Albumin synthesis in humans increases immediately following the administration of endotoxin

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ABSTRACT

In order to investigate the immediate (i.e. within 3 h) response of albumin synthesis to the administration of endotoxin, as a model of a moderate and well controlled catabolic insult, two measurements employing L-[2H5]phenylalanine were performed in 16 volunteers. One group (n = 8) received an intravenous injection of endotoxin (4 ng/kg; lot EC-6) immediately after the first measurement of albumin synthesis, whereas the other group received saline. A second measurement was initiated 1 h later. In the endotoxin group, the fractional synthesis rate of albumin was 6.9 ± 0.6%/day (mean ± S.D.) in the first measurement. In the second measurement, a significant increase was observed (9.6 ± 1.2%/day; P < 0.001). The corresponding values in the control group were 6.6 ± 0.6%/day and 7.0 ± 0.6%/day respectively (not significant compared with first measurement and P < 0.001 compared with the second measurement in the endotoxin group). The absolute synthesis rates of albumin were 148 ± 35 and 201 ± 49 mg [kg−1 · day−1 before and after endotoxin (P < 0.01). In the control group, the corresponding values were 131 ± 21 and 132 ± 20 mg · kg−1 · day−1 (not significant compared with the first measurement and P < 0.01 compared with the second measurement in the endotoxin group). In conclusion, these results indicate that albumin synthesis increases in the very early phase after a catabolic insult, as represented by the administration of endotoxin.

INTRODUCTION

Albumin is the individual export protein that is most abundantly synthesized by the liver in healthy subjects, contributing about 15% of total liver protein synthesis in the rat [1,2]. The decreased plasma albumin concentration that is one hallmark of catabolic states [3,4] is strongly associated with an increase in the transcapillary rate of escape of albumin [5,6]. Furthermore, earlier studies, primarily in animals, have shown decreased albumin synthesis rates under these conditions [7,8]. However, in recent years, several reports have been presented showing increased rates of albumin synthesis in catabolic states, e.g. after stress hormone infusion [9], in conjunction with surgery [10], as well as in critical illness [11–14].

There have also been inconsistencies regarding the changes in synthesis rates of total liver protein observed in response to catabolic states. These changes seem to be related to the severity of the insult and possibly also to the time factor (i.e. when in relation to the insult the measurement is performed). In severe catabolism (e.g. sepsis and trauma), increased liver protein synthesis is generally observed, probably representing the so-called acute-phase response [15–18]. However, recent studies have shown that elective laparoscopic surgery is accompanied by a rapid (i.e. within 1 h) decrease in the total

Key words: hepatic, mass spectrometry, protein, surgery.

Abbreviations: CRP, C-reactive protein; FSR, fractional synthesis rate; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; WBC, white blood cell count.

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liver protein synthesis rate, when measured during the procedure [19,20]. The same and similar studies also indicate that the rate of synthesis of albumin remains unchanged, or possibly even decreases, during the course of surgery [20].

The aim of the present study was to further elucidate the early (i.e. within hours) effects of a catabolic insult on albumin synthesis in humans. Administration of endotoxin to volunteers has been used previously to mimic the immunological and metabolic abnormalities observed after a catabolic insult, such as trauma and infection [21,22]. Therefore albumin synthesis was measured before and within 3 h after the administration of endotoxin (as a model of a moderate and well controlled catabolic insult) in healthy volunteers, and compared with that in control subjects.

MATERIALS AND METHODS

Materials

L-[^1H]Phenylalanine (99 atom%; Mass Trace Inc., Woburn, MA, U.S.A.) was dissolved in sterile water together with unlabelled phenylalanine (Ajinomoto Co., Tokyo, Japan) to a concentration of 20 g/l, with 10 and 20 mol% excess.

Volunteers

A total of 16 healthy male volunteers, not taking regular medication, were investigated [mean age 27 years (range 20–33 years); height 182 cm (173–195 cm); weight 78 kg (58–98 kg)]. The nature, purposes and potential risks of the experimental procedures were explained to the volunteers before obtaining their voluntary consent. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki, and had received prior approval by the Ethical Committee as well as the Isotope Committee (blood volume measurements) of the Karolinska Institute, Stockholm, Sweden. The results of the effects of endotoxin on protein synthesis in white blood cells in these volunteers have been presented previously [23].

The volunteers were investigated in the post-absorptive state (after a 10–12 h fast) and were randomly allocated into an endotoxin group (n = 8) or a control group (n = 8). Before the first measurement of albumin synthesis, bilateral antecubital venous lines were inserted, one of which was used for blood sampling and the other for the injection of L-[^1H]phenylalanine, for the two measurements of albumin synthesis. At 08.00 hours, following initial blood sampling (see below), L-[^1H]phenylalanine (45 mg/kg, 10 mol% excess) was given intravenously over 10 min (time point –1.5 h), followed by blood sampling for the first measurement of albumin synthesis during 90 min (Figure 1). Immediately after the end of the first measurement, the subjects in the endotoxin group received an intravenous injection of endotoxin (4 ng/kg; lot EC-6; Royal Pharmaceutical Society of Great Britain), whereas the subjects in the control group received saline (time point 0 h). After a further 1 h, another intravenous injection of L-[^1H]phenylalanine (45 mg/kg, 20 mol% excess) was given over 10 min (time point 1 h), followed by blood sampling for the second measurement of albumin synthesis. In order to assess the clinical effects of a systemic inflammatory response, body temperature, heart rate and mean arterial pressure were registered at regular intervals.

Blood sampling protocol

The sampling protocol has been used in previous investigations, but some minor modifications have been made in the present study [19,20,24]. During measurements of albumin synthesis, venous blood samples were drawn at 0, 5, 10, 15, 30, 50, 70 and 90 min after the injection of phenylalanine for the determination of isotopic enrichment in both plasma and albumin. Blood samples at time points –1.5 and 1 h were also used to determine plasma albumin concentrations and haematocrit.

Figure 1 Experimental protocol for assessment of the effect of endotoxin on albumin synthesis in a group of volunteers

Injection of endotoxin or saline was given at time point 0. PHE, phenylalanine; MPE, mol% excess.
verify that the injection of endotoxin evoked a significant systemic inflammatory response in the endotoxin group, blood samples for C-reactive protein (CRP), white blood cell count (WBC), as well as levels of the pro-inflammatory cytokines, tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), were taken at time points — 1.5, 0, 1 and 2.5 h [25]. All blood samples were stored at −80 °C prior to analysis.

For analytical reasons, measurements of plasma volume could only be performed on one occasion. It was decided to perform that measurement during the second measurement of albumin synthesis, beginning 30 min after the injection of phenylalanine, using 131I-labelled albumin (Institutt for EnergiTeknikk, Kjeller, Norway) corresponding to 100 kBq. Blood samples were taken at 0, 20, 30, 40 and 45 min to assess isotope dilution.

**Albumin synthesis**

Measurement of the rate of synthesis of albumin employing the flooding technique and L-[3H]phenylalanine has been described in detail previously [24,26,27]. Briefly, albumin in plasma samples was isolated using acid ethanol extraction, followed by extensive washing in order to remove traces of free phenylalanine and then hydrolysis with HCl. After enzymic conversion into phenylethylamine, the enrichment of L-[3H]phenylalanine from albumin hydrolysates was determined by monitoring the ions, at m/z 106 and 109, of the n-heptafluorobutyryl derivative of phenylethylamine on a VG MD quadrupole gas chromatography mass spectrometer (Fisons Instruments Inc., Beverly, MA, U.S.A.). Analysis of plasma free phenylalanine enrichment was performed after acid precipitation and cation-exchange chromatography by monitoring the ions, at m/z 336 and 341, of the t-butyldimethylsilyl derivative on a HP 5972 mass spectrometer (Hewlett Packard, Palo Alto, CA, U.S.A.).

**Other analytical procedures**

Haematocrit, the serum concentrations of CRP and WBC and the plasma albumin concentration were analysed using routine laboratory methods. TNF-α and IL-6 were analysed using sandwich ELISAs in accordance with the instructions of the manufacturers (reagents from Biosource, Nivells, Belgium, for TNF-α, and from Research and Diagnostic System Inc., Minneapolis, MN, U.S.A., for IL-6).

**Calculations and statistics**

The fractional synthesis rate (FSR) of albumin, i.e. the fraction of the intravascular albumin pool that is synthesized per unit time, was calculated using the formula described previously [28]:

\[
\text{FSR (%/day)} = \left( P_f - P_t \right) \times 100 / \text{AUC}
\]

where \( P_f \) and \( P_t \) represent the enrichment of phenylalanine in albumin at two time points, \( t_1 \) and \( t_2 \), after the curve of enrichment becomes linear, based on three samples (at 50, 70 and 90 min). AUC is the area under the curve for the enrichment of plasma free phenylalanine between time points \( t_1 \) and \( t_2 \), adjusted for the secretion time \( (T_s) \), i.e. the temporal lag period before the appearance of labelled albumin in plasma. The secretion time was assessed by plotting each individual’s regression line for the linear part of the albumin enrichment curve and extrapolating to baseline enrichment [28]. The absolute synthesis rate for albumin was calculated as the product of the FSR and the intravascular albumin mass, calculated from the plasma albumin concentration and the measured plasma volume in the second measurement of albumin FSR in each group. Calculations for values of plasma volume in the first measurement of albumin FSR (PV₁) were based on the measured values for plasma volume in the second measurement (PV₂) and changes in haematocrit (Hct₁ and Hct₂), i.e. basically \( PV_1 = PV_2 \times Hct_2 / Hct_1 \). However, blood loss due to sampling was also estimated and taken into account in the calculations of PV₁.

Data are presented as means ± S.D. Differences among groups were assessed by ANOVA for repeated measures, and, if significant \((P < 0.05)\), by Student’s \( t \) tests for comparisons within and between groups.

**RESULTS**

The FSR of albumin was similar in the two groups for the first measurement, i.e. 6.9 ± 0.6%/day in the endotoxin group and 6.6 ± 0.6%/day in the control group (Figure 2). However, in the endotoxin group, albumin FSR was higher in the second measurement than in the first (9.6 ± 1.2%/day; \( P < 0.001 \)), whereas the value for the control group was similar to the first measurement (7.0 ± 0.6%/day). Accordingly, there was a difference in the second measurements of albumin synthesis between the two groups \((P < 0.001)\). The
absolute synthesis rate of albumin for the first measurement was $148 \pm 35 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in the endotoxin group and $131 \pm 21 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in the control group (not significant). For the second measurement, the corresponding values were $201 \pm 49 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in the endotoxin group ($P < 0.01$ compared with both the first measurement and the second measurement in the control group) and $132 \pm 20 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in the control group (not significant compared with the first measurement) (Figure 3).

Plasma albumin concentrations were similar in the two groups for the first measurement (Table 1). However, at the second measurement small decreases in albumin concentration were observed in both groups ($P < 0.01$ in both cases). Also, there were small differences between the results for plasma volume between, but not within, the groups ($P < 0.05$), whereas values for haematocrit were similar in the two groups. However, taken together, the differences observed in some of the parameters used for the calculation of the intravascular albumin mass did not result in any differences within or between the groups for that parameter.

The albumin secretion time (i.e. the time that elapsed before isotopically labelled albumin started to appear in peripheral blood) was the same for the two groups at both occasions of measurement.

The serum concentrations of CRP were normal (<10 mg/ml) in all volunteers at time points 1.5, 0, 1 and 2.5 h in relation to the injection of endotoxin/saline. In the endotoxin group at 1 h after the administration of endotoxin, the WBC had decreased ($P < 0.01$), whereas the serum concentration of TNF-$\alpha$ had increased ($P < 0.001$) (Table 2). The latter remained elevated 2.5 h after the injection, when an increase in the serum

### Table 1 Plasma albumin concentration, haematocrit, plasma volume, intravascular albumin mass (IAM) and secretion time in conjunction with albumin synthesis measurements in the two groups of subjects, investigating the effect of endotoxin on albumin synthesis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasm albumin concentration (g/l)</td>
<td>40.0 ± 1.7</td>
<td>38.0 ± 2.2 **</td>
<td>41.9 ± 2.5</td>
<td>39.4 ± 3.1 **</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>41.5 ± 3.1</td>
<td>40.2 ± 1.8</td>
<td>41.1 ± 3.1</td>
<td>40.4 ± 2.9</td>
</tr>
<tr>
<td>Plasma volume (litres)</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.3</td>
<td>3.4 ± 0.4 †</td>
<td>3.5 ± 0.5 †</td>
</tr>
<tr>
<td>IAM (g)</td>
<td>153 ± 13</td>
<td>149 ± 18</td>
<td>143 ± 20</td>
<td>138 ± 24</td>
</tr>
<tr>
<td>Secretion time (min)</td>
<td>36.3 ± 2.6</td>
<td>36.1 ± 1.6</td>
<td>36.0 ± 2.1</td>
<td>35.9 ± 1.6</td>
</tr>
</tbody>
</table>

Values are means ± S.D. Significance of differences: **$P < 0.01$ compared with first measurement in the same group; †$P < 0.05$ compared with corresponding measurement in the endotoxin group.

### Table 2 WBC and serum concentrations of the two pro-inflammatory cytokines TNF-$\alpha$ and IL-6 measured at four time points

Measurements were obtained before the first albumin synthesis determination (−1.5 h), before the injection of endotoxin/saline (0 h), before the second albumin synthesis determination (1 h) and at the end of the study (2.5 h). Reference values are presented within parentheses. Values are means ± S.D. Significance of differences: *$P < 0.05$, **$P < 0.001$ within the same group compared with time point 0 h; ††$P < 0.01$, †††$P < 0.01$ refer to differences between groups at the same time point.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ($\times 10^9$/l)</td>
<td>−1.5</td>
<td>5.2 ± 1.0</td>
<td>5.9 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>([4–9] $\times 10^9$/l)</td>
<td>0</td>
<td>5.2 ± 1.0</td>
<td>5.5 ± 1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.0 ± 0.6 †† †</td>
<td>5.6 ± 2.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>4.5 ± 1.3</td>
<td>5.6 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>TNF-$\alpha$ (pg/ml)</td>
<td>−1.5</td>
<td>16 ± 7</td>
<td>19 ± 15</td>
<td></td>
</tr>
<tr>
<td>(&lt; 95 pg/ml)</td>
<td>0</td>
<td>16 ± 8</td>
<td>16 ± 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1150 ± 561 †† †††</td>
<td>17 ± 14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>1385 ± 454 †† †††</td>
<td>17 ± 13</td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>−1.5</td>
<td>0.9 ± 0.3 *</td>
<td>0.6 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>(&lt; 24 pg/ml)</td>
<td>0</td>
<td>0.6 ± 0.3</td>
<td>0.7 ± 0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>21.0 ± 26.7</td>
<td>1.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>&gt; 300 †† †† ††</td>
<td>1.0 ± 0.5 *</td>
<td></td>
</tr>
</tbody>
</table>

The serum concentrations of CRP were normal ($< 10 \text{ mg/ml}$) in all volunteers at time points −1.5, 0, 1 and 2.5 h in relation to the injection of endotoxin/saline. In the endotoxin group at 1 h after the administration of endotoxin, the WBC had decreased ($P < 0.001$), whereas the serum concentration of TNF-$\alpha$ had increased ($P < 0.001$) (Table 2). The latter remained elevated 2.5 h after the injection, when an increase in the serum
Table 3  Body temperature (BT), heart rate (HR) and mean arterial pressure (MAP) at four time points
Endotoxin/saline was given at time point 0 h, and albumin synthesis measurements (of 90 min duration) were initiated at −1.5 and 1 h. Values are means ± S.D.
Significance of differences: *P < 0.05 and **P < 0.001 within the same group compared with time point 0 h; †P < 0.05 refers to differences between groups at the same time point.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measurement</th>
<th>Endotoxin</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BT (°C)</td>
<td>−1.5</td>
<td>35.8 ± 0.6</td>
<td>35.7 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>35.9 ± 0.3</td>
<td>35.7 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>36.3 ± 0.7</td>
<td>35.8 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>37.5 ± 0.9</td>
<td>36.0 ± 0.6</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>−1.5</td>
<td>64 ± 10</td>
<td>67 ± 9</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>59 ± 9</td>
<td>59 ± 9</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>66 ± 10</td>
<td>62 ± 13</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>81 ± 11***†</td>
<td>69 ± 13</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>−1.5</td>
<td>99 ± 9</td>
<td>95 ± 12</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>95 ± 8</td>
<td>91 ± 12</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>103 ± 8</td>
<td>88 ± 12</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>100 ± 7</td>
<td>90 ± 7</td>
</tr>
</tbody>
</table>

concentration of IL-6 was also observed. In the control group, no changes in WBC, TNF-α or IL-6 were observed (Table 2).

In the endotoxin group, there was a tendency towards increased body temperature towards the end of the measurement period (at 2.5 h), but this did not attain significance (Table 3). Although the mean arterial pressure remained unchanged in the endotoxin group, an increase in heart rate was observed at 2.5 h after the injection of endotoxin.

**DISCUSSION**

In the present study, it was demonstrated that albumin synthesis increased by approx. 40% within 2 h following the intravenous administration of endotoxin to healthy volunteers. These results further substantiate recently presented data indicating that albumin synthesis increases in states of catabolism in humans [11–14]. Of particular interest is the fact that albumin synthesis was affected so soon after the introduction of endotoxin. Although the volunteers in the endotoxin group had biochemical evidence of an acute systemic inflammatory reaction, as indicated by the increased serum concentrations of the pro-inflammatory cytokines TNF-α and IL-6 as well as a decreased WBC [21,25], the clinical signs of an inflammatory response were relatively few at the time of measurement, and did not include significant changes in body temperature or mean arterial pressure (Tables 2 and 3) [29]. Based on the results of our study, it therefore appears that albumin synthesis is affected very early in a systemic inflammatory reaction.

In contrast with the findings of the present and previous studies, albumin synthesis rates were shown to remain unchanged, or possibly even decrease, during the first 1 h of laparoscopic surgery [20]. In discussing possible mechanisms for these apparently contradictory findings, two aspects above all must be considered. Thus the effect of a catabolic insult on albumin synthesis may be influenced by the time factor, i.e. when in the course of the catabolic state sampling is performed, as well as by the degree and/or type of catabolic insult (e.g. controlled surgical trauma compared with fulminant sepsis). Regarding the time factor, previous animal studies, in which measurements were performed during the first 24 h after the insult, have indicated a decrease in albumin synthesis in states of catabolism [30]. Similar results have also been presented in studies in humans [8]. Mansoor et al. [13] have suggested that there may be a bi-temporal pattern to the changes in albumin synthesis in response to a catabolic insult, i.e. first a decrease, then an increase. However, in a recent study in the rat, which extended over 10 days, albumin synthesis was shown to decrease also in the later phase of an inflammatory process [31]. The results presented here, taken together with our previous results, indicate that the time factor is not of major importance, since quite opposite effects on albumin synthesis are observed, despite comparable time frames for the investigations (Figure 2 and [20]). Therefore it seems more plausible that the degree and/or type of catabolic insult is more important. However, it is very difficult to define a catabolic insult in quantitative terms, as there are no parameters available that enable us to measure adequately just how `catabolic’ a subject is. Obviously, it is debatable whether or not a laparoscopic procedure entails less of a catabolic insult than the administration of endotoxin to volunteers. The subjects in the present study showed few signs of a systemic inflammatory response during the period of measurement, despite the fact that albumin synthesis increased (Table 3). What can be said, however, given the increased albumin synthesis rate that is observed also in the critically ill [13,14], is that the increase presented here indicates that the underlying triggering mechanisms are more similar to the ones involved in critical illness than to those in elective laparoscopic surgery. Also, the possibility that there are species-specific changes in albumin synthesis in response to a severe catabolic insult must be borne in mind (i.e. increase in humans; decrease in rats) [31].

It is also important to consider changes in the rate of synthesis of total liver protein following a catabolic insult. Whereas several previous reports have indicated increased liver protein synthesis in severe catabolic states in both animals and humans [15–18], we have shown previously that the rate of synthesis of total liver protein decreases rapidly during laparoscopic surgery [19,20].
Therefore the discussion regarding the changes in liver protein synthesis in catabolic states is similar to the one on albumin synthesis. Also, an interesting aspect is whether or not the changes in the rates of synthesis of total liver protein and albumin go in the same direction in severe catabolic states. Previous studies in animals following injection of IL-1β or turpentine have indicated that total liver protein synthesis increases, whereas albumin synthesis decreases, when both are expressed as mg of protein/100 mg body weight [30]. In humans, however, the present and previous results suggest that both rates might increase [13–15,17], which is also supported by the results from a recent study in a rat model of sepsis [32]. In order to clarify these findings further, in the future, it is important that the rates of synthesis of various proteins are studied separately and related to one another, as well as to other variables of protein metabolism, such as protein degradation and mRNA levels [31,33,34].

The most notable aspect of the present findings is the rapidity with which albumin synthesis responded to endotoxin injection (within about 2 h). This might have important implications with regard to the mechanisms involved. There are two alternative mechanisms: an increase in total liver protein synthesis affecting the translation of all mRNAs, including that for albumin, and a selective increase in the translation of albumin mRNA. There are insufficient data to identify which of these possible mechanisms occurs in endotoxaemia; however, whereas rapid changes in total liver protein synthesis have been reported previously in humans in response to surgery [20], rapid changes in albumin synthesis as a proportion of total liver protein synthesis have not been observed, possibly because this requires the induction of more albumin mRNA. This is additional evidence suggesting that the increase in albumin synthesis after endotoxin might reflect an increase in total liver protein synthesis.

The results for albumin FSR found at the first measurement in the two groups in the present study were in accordance with previous results obtained in healthy volunteers, employing the same methodology [28]. Perhaps more importantly, no change was observed in the control group at the second measurement, despite the fact that the subjects had already received one injection of enriched phenylalanine for the first measurement. Thus the first injection of phenylalanine did not appear to affect the results of the second measurement. Also, at the second measurement the fasting period had been 2.5 h longer than at the first. In most previous studies of healthy volunteers, the subjects have acted as their own controls. In the present study, by adding a control group that was investigated twice, the risk of confounding factors being of importance was reduced.

In conclusion, the results of the present study show that albumin synthesis increases very rapidly after the administration of endotoxin to healthy volunteers. Since several recent studies have indicated that albumin synthesis also increases in severe catabolic states, such as critical illness, and not the opposite as was previously believed, the present study model may be employed in the future to investigate possible underlying mechanisms behind this increase.

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