Laboratories, Woburn, MA) prepared in 4.5 g/l 
NaCl was infused to measure the rates of synthesis of the 
four nutrient transport proteins albumin, transthyretin, 
VLDL-apoB-100, and high-density lipoprotein apolipoprotein 
A-1 (HDL-apoA-1) and three positive acute-phase proteins 
ﬁbrinogen, haptoglobin, and α1-antitrypsin.

After a 10-h overnight fast, the weight and height of each 
subject were measured and venous catheters were inserted 
under local anaesthesia into each arm. One catheter was 
used for infusion of isotope and the other for blood sampling. 
The hand and forearm with the sampling catheter were 
wrapped in a heating pad to arterialize venous blood. A 
stereol solution of [2H5]phenylalanine was infused continu-
ously for 6 h at 4 μmol·kg⁻¹·h⁻¹ through the catheter in one 
forearm after a priming dose of 4 μmol/kg was injected. A 
sample of blood (6 ml) was drawn before the start of the 
infusion and at hourly intervals throughout the infusion.

To estimate plasma volume, each subject was administered 
a dose of 5 mg/kg of Evans blue dye by intravenous injection, and 
a blood sample was withdrawn after 1 h of priming (13).

Sample analyses. Blood was drawn in prechilled tubes 
(containing Na2EDTA and a cocktail of sodium azide, mer-
thiolate, and soybean trypsin inhibitor) and immediately 
centrifuged at 1,000 g for 15 min at 4°C. The plasma was 
removed and stored at −70°C for later analysis.

Plasma amino acid concentrations were determined using 
reverse-phase high-performance liquid chromatography 
(Pico-Tag, Waters, Millipore, Milford, MA). Plasma interleu-
kin 6 (IL-6) concentrations were measured by standard en-
zyme-linked immunosorbent assay using ELISA kits (Quan-
tikine, R&D Systems, Minneapolis, MN).

Plasma concentrations of six proteins (albumin, HDL-
apoA-1, transthyretin, α1-antitrypsin, haptoglobin, and fi-
brinogen) were measured by radial immunodiffusion using 
NL RID kits (The Binding Site, San Diego, CA). The concen-
tration of VLDL-apoB-100 was measured as the apoB-100 
concentration in the VLDL supernatant by radial immuno-
diffusion, as previously described by Egusa et al. (8). VLDL 
was removed from 1 ml of plasma by ultracentrifugation at 
30,000 g for 2 h at a density of 1.06 g/ml, and apoB-100 was 
extracted with isopropanol. EDTA-NaBr buffer (1 ml, 0.1012 
mol/l) was injected. A sterile solution of [2H5]phenylalanine was infused continu-
ously for 6 h at 4 μmol·kg⁻¹·h⁻¹ through the catheter in one 
forearm after a priming dose of 4 μmol/kg was injected. A 
sample of blood (6 ml) was drawn before the start of the 
infusion and at hourly intervals throughout the infusion.

Plasma amino acid concentrations were determined using 
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kin 6 (IL-6) concentrations were measured by standard en-
zyme-linked immunosorbent assay using ELISA kits (Quan-
tikine, R&D Systems, Minneapolis, MN).

Part of Table 1. Characteristics of 6 normal adults and the 
energy and protein consumed during 2 study periods

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>38.0 ± 2.0</td>
<td>27.3 ± 1.5</td>
<td>32.7 ± 6.1</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.78 ± 0.08</td>
<td>1.68 ± 0.04</td>
<td>1.73 ± 0.08</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.6 ± 10.5</td>
<td>63.8 ± 1.0</td>
<td>67.5 ± 6.9</td>
</tr>
<tr>
<td>Body mass index, m/kg²</td>
<td>22.9</td>
<td>22.6</td>
<td>22.6</td>
</tr>
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</table>

**Study 1**

<table>
<thead>
<tr>
<th></th>
<th>Energy intake, MJ/day</th>
<th>Protein intake, g/day</th>
<th>Resting energy expenditure, kJ·kg⁻¹·day⁻¹</th>
<th>apoB-100 (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.9 ± 0.85</td>
<td>8.3 ± 0.10*</td>
<td>96.7 ± 2.6</td>
<td></td>
</tr>
</tbody>
</table>

**Study 2**

<table>
<thead>
<tr>
<th></th>
<th>Energy intake, MJ/d</th>
<th>Protein intake, g/d</th>
<th>Resting energy expenditure, kJ·kg⁻¹·day⁻¹</th>
<th>apoB-100 (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12.0 ± 0.21</td>
<td>8.67 ± 0.18**</td>
<td>96.1 ± 3.0</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Study 1, while consuming the habitual 
level of dietary protein. Study 2, following 7 days consuming a diet 
that provided a marginal intake of protein. *P < 0.01; **P < 0.001.
protein was separated from the antibody on a 5% SDS-PAGE gel using pure apoB-100 as the standard. The gel band corresponding to the protein was cut, washed, dried, and hydrolyzed, and the amino acid was released, purified, and derivatized. The isotopic enrichment of the phenylalanine was determined. It was 3.67 mol% excess in the antibody extracted specimen and 4.0 mol% excess in the specimen extracted with isopropanol.

Albumin was extracted from plasma with acidified ethanol, fibrinogen was extracted as fibrin by thrombin precipitation, and VLDL-apoB-100 was separated by ultracentrifugation and isopropanol precipitation. The high-density lipoprotein (HDL) fraction was separated on a 1.21 g/ml NaBr-EDTA gradient by ultracentrifugation at 450,000 g and 22°C for 16 h (21). Transthyretin, haptoglobulin, and α1-antitrypsin were isolated from plasma by sequential immunoprecipitation with anti-human transthyretin, haptoglobulin, and α1-antitrypsin (Behring, Somerville, NJ) as previously described (23). The immunoprecipitates and protein precipitates were subjected to SDS-gel electrophoresis to separate the particular protein from its specific antibody and to separate apolipoprotein A-1 from HDL. A pure standard of the protein (Sigma, St. Louis, MO) and low molecular weight standards (Bio-Rad Laboratories, Richmond, CA) were also included in the gel (23). After the bands corresponding to the protein standard were stained with Coomassie brilliant blue dye, they were cut out and washed several times. The dried protein precipitates and gel bands were hydrolyzed in 6 mol/l HCl at 110°C for 12 h. Amino acids released from hydrolysis of the proteins, plasma amino acids were extracted by cation-exchange chromatography, and the tracer-to-tracee ratio of the phenylalanine was determined by negative chemical ionization gas chromatography-mass spectrometry on a Hewlett-Packard 5988A GC/MS (Palo Alto, CA). The amino acid was converted to the heptafluorobutyramide derivative and phe-nylalanine isotope ratio was determined by monitoring ions at m/z 383 to 388.

Calculations and statistics. The fractional synthesis rate (FSR) of all proteins were calculated with the precursor-product equation

$$\text{FSR} \text{(%/day)} = \left( \frac{\text{IR}_{t2} - \text{IR}_{t1}}{\text{IR}_{\text{pl}}} \right) \left( \frac{2,400}{t_{t2} - t_{t1}} \right)$$

Values are means ± SE. Study 1, while consuming the habitual level of dietary protein, 92 g/day. Study 2 following 7 days consuming a diet which provided 40 g protein/day. The differences between groups are by paired t-test.

Table 2. Plasma concentrations of amino acids (µmol/l) in 6 normal adults during 2 study periods

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Study 1</th>
<th>Study 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine</td>
<td>117 ± 8.5</td>
<td>111 ± 8.7</td>
<td></td>
</tr>
<tr>
<td>Isoleucine</td>
<td>56 ± 4.4</td>
<td>56 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>Valine</td>
<td>194 ± 14</td>
<td>181 ± 12</td>
<td></td>
</tr>
<tr>
<td>Threonine</td>
<td>116 ± 7</td>
<td>129 ± 5.4</td>
<td></td>
</tr>
<tr>
<td>Lysine</td>
<td>167 ± 13</td>
<td>166 ± 15</td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>46 ± 5.4</td>
<td>42 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>53 ± 2.5</td>
<td>53 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>12 ± 0.9</td>
<td>13 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td>72 ± 4.1</td>
<td>71 ± 4.2</td>
<td></td>
</tr>
<tr>
<td>Arginine</td>
<td>188 ± 7.8</td>
<td>100 ± 6.2</td>
<td></td>
</tr>
<tr>
<td>Alanine</td>
<td>279 ± 29</td>
<td>379 ± 18</td>
<td>0.01</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>167 ± 41</td>
<td>170 ± 41</td>
<td></td>
</tr>
<tr>
<td>Glutamine</td>
<td>410 ± 24</td>
<td>508 ± 58</td>
<td></td>
</tr>
<tr>
<td>Proline</td>
<td>135 ± 21</td>
<td>144 ± 9.6</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>198 ± 18</td>
<td>250 ± 17</td>
<td>0.01</td>
</tr>
<tr>
<td>Serine</td>
<td>108 ± 6.7</td>
<td>126 ± 8.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Cystine</td>
<td>13 ± 2.4</td>
<td>12 ± 3.3</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>50 ± 4.8</td>
<td>53 ± 4.4</td>
<td></td>
</tr>
</tbody>
</table>

The absolute intravascular synthesis rate (ivASR) of albumin (or transthyretin, HDL-apoA-1, fibrinogen, haptoglobulin, α1-antitrypsin-bound phenylalanine over the period t₀–t₄ h of the infusion, and IRₚ is the plateau isotopic enrichment of VLDL-apoB-100-bound phenylalanine. In this calculation, the plateau tracer/tracee ratio of VLDL-apoB-100-bound phenylalanine in plasma is assumed to represent the tracer/tracee ratio of the intravascular pool from which albumin and the other secretory proteins are synthesized (21). Steady-state tracer/tracee ratio was obtained by finding the average of the individual tracer/tracee ratio values after the tracer/tracee ratio-time curve reached a plateau (Fig. 1). Plateau was defined as follows: the tracer/tracee ratio at each time point was normalized to the last value obtained at the end of the 6-h infusion. These values were then analyzed by linear regression against time of infusion as the independent variable. Plateau was verified when the slope of the normalized tracer/tracee ratio/time line was not significantly different from zero. The criterion was made stringent by setting the level of significance at P < 0.25. In the case of VLDL-apoB-100, the FSR was calculated, as described by Lichtenstein et al. (26), from the rate of incorporation of [2H₅]phenylalanine into the protein during the rise to a plateau and the isotopic enrichment of the protein at plateau.

The absolute intravascular synthesis rate (ivASR) of albumin (or transthyretin, HDL-apoA-1, fibrinogen, haptoglobulin, α1-antitrypsin) was estimated as the product of FSR and the intravascular mass of the protein: ivASR (mg·kg⁻¹·day⁻¹) = intravascular protein mass × FSR; where the intravascular mass of a protein is the product of the plasma volume and the plasma concentration of the particular protein.

The plasma volume of each subject was calculated by the dye-dilution technique as described by Gibson and Evans (13). The standard steady-state equation was used to calculate the flux of phenylalanine in the circulation: flux = (IR₀e - 1)IRₚ × D; where IR₀e and IRₚ are the isotope ratios of the tracer amino acid in the infusate and in plasma at isotopic steady state and D is the rate of infusion of the tracer (in µmol·kg body wt⁻¹·h⁻¹). The units of flux are micromoles per kilogram per hour.

AJP-Gastrointest Liver Physiol • VOL 281 • NOVEMBER 2001 • www.ajpgi.org
Fig. 2. Six normal adults received a prime and continuous intravenous infusion of [2H5]phenylalanine for 6 h before (study 1) and after (study 2) consuming a diet that provided a marginal level of protein for 7 days. The plateau concentration, FSR, and ASR of plasma albumin in 6 normal adults before and following studies 1 and 2 are shown for albumin between studies 1 and 2, Table 3.

Data are expressed as means ± SE for each group. Differences between the first and second study period were assessed by paired t-test. A probability of 5% (P < 0.05) was taken to represent statistical significance.

RESULTS

All subjects were able to keep to the reduced protein diet without problems (as shown in Table 1) for the 7 days before study 2, and energy consumption was maintained at ~10.5 MJ/day with protein consumption reduced from 92 to 40 g/day. Therefore, protein consumption was decreased from 1.4 g·kg⁻¹·day⁻¹, or 15% of dietary energy, to 0.6 g·kg⁻¹·day⁻¹, or 6.5% of dietary energy. On the marginal protein diet, carbohydrate provided 50% of energy and lipid provided 44% of energy.

As shown in Table 2, the plasma concentration of three amino acids increased significantly from study 1 to study 2. These were alanine (36%), glycine (26%), and serine (17%). The plasma flux of phenylalanine decreased significantly from 48 to 39 μmol·kg⁻¹·h⁻¹ between studies 1 and 2. The plateau level of enrichment in plasma phenylalanine during the two studies is shown in Fig. 2, and a comparison is drawn with the plateau level of enrichment in phenylalanine in the VLDL-apoB-100 isolated from plasma. For both studies 1 and 2, enrichment in plasma was significantly higher than in VLDL-apoB-100, by ~50%, with the ratio of tracer/tracee in VLDL-apoB-100 to plasma phenylalanine being 0.6 in both studies.

Table 3 shows the plasma concentration, the FSR, and the absolute synthesis rate (ASR) of albumin in the two studies. The plasma concentration was not different between the two studies, but after 7 days on the low-protein diet, both FSR and ASR were significantly reduced by ~40%. The table also shows that the absolute values for FSR and ASR are different depending on whether the plateau enrichment of free phenylalanine in plasma or the phenylalanine that is bound in VLDL-apoB-100 is used in the calculation to represent the enrichment in the precursor pool from which amino acids are drawn for the synthesis of albumin. The values are 60% greater when the phenylalanine enrichment in VLDL-apoB-100 is used to represent the precursor pool. We have assumed that the enrichment in VLDL-apoB-100 better represents the enrichment within hepatocytes, and, therefore, this has been used for all subsequent calculations (6, 21). Clearly, this will make an important difference to the ASRs, which are derived for individual proteins. Importantly, it will not affect the relative change between two states, as, for example, shown for albumin between studies 1 and 2, Table 3.

Figure 3 shows the plasma concentrations, FSRs, and ASRs for three nutrient-transport proteins, transthyretin, and VLDL-apoB-100 and HDL-apoA-1 before and after 7 days consuming the reduced protein diet. For transthyretin, plasma concentration, FSR, and ASR are not different before and after the controlled dietary intervention. For VLDL-apoB-100, there was a significant decrease in plasma concentration of 20% after the lower protein diet, associated with no change in FSR, but a similar significant reduction in ASR of 20%. In contrast, for HDL-apoA-1, there were...
significant reductions in plasma concentration (6%), FSR (13%), and ASR (16%).

The response in the hepatic secretory proteins that have been characterized as positive acute-phase proteins is shown in Fig. 4. There were no changes in plasma concentration, FSR, or ASR for α1-antitrypsin. For fibrinogen and haptoglobin, although there were no changes in plasma concentration, there were significant differences in synthesis rates. On the reduced protein diet, the FSR for fibrinogen was significantly increased by 38%, and the ASR was increased by 50%. For haptoglobin, the changes in synthesis in response to the reduced protein diet were even more marked, with highly significant increases in FSR (78%) and ASR (90%).
Figure 5 shows the concentration of interleukin (IL)-6 in plasma before and after the consumption of the low protein diet for 7 days, at which time the plasma concentration had increased by \( \sim 30\% \).

**DISCUSSION**

The objective of this study was to determine the extent to which there were identifiable changes in the pattern and rates of synthesis of hepatic secretory proteins when normal adults consumed a diet containing a marginal but adequate level of protein. The data show that although normal adults appear to maintain good health in the short term when the protein consumed is reduced to the requirement level, there were significant changes in phenylalanine flux and the synthesis rates of hepatic secretory proteins. These changes are associated with the consumption of a diet that provided a marginal level of protein for 7 days to determine the FSR and ASR and the concentration of plasma fibrinogen, haptoglobin, and \( \alpha \)-1-antitrypsin. Values are means ± SE, with significant differences determined by paired t-test; \( *P < 0.05; **P < 0.001 \).
changes were similar for men and women. For most of the proteins studied, albumin, transthyretin, fibrinogen, haptoglobin, and α1-antitrypsin, there was no change in plasma concentration. There were, however, modest but significant falls in the plasma concentration of VLDL-apoB-100 and HDL-apoA-1. The picture was very different when the rates of synthesis for the different proteins were considered. The rates at which albumin, VLDL-apoB-100, and HDL-apoA-1 were being synthesized all decreased substantially (by 13–40%). By contrast, there was a marked increase in the rate of synthesis of fibrinogen and haptoglobin, with no change for α1-antitrypsin. This pattern of change is similar to that usually identified with a stress or the acute-phase response: that is a reduction in the formation of nutrient transport proteins and enhanced synthesis of positive acute-phase proteins. Although there was no overt evidence to suggest a change in the health or wellbeing of the subjects between the two study periods, the plasma concentration of the inflammatory cytokine IL-6 increased significantly, by 30%, between studies 1 and 2.

Remarkably, along with a reduction in the synthesis of albumin, there was a significant reduction in both the concentration and synthesis rates for VLDL-apoB-100 and HDL-apoA-1 on the lower protein diet. So far as we are aware, this is the first report of a significant effect of dietary protein on either the concentration or rates of synthesis of VLDL-apoB-100 and HDL-apoA-1, which play a central role in the movement of lipid around the body. Thus the present data raise the possibility that the movement of lipid around the body, either as triacylglycerides or bound to albumin as non-esterified fatty acids, might be modulated by the level of protein consumed. Studies in vitro show an inverse relationship between the concentration of amino acids in the medium and the rate at which HepG2 cells secrete apoB-100, with specific amino acids having a particularly marked effect (7, 40). It is almost invariable that reducing the dietary protein from 90 to 40 g/day means a substantial reduction in the consumption of meat protein (20), and this will also mean a change in other aspects of the macronutrient composition of the diet, especially the pattern of lipids consumed. After 4 wk on a diet enriched with fish oil, there was a decrease in the pool size of VLDL-apoB-100, no change in FSR, but a 30% decrease in the ASR (4). Therefore, although it is not possible to relate the change in the synthesis of these two proteins directly to the reduced dietary protein, it is important that their synthesis was modified by a pattern of dietary change that is widely seen across habitual intakes (20).

It was surprising to find that for two of the proteins, fibrinogen and haptoglobin, there was a highly significant increase in both the FSR and ASR. The plasma concentration of fibrinogen in the young subjects reported here was very similar to that reported previously, and when allowance is made for the method of derivation (see above), the FSR is similar for the two studies (12). We do not know of any other reports for the rate of haptoglobin or α1-antitrypsin synthesis in normal adults. It is not clear why there should have been an increase in the synthesis rate for fibrinogen and haptoglobin but not α1-antitrypsin, although the general pattern of overall change is similar to that usually associated with an inflammatory stimulus.

It has been suggested that the pattern of proteins synthesized by the liver is determined by the availability of amino acids relative to the pattern of amino acid composition of individual proteins. Thus, for example, in vitro hepatocytes are to maintain the rate of albumin secretion, they have to be provided with an unusual mixture of amino acids, especially rich in the nonessential amino acids glycine, glutamine, and arginine (16). Similarly, it has been suggested that different patterns of synthesis require different mixes of amino acids (19) and that the formation of acute-phase proteins in particular requires relatively large amounts of the aromatic amino acids (35). In the present study, there was no change in the plasma concentration of most amino acids between the two study periods, but there was a significant increase in three amino acids: alanine, glycine, and serine (Table 2). This pattern of change in the amino acid profile with a relative increase in the nonessential amino acids compared with the essential amino acids is similar to that reported in rat studies when the energy intake is maintained but the protein intake is reduced (27). As the protein in the diet is progressively reduced, the concentration of nonessential amino acids in the circulation increases, especially alanine, glycine, and serine, and at the same time, there is a progressive fall in albumin concentration (27, 28). In the present study, there was no change in the plasma concentration of phenylalanine, but there was a significant reduction in the plasma flux of the amino acid by ~20% on the marginal protein intake. The flux of this essential
Amino acid was not maintained as well as that of nonessential amino acids (14). Thus the concentration of individual amino acids in plasma cannot be taken to reflect changes in flux. It is likely that on the marginal level of protein consumption, the flux of amino acids better reflects the availability of specific amino acids to maintain adequate rates of synthesis for hepatic secretory proteins. However, on the basis of the pattern of change in plasma amino acid concentration and the increased risk for a one-third of fibrinogen and haptoglobin. The synthesis and secretion of apolipoprotein B is inhibited in vitro by IL-6 (31). The finding of a significant increase in the plasma concentration of IL-6 after 1 wk of the lower protein diet would give support to the proposal of an ongoing low-grade inflammatory process. There is a significant increase in mRNA for IL-6 in the small intestine and peripheral blood mononuclear cells of rats placed on a zero-protein diet for 14 days (29). Purified human apolipoprotein A-1 inhibits the endotoxin-stimulated release of cytokines, and, therefore, a lower level of production of HDL-apoA-1 would likely contribute to enhance a low-grade inflammatory state (11). These possibilities require further investigation but together raise the possibility that adaptation to a lower protein diet predisposes to a low-grade inflammatory state and hence a potentially atherogenic metabolic set. In the “Nurses’ Health Study,” there was a significant relationship between protein consumption and the risk of ischemic heart disease, with a reduction in risk of ~25% for women in the highest fifth of protein consumption (15). This relationship remained when allowance had been made for other possible confounding variables such as smoking, the pattern and amount of different dietary fatty acids, and other lifestyle characteristics. The relationship was present for both animal and vegetable proteins. However, the relationship was demonstrated over a range of protein consumption far higher than that in the present study: from 15% of total energy in the lowest fifth to 24% of total energy in the highest fifth. Nevertheless, in a meta-analysis of prospective studies that related inflammatory factors with coronary heart disease, there was an 80% increase in risk for the top compared with the lowest third of fibrinogen concentration and a 50% increased risk for a 4-g/l reduction in plasma albumin concentration (8). Therefore, the pattern of change in fibrinogen and albumin synthesis identified in this study on the lower protein diet would, if reflected in changes in concentration, fit a profile associated with increased risk of ischemic heart disease.

There is a considerable literature on the factors that determine the plasma concentration, synthesis, and distribution of albumin from experimental work in animals and humans (33). Much of the work on albumin kinetics explores the effect of extreme dietary manipulations or the response to different pathological states but very little on changes within the normal range of protein intake. There is down-regulation of the albumin transcription gene in the rat during starvation or while consuming a very low-protein diet (25, 30, 34). In adult humans, the FSR for albumin varies from 5 to 11% per day, depending on dietary history and clinical state (1–3). The synthesis rate is within a similar range during pregnancy and in older people (12, 32). When plasma-free phenylalanine was used to estimate the enrichment in the precursor pool in the present work, FSR was 8.2% per day on the habitual protein intake and 5.1% per day on the marginal protein intake, similar to other reports. However, when the enrichment in bound phenylalanine in VLDL-apoB-100 was used to represent enrichment in the precursor pool (6, 21, 26), albumin FSR decreased from 13.7% per day on the habitual diet to 8.1% per day on the marginal protein diet.

The present work has shown that in normal adults, the rate of albumin synthesis is probably 50% greater than estimated in most published reports. After 7 days consuming a diet that is marginally adequate in protein, normal adults appear to maintain good health. However, adaptation to the diet is associated with reduced protein turnover and changes in the pattern of hepatic secretory proteins that are probably of functional importance and carry a significant metabolic cost. There was a significant reduction in the synthesis of albumin, VLDL-apoB-100, and HDL-apoA-1 with a significant increase in the synthesis of fibrinogen and haptoglobin. This pattern of change has similarities to that expected during a low-grade inflammatory response, a suggestion that is supported by the finding of a significant increase in the circulating level of IL-6. There is the need to determine in greater detail the extent of the functional changes of this level of protein consumption, the basis of the change in response, and the level of consumption at which such potentially damaging effects are not observed.

We thank our subjects for agreeing to participate in this study, and we are grateful to M. Frazer and M. del Rosario for skilled technical assistance.

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HEPATIC PROTEIN SYNTHESIS ON MARGINAL PROTEIN DIET

G1187


