The Acute Phase Response of Plasma Protein Synthesis during Experimental Inflammation*

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The effect of acute inflammation on the synthesis of plasma proteins by the liver was studied in rats. The rates of incorporation of L-[1-14C]leucine into proteins in the bloodstream changed 24 h after injection of turpentine, by the following factors: total serum protein, 1.8: α1-acid glycoprotein and major acute phase α1-protein, 20; fibrinogen, 4.8; transferrin, 1.3; albumin, 0.4.

The changes in incorporation rates preceded changes in concentrations of the above proteins in plasma.

The total body pools, measured in whole rat homogenates 3 days after inducing inflammation, increased 18-fold for major acute phase α1-protein, 14-fold for α1-acid glycoprotein, and decreased for albumin to 0.68 of the value in healthy rats. The total body pool of transferrin remained constant for about 24 h and increased slightly after 3 days to a value about 1.3 times larger than that in healthy rats. The rate of degradation of transferrin was not influenced by inflammation.

The rates of synthesis of specific plasma proteins in healthy rats (steady state) were determined from the total body pools and the turnover of injected 125I-labeled proteins. The proportions of the rates of synthesis were the same as those of the rates of incorporation, after correcting for differences in leucine content, suggesting that these proteins were synthesized from the same intracellular leucine pools.

Using the constant rate of synthesis of transferrin as a reference, the following changes in net synthesis rates, 24 h after inducing inflammation, were calculated: albumin, 91 to 32; major acute phase α1-protein, 2.3 to 64; α1-acid glycoprotein, 1.0 to 22 mg/100 g of body weight/day. The synthesis of serum total protein increased from 234 to 380 mg/100 g of body weight/day after inflammation for 24 h.

Distinct and coordinated changes in the concentration of individual proteins in the plasma can be observed during acute inflammation (for review see Ref. 1). Increased rates of incorporation of radioactive amino acids into proteins in the plasma during inflammation, such as those described for the major acute phase α1-protein of the rat (2) and for α1-acid glycoprotein in in vitro studies with liver slices (3) or hepatocytes in culture (4) suggest that, at least in part, the increase in the plasma concentration of the acute phase reactants during inflammation is due to increased rates of synthesis.

In the following, the acute phase response of the protein-synthesizing system in rat liver is characterized for five different proteins by monitoring the plasma concentration and incorporation of L-[1-14C]leucine. A comparison of the ratios of the rates of synthesis of the proteins determined by turnover studies under steady state conditions with the ratios of the rates of incorporation of L-[1-14C]leucine suggests that the same intracellular pools of leucine in the liver are used for the biosynthesis of the proteins studied. Determinations of the total body pool and the rate of degradation of transferrin at different times after subcutaneous injection of turpentine indicated that the rate of synthesis of transferrin did not change during the first 24 h of the acute phase response. Therefore, the rates of synthesis of acute phase proteins could be calculated from the rates of incorporation of leucine using the synthesis of transferrin as a standard.

EXPERIMENTAL PROCEDURES

RESULTS

Concentrations of Proteins in Plasma in Rats during the Acute Phase Response to Inflammation—The concentrations of various proteins in plasma or serum were measured at different times after inducing inflammation. The results are shown in Fig. 1. The smallest changes in concentration were found for transferrin. Its level in plasma ranged from 3.5 to 4.5 g/liter in healthy animals and remained in that range 48 h after injection of turpentine. In contrast, the concentration of α1-macroglobulin (not included in the figure) increased from 0.014 to 4.5 g/liter, i.e. 320-fold. The concentration of α1-acid glycoprotein changed from 0.17 to 3.2 g/liter, and that of major acute phase α1-protein changed from 0.46 to 7.0 g/liter after 48 h. The serum level of albumin decreased from 35 to 23 g/liter 2 days after inducing inflammation. The maximum of the changes in concentration of plasma proteins occurred at about the same time at which the rate of sedimentation of erythrocytes increased to a maximum value of 20 mm/h compared with 2 mm/h in healthy rats. An increase in the number of leucocytes in the bloodstream started only after 4 days and had not reached its maximum after 6 days.

Rates of Incorporation of L-[1-14C]Leucine into Plasma Proteins during the Acute Phase Response—In Fig. 2 the rate of incorporation of radioactive leucine is plotted against the time after inducing inflammation. During inflammation,
The Acute Phase Response of Plasma Protein Synthesis

**Fig. 1.** Concentrations of proteins in plasma or serum during acute inflammation. For determination of proteins and induction of inflammation see under "Experimental Procedures." Concentrations of fibrinogen and transferrin were measured in plasma, and all other concentrations were determined in serum. Between 3 and 5 rats were killed per time point.

**Fig. 2.** Incorporation of L-[1-14C]leucine into plasma proteins during acute inflammation. For technical details see under "Experimental Procedures." The figures for transferrin and fibrinogen were taken from an experiment in which radioactive leucine was injected into the portal vein and proteins were isolated from plasma. All other figures are from experiments with intraperitoneal injection and isolation of proteins from serum. Between 3 and 5 rats were killed per time point.

The rate of labeling changed drastically for α1-acid glycoprotein and major acute phase α1-protein. At 24 h after inducing inflammation, incorporation increased only little, namely 1.3-fold (from 8,200 dpm/ml to 10,600 dpm/ml) for transferrin, and it decreased to 40% of the value in healthy rats (from 86,000 dpm/ml to 33,000 dpm/ml) for albumin. The maximum changes of the rates of incorporation preceded those of concentration.

**Determination of the Net Rates of Synthesis of Plasma Proteins in Healthy Rats**—Under steady state conditions, i.e., in healthy adult animals, turnover, total body pools, and rates of synthesis can be derived from the rate of replacement of injected 125I-labeled proteins in the blood. After equilibration of the injected labeled protein between intravascular and extravascular compartments, straight lines were obtained for all of the proteins studied upon plotting the logarithm of their specific radioactivity in the plasma against time after injection. As an example, the data for α1-acid glycoprotein are given in Fig. 3. The half-lives of proteins were calculated from the slopes of the straight sections of the curves. For injection, both freshly iodinated proteins and 125I-labeled proteins which had been "screened" for 48 h were used. The "screening" consisted of injection of the 125I-labeled protein into rats from which plasma was obtained after 48 h. This plasma was then injected into the experimental animals. The purpose of the screening was the removal of denatured protein. The half-lives obtained for screened and nonscreened α1-acid glycoprotein and also for major acute phase α1-protein were identical within the limits of variation of the method. In the case of transferrin, two screened preparations, differing in sialic acid content (5), were used. The half-life for transferrin containing 2 sialic acid residues was found to be 1.96 ± 0.015 days (S.E.), and that for transferrin with 3 sialic acid residues was 2.16 ± 0.08 days (S.E.). The average value is given in Table I together with the values obtained for the other 125I-labeled proteins. Total body pools were determined directly in whole body homogenates. The concentration of individual proteins was determined in these homogenates by immunoprecipitation (see under "Experimental Procedures"). The recovery was checked by measuring the yield of 125I-labeled transferrin which had been injected into the animals before they were killed. This recovery was better than 98%. The values obtained for the total body pools are shown in the second row of Table I. The observed variation was considerably smaller than that...
of the values for total body pools calculated from the intercept with the ordinate obtained by extrapolation according to Sterling (6), although mean values found with the two methods were similar. Direct determination of the total body pool was not feasible for fibrinogen, since only very small amounts of fibrinogen could be detected in the homogenates, possibly because fibrinogen was converted into fibrin despite prior addition of 40 mg of heparin per rat.

The rates of synthesis of the proteins were then calculated from the half-lives (row 1) and the total body pools (row 2). The results are given in row 3 of Table I. The value for albumin was calculated using the average of values reported for its half-life (7). The rates of synthesis obtained for both albumin and transferrin agree well with data in the literature (7, 8).

The Same Intracellular Pool of Leucine in the Liver is Used for the Biosynthesis of Plasma Proteins—Similar proportions can be expected for the rates of synthesis and the rates of incorporation of radioactive amino acid for proteins made from the same intracellular amino acid pool if corrections are made for differences in amino acid content of proteins and in distribution of newly synthesized proteins in the body.

The leucine content of albumin, transferrin, major acute phase α-protein, and α-acid glycoprotein of the rats has been determined previously (2, 5, 9, 10). The distribution space for the four proteins, 90 min after secretion, was found to be similar in healthy rats, namely 1.5 and 1.7 times the intravascular space, as outlined in the Miniprint. After correcting for different leucine content, radioactive leucine was found to be incorporated into albumin, transferrin, major acute phase α-protein, and α-acid glycoprotein in the ratio 650:100:12:6.2. The ratio of the rates of synthesis for the four proteins, determined by methods not involving incorporation of radioactive amino acids (described in the preceding section and summarized in Table I) was 490:100:12:5.4. The observation of similar proportions (within the limits of variation) for the rates of incorporation of leucine and of synthesis suggested that the same intracellular pools of leucine were used for the synthesis of albumin, transferrin, major acute phase α-protein, and α-acid glycoprotein.

The Rate of Synthesis of Transferrin Remains Constant during the Early Acute Phase Response—Fig. 4 shows the total body pools of albumin, major acute phase α-protein, transferrin, and α-acid glycoprotein determined at different times after injection of turpentine. Whereas the amount of albumin decreased and that of major acute phase α-protein and α-acid glycoprotein increased considerably, the content of transferrin in the body did not change 24 h after inducing inflammation and increased only little thereafter. In another experiment, the effect of inflammation on the rate of degradation of transferrin was investigated. Transferrin was labeled with $^{125}$I and, after screening for 48 h, injected into 3 male Buffalo rats. Radioactivity was measured in a total body counter as described under “Experimental Procedures.” After 2 days, turpentine was injected subcutaneously into 2 rats. In Fig. 5 measured radioactivity values are plotted against time after injection of radioactive transferrin. The radioactivity decreased with a half-life of about 2 days in both normal and turpentine-injected rats except for a deviation from the straight line in the semi-log plot of radioactivity against time, immediately after injection of turpentine. The injection of turpentine under the skin induces an edema with accumulation of fluid containing serum proteins (11). Thus, efficiency of counting of $^{125}$I-transferrin increased transiently (the half-thickness of rat tissue for the radiation emitted by $^{125}$I was found to be 2.0 cm); however, after dissipation of the edema, the decay curve for the rats suffering from an inflammation returned to the same straight line as measured before injection of turpentine, suggesting that degradation of transferrin had proceeded without interruption. If total body pool and rate of degradation do not change significantly, it may be concluded that the rate of synthesis of transferrin does not change significantly after the injection of turpentine. The slight increase in the rate of incorporation of radioactive leucine into transferrin 1 day after injection of turpentine (Fig. 2) was interpreted as being caused by changes in precursor leucine pools of similar extent as that observed in total extravascular content of leucine of the liver (see Miniprint).
Rates of Synthesis of Acute Phase Proteins in Rats Suffering from an Inflammation for 24 h—Steady state conditions are required for the determination of the rates of synthesis of plasma proteins from turnover and total body pools. Neither fasting nor inflammation can be regarded as a steady state condition. However, rates of synthesis of proteins can be calculated from rates of incorporation of amino acids if a comparison can be made with a reference protein. The data in this paper suggest (a) that the rate of synthesis of transferrin does not change during inflammation and (b) that the same pools of leucine are used in the biosynthesis of plasma proteins in the liver. This permits the following calculation.

The rates of incorporation of L-[1-14C]leucine into albumin, transferrin, major acute phase α-protein, and α-acid glycoprotein as a percentage of that into total protein were 41, 5.1, 0.53, and 0.24, respectively, for healthy rats and 9.2, 3.1, 9.0, and 3.2 for rats 24 h after induction of inflammation (Table II). The changes in the rate of incorporation were, therefore, 0.22, 0.61, 17, and 13.3 for these proteins. The rate of synthesis of transferrin did not change during inflammation for at least 24 h. Hence, the factor of 0.61 obtained for the change of incorporation of leucine into transferrin is taken as a measure of changes in the specific activity of the leucine pool and changes in the rate of total protein synthesis during inflammation. Since all of the proteins are synthesized from the same amino acid pools this same factor (0.61) is used to correct the incorporation values obtained for albumin, major acute phase α-protein, and α-acid glycoprotein. Thus, the corrected changes in the rates of incorporation become 0.37, 1, 28, and 22 for albumin, transferrin, major acute phase α-protein, and α-acid glycoprotein, respectively (Table II). This method of calculation is independent of the leucine content of the proteins studied and does not require prior knowledge of the absolute rates of synthesis of any of the proteins. The corrected changes in rates of incorporation represent the changes in net synthesis rates. Multiplication with the net synthesis rate obtained for healthy rats from turnover and total body pool gives the synthesis rates for the inflamed state in milligrams/100 g of body weight/day (last row of Table II). The figures indicate that, during inflammation, the rates of synthesis of major acute phase α-protein and α-acid glycoprotein increased 28-fold and 22-fold, respectively, compared with the rates of synthesis found for healthy rats. In contrast, the rate of synthesis of albumin decreased to 37% of the value in healthy rats. Thus, during inflammation, the rates of synthesis of major acute phase α-protein and α-acid glycoprotein can become similar in magnitude to or even larger than the rate of synthesis of albumin.

**DISCUSSION**

Changes in protein concentrations in plasma during injury and diseases have been recorded in the human for a long time (12-18). The curves summarized in Fig. 1 together with data reported elsewhere (19, 20) give a comprehensive description of the changes of plasma protein levels during inflammation in the rat.

The influence of various factors has to be considered when net rates of synthesis of proteins are derived from rates of incorporation of amino acids. The existence of different amino acid pools for the synthesis of proteins in liver has been demonstrated (21-23). Free and membrane-bound polyribosomes utilize different pools of amino acids for synthesis of proteins (24), such as albumin and ferritin (25). An important finding reported here is that the plasma proteins studied were synthesized from the same leucine pools or from leucine pools with similar specific radioactivity after injection of radioactive leucine. This permitted the calculation of synthesis rates during inflammation (Table II) from rates of amino acid incorporation by a method which did not require determination of amino acid pools. The method included the assumption that the synthesis rate of transferrin did not change during the first 24 h after inducing inflammation. Since neither the total body pool of transferrin (Fig. 4) nor its fractional turnover rate (Fig. 5) changed during the first day after injection of mineral turpentine it was concluded that the rate of synthesis of transferrin remained constant during that time.

**TABLE II**

<table>
<thead>
<tr>
<th>State of rat</th>
<th>Albumin</th>
<th>Transferrin</th>
<th>Major acute phase α-protein</th>
<th>α-acid glycoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Rate of incorporation in % of that into plasma total protein</td>
<td>H</td>
<td>41</td>
<td>5.1</td>
<td>0.53</td>
</tr>
<tr>
<td>2. Factor by which the rate of synthesis changes 24 h after inducing inflammation</td>
<td>I</td>
<td>9.2</td>
<td>3.1</td>
<td>9.0</td>
</tr>
<tr>
<td>3. Rate of synthesis in healthy rats (from row 3 in Table I) in mg/100 g of body weight/day</td>
<td>0.27</td>
<td>1.0</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>4. Rates of synthesis 24 h after inducing inflammation in mg/100 g of body weight/day</td>
<td>91</td>
<td>19</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>*Calculated using the assumption that the rate of synthesis of transferrin did not change 24 h after inducing inflammation. For details of calculation see Miniprint.</td>
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<tr>
<td><strong>Value corrected for increase in space of distribution of major acute phase α-protein during inflammation (see Table III of Miniprint).</strong></td>
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The level of serum total protein remained fairly constant during inflammation (Fig. 1). Assuming that all plasma proteins are made from the same pools of leucine, it is possible to calculate the synthesis rate of total protein from the rate of incorporation of leucine and the rate of synthesis known for one individual protein as follows. First, the rate of incorporation of leucine is corrected for differences in leucine content of proteins. For example, the leucine content of serum total protein in healthy rats is 10.1%, that in rats with inflammation is 9.9% (Table I), and that of albumin is 10.8% (9). The ratio of the corrected incorporation rates is then multiplied by the rate of synthesis known for one individual protein, for example 91 and 32 mg/100 g of body weight/day for albumin in healthy rats and in rats with inflammation, respectively (Table II). Thus, a rate of synthesis of 234 and 380 mg/100 g of body weight/day was obtained for serum total protein in healthy rats and rats with inflammation for 24 h, respectively. Despite the extraordinary increase in the rates of synthesis of some acute phase proteins (Table II), the rate of synthesis of serum total protein made in the liver changed only moderately during inflammation.

The increase in the rate of synthesis of acute phase proteins causes an increase in the demand for aminoacyl-tRNA, GTP, ATP, etc., in the liver cell. However, a large overall increase in this demand is prevented by a simultaneous decrease in the rates of synthesis of other proteins, in particular, albumin. Albumin is most appropriate for this metabolic adaptation. Its half-life is very long, and its total body pool is by far the largest among the plasma proteins. Furthermore, it has no specific functions indispensable for life as indicated by the existence of apparently healthy albumin-deficient individuals in both man (for review see Ref. 26) and rat (27).

Acknowledgments—We are very grateful to H. Dryburgh and E. M. J. Parkhill for their expert technical assistance and to E. Gill for her help in the preparation of the manuscript.

REFERENCES


Additional references are found on p. 10277.
TABLE I

<table>
<thead>
<tr>
<th>Acidic amino acid composition of serum total protein in healthy rats and in rats suffering from an inflammatory disease</th>
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<tbody>
<tr>
<td>Healthy rats</td>
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<tr>
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</tr>
<tr>
<td>Leu</td>
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<td>Ile</td>
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<td>Val</td>
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<td>Met</td>
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<td>Tyr</td>
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<td>Phe</td>
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<td>Sum</td>
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*excluding (Leu and Trp)
The Acute Phase Response of Plasma Protein Synthesis

Table III

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<tr>
<th>Protein Type</th>
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<tr>
<td>1. Albumin</td>
<td>110 ± 6</td>
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<td>2. Transferrin</td>
<td>16.5 ± 0.1</td>
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<td>3. Major acute-phase glycoprotein</td>
<td>15.7 ± 1.8</td>
<td>35.6 ± 1.0</td>
<td>2.10 ± 0.25</td>
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<td>4. α2-Macroglobulin</td>
<td>0.8 ± 0.1</td>
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The data are expressed as mean ± SEM. The values correspond to those given in Table I.

For screening the isolated protein samples were injected into a group of rats from which blood was removed 2 h later. The sera obtained from this blood contained 1.1 x 10^6 cpm. Six healthy rats and six rats with inflammation weighing between 250 and 300 g were tested overnight. Under ether anaesthesia, each rat received an injection of 2.32 ml of the serum in the tail vein. After 5 min, blood was withdrawn from the caudal veins of three rats in each group, and the specific radioactivity of the injected serum and the specific radioactivity of the injected serum and the specific radioactivity of the injected serum were determined as described above. The specific radioactivity of the serum was estimated from the dilution of the specific radioactivity of the injected sample. (a) Fasted rats

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(b) Fasted rats after injection of turpentine

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Table III shows the distribution and concentration of the injected serum in the body. The distribution of the injected serum was determined by injection of the serum into the tail vein. After injection of the serum, the specific radioactivity of the serum was determined as described above. The specific radioactivity of the serum was estimated from the dilution of the specific radioactivity of the injected sample. (a) Fasted rats

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