Phenylalanine and tyrosine kinetics in compensated liver cirrhosis: effects of meal ingestion

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The mechanism(s) of the increased Phe and Tyr concentrations, Phe and Tyr Ra, Phe Hy, and % Tyr Ra not deriving from
50% greater (P ≤ 0.05 or less vs. basal) Phe and Tyr
concentrations, Phe and Tyr Ra, Phe Hy, and % Tyr Ra not deriving from Hy in both groups. Hy and Tyr Ra remained ≥50% greater (P ≤ 0.04 to
P ≤ 0.01) in patients, whereas Phe Ra was more modestly increased. Phe utilization for protein synthesis increased similarly in both groups. Tyr
clearance was normal, whereas Phe clearance tended to be lower (P = 0.09, intracellular model) in the patients. In summary, in compensated liver cirrhosis studied under fasted and fed states, 1) Tyr Ra is increased; 2) Phe Hy and Phe Ra (plasma model) are increased; 3) Tyr clearance is normal; and 4) Phe clearance is slightly decreased. In conclusion, in cirrhosis increased total tyrosine Ra and hydroxylation contribute to fasting and postmeal hypertryrosinemia, whereas the mechanism(s) responsible for the hyperphenylalaninemia may include both increased production and decreased disposal.

compensated liver cirrhosis; mixed meal; tyrosine hydroxylation; stable isotopes

INCREASED CONCENTRATIONS of the aromatic amino acids phenylalanine (Phe) and tyrosine (Tyr) are commonly found in liver cirrhosis, and they can be responsible for many clinical and metabolic alterations typical of this disease, particularly at advanced stages (8, 11, 14). Besides being an index of poor nutrition, elevated aromatic amino acid concentrations exert adverse effects on cerebral function (3, 8, 11, 14). Meal ingestion commonly exacerbates these alterations (24, 25, 29). Therefore, knowledge of the mechanism(s) leading to increased aromatic amino acid concentrations in cirrhosis is required also to adopt dietary manipulations aimed at preventing these abnormalities (3, 18).

The mechanism(s) of the increased Phe and Tyr concentrations in cirrhosis, in both the postabsorptive and fed states, are poorly understood. Both increased production and decreased disposal of the amino acids (through either catabolic or anabolic routes) can play a role (17, 29). In addition, a reduced first-pass splanchnic (likely hepatic) uptake of these amino acids can occur (25), suggesting a decreased disposal of these amino acids across the splanchnic area, which can contribute to postprandial hyperphenylalaninemia. In this respect, some liver-located metabolic steps (both catabolic and anabolic) can be involved. Phe is a significant source of circulating Tyr through hydroxylation (6), which takes place to a large extent in the liver (4, 16, 22), although the kidney is a significant site too (28). An altered Phe disposal through hydroxylation could thus theoretically occur during meal absorption and account for the postprandial hypertryrosinemia in cirrhosis. Alternatively, a reduced amino acid utilization for protein synthesis can also take place. Whole body protein synthesis, measured with leucine tracers, was indeed decreased in compensated cirrhosis following either a mixed meal ingestion (29) or the intravenous infusion of amino acids with insulin (26). Therefore, an altered use of the aromatic amino acids through both anabolic and catabolic purposes can occur in this disease.

Phe and Tyr kinetics, as well as phenylalanine hydroxylation, can be determined in vivo with Phe and Tyr combined isotope infusions (6, 7, 30). In this study, we have applied this technique to the study of fasting and postprandial Phe and Tyr kinetics in patients with stable cirrhosis.

METHODS

Subjects. Eight male patients with established liver cirrhosis and eight male healthy controls were recruited. Their clinical characteristics are reported on Table 1. All subjects were informed about the aims of the study and signed their consent to it. The study was approved by the Ethical Committee of the Medical Faculty at the University of Padova, Italy, and it was performed according to the Helsinki Declaration (as revised in 1983) and following the recommendations of the local Radiation Safety Officer. All the cirrhotic subjects were freely ambulant and in good health except for their liver disease. All subjects were adapted to a standard weight-maintaining diet (25–30 kcal/kg body wt) containing ~50% of calories as carbohydrates, ~20% as proteins, and ~30% as lipids, for at least 1 yr prior to the study. The adherence to the diet was periodically assessed by telephone interview and survey before the test day. The data of whole body leucine kinetics and of albumin synthesis of six of the cirrhotic subjects as well as seven of the healthy controls was reported previously (29). In all patients, the diagnosis of cirrhosis was carefully established through medical history, clinical examination, ultrasound

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criteria, and biochemical data, as well as by laparoscopy. In addition, in seven patients a liver biopsy was performed. Chronic hepatitis C virus infection (n = 5), hepatitis B virus infection (n = 1), and autoimmune hepatitis (n = 1) were diagnosed. In the nonbiopsied patient, cirrhosis was defined as cryptogenic. Only one patient had (minimal) endoscopic signs of esophageal varices (F1W, i.e., white and straight varices) (2). According to Child-Pugh classification (5, 19), five patients were included into Class A and three into Class B (Table 1). Albumin concentrations was near normal in most of the patients (Table 1). However, such a small age difference did not affect pharmacological therapy for at least 1 mo prior to the study. Age in observations). Lean body mass (LBM, in kg) was estimated in all subjects by Hume’s formula (9). In addition, in six cirrhotic patients LBM was directly measured by dual-energy X-ray absorptiometry (DEXA) (10). In these patients, DEXA-determined LBM (56.5 ± 2 kg, mean ± SE) was not different from that calculated by Hume’s formula (60.9 ± 2.0 kg). Therefore, we used for all subjects the LBM values determined by Hume’s formula. LBM was greater in the patients than in controls (Table 1). Conversely, the fraction of body weight accounted for by LBM was slightly lower in the patients than in the control group (77 ± 1% vs. 82 ± 1%, P < 0.05).

No cirrhotic subject had either diabetes or glucose intolerance, as assessed by the oral glucose tolerance test (21). In the control subjects there was no clinical or familiar history of glucose dysregulation. Isotopes. l-[^ring-2H5]-phenylalanine (D5-Phe) and l-[^2H2]-tyrosine (D2-Tyr) were purchased from Masstrace (Woburn, MA). l-[^ring-3H2]-tyrosine (D3-Tyr) was obtained from Eurisotop (Gif-Sur-Yvette, France). The stable isotopes were >99% mole percent enriched. All tracers were dissolved in sterile saline and proven to be sterile and pyrogen free before use.

Experimental design. The study was performed as described in detail previously (29). Briefly, a polyethylene catheter was placed percutaneously in retrograde fashion into a superficial vein of one arm, which was kept at +6°C in a heated box for arterialized-venous blood sampling. Another catheter was placed into an antecubital vein of the opposite arm, for isotope infusions. At ~240 min, continuous infusions of D5-Phe (0.06–0.07 μmol·kg−1·min−1) and of D2-Tyr (0.030 μmol·kg−1·min−1) were started by means of calibrated pumps (Fig. 1). In addition, the l-[^1-14C] leucine tracer was infused as detailed in Ref. 29. Priming doses of these isotopes (in the amount of 60 times the constant infusion rate per minute), as well as a priming dose of D2-Tyr (0.08 mg/kg), were also administered at ~240 min as boluses. Blood samples were frequently taken over 3 h to allow the achievement of the steady state in plasma amino acid concentrations and phenylalanine and tyrosine enrichments. Steady state was defined as absence of a slope significantly different from 0, as well as of changes in concentrations, specific activities, and enrichments greater than 5%, and it was usually achieved after ~2.5 h (data not shown). Between ~60 and 0 min, four 10-ml blood samples were collected at 20-min intervals (Figs. 1 and 2) into EDTA tubes and rapidly centrifuged at +4°C. The plasma was then stored at −20°C before assay.

At 0 min, the administration of a mixed liquid meal of defined composition (Nutrodrip Protein, Sandoz Nutrition, Wander Italia, Milan, Italy) was started. The meal contained 14.8 g/100 ml carbohydrates, 6.6 protein hydrolysate, 4 lipids, minerals, and vitamins. The proteins were derived from soy and casein. The lipids were constituted by 40% linoleic acid, 6.5% medium chain triglyceride oil, the remainder by mono- and diglycerides. Thus ~49% of calories were repre...
sented by carbohydrates, ~22% by proteins, and ~29% by lipids. The entire meal (~62 kJ/kg body wt, providing ~45% of total daily calories and protein intake) was administered as isocaloric aliquots of 0.94 ml/kg body wt every 20 min over 4 h. Blood samples were again collected at 170, 190, 210, 230, and 250 min, i.e., 10 min after the administration of each meal aliquot, after the achievement of the new steady state (Figs. 1 and 2), as reported elsewhere (29). This pattern of meal administration (i.e., continuous) might not be considered entirely physiological, since no pulse meal was administered and no acute changes in substrate and hormone concentrations were detected. It nevertheless allowed to perform all kinetic measurements at near steady state, thus avoiding uncertainties due to time-dependent changes in amino acid pool sizes and specific activities following a bolus meal.

Analytical measurements. Plasma amino acid concentrations were determined by ion-exchange chromatography using a Beckman amino acid analyzer. Plasma D3-Phe, D3-Tyr, and D2-Tyr molar percent enrichments were determined by GC-MS as tert-butyl-dimethyl-silyl derivatives and electron impact ionization (23). The mass-to-charge ratios of monitored fragments were 239/234 for D3-Phe, 468/466 for D3-Tyr, and 470/466 for D2-Tyr. Enrichments were expressed as tracer-to-tracee ratios (TTR) (32). We used the plasma leucine and α-ketoisocaproate (KIC) specific activities (30) to estimate indirectly intracellular enrichments, as reported in detail (30). The 14C-leucine 14C-KIC SA data (see Ref. 29 for full results) will be reported here just as the ratios of 14C-KIC to 14C-leucine SA. Insulin and glucagon concentrations were measured by radioimmunoassay as referenced elsewhere (29). Plasma glucose was determined by using a Beckman glucose analyzer 2.

Calculations. Plasma phenylalanine and tyrosine enrichments in the two steady-state periods, i.e., in the last 60 min of the basal, postabsorptive state, as well as in the last 60 min of meal administration (i.e., between 190 and 250 min), were averaged. All calculations were performed using these mean values and expressed over LBM.

Whole body phenylalanine and tyrosine kinetics were calculated using both “plasma” enrichments and estimates of intracellular D3-phenylalanine and D2-tyrosine enrichments as described in Ref. 30. As regards the latter approach, for phenylalanine in the postabsorptive state, as well as tyrosine in both the postabsorptive and the fed state, the adjusted intracellular TTR values were calculated by multiplying the “crude” plasma TTR times the individually determined ratios between plasma KIC and leucine 14C-specific activities (30). In the cirrhotic group, these ratios were 0.83 ± 0.02 and 0.88 ± 0.02 in the postabsorptive and the fed states, respectively, whereas they were 0.79 ± 0.03 and 0.80 ± 0.05, respectively, in the controls. The phenylalanine TTR measured in plasma in the fed state was not adjusted further, because the ratio between plasma phenylalanine and Apo B 100-bound phenylalanine enrichment was ~1 in the fed state (20). Plasma D3-Tyr TTR was not modified, because it is produced intracellularly as such. With these adjustments of TTRs, phenylalanine and tyrosine rates of appearance (Ra) were calculated at steady state by using standard formulas (6, 33).

Whole body phenylalanine hydroxlytically to tyrosine (Hy) was

\[ \text{Hy} = \frac{\text{Ra Tyr}}{\text{D4 - tyr TTR}} \times \frac{\text{D4 - phe TTR}}{\text{D3 - phe TTR}} \]

where Ra Tyr is the rate of appearance of tyrosine (in μmol·kg LBM\(^{-1}\)·min\(^{-1}\)) and D4-Tyr TTR and D3-Phe TTR are the TTR of D4-tyrosine and D3-phenylalanine, respectively, either uncorrected or corrected as indicated above. The rate of non-hydroxylative phenylalanine disposal (NHPD), indicating incorporation into protein, was calculated by subtracting Hy from Phe Ra.

Phenylalanine (Phe) and Tyr clearances (expressed as μl·kg LBM\(^{-1}\)·min\(^{-1}\)) were calculated by dividing the total Ra (equal to rate of disappearance at steady state) of the amino acid over its plasma concentration.

Statistical analysis. All data were expressed as mean ± SE. The comparison between the two groups in the postabsorptive amino acid kinetic data (i.e., Phe and Tyr Ra; Phe Hy; NHPD), as well as between one set of data of each group (such as the relative changes vs. basal) was performed by the two-tailed Student’s t-test for unpaired data. The two-way ANOVA for repeated measurements (using the Corel Word Perfect Suite 7, Corel, Ottawa, ON, Canada) was employed to compare comprehensively postabsorptive and postprandial data between the two groups. When data distribution was not normal, log transform or nonparametric tests were used. With the present number of subjects studied, power analysis to detect a 15% difference between groups is ~0.8. A P value <0.05 was considered statistically significant.

RESULTS

Substrate concentrations, specific activities, and enrichments. Meal ingestion increased (P < 0.01) plasma glucose and insulin concentrations in both groups (Table 2); in the patients, however, the increments were greater than those in controls (P < 0.002 for glucose, and P < 0.02 for insulin, respectively). Total amino acid concentrations increased in both groups to a similar extent with the meal, whereas the increments of phenylalanine and tyrosine concentrations were greater in the cirrhotic patients than in controls (Table 2).

Plasma isotope enrichments and specific activities decreased with meal ingestion in both groups, as a result of isotope dilution from entry into the circulation of unlabeled substrates deriving from the diet (Table 2 and Fig. 2). Only the postmeal value of D2-Tyr TTR was different (i.e., significantly smaller, P < 0.05) in the patients than in the controls.

Table 2. Steady-state plasma glucose, insulin, glucagon, and AA concentrations and D3-Phe, D3-Tyr, and D2-Tyr TTRs in the basal state (i.e., between ~60 and 0 min) and following meal administration (180–240 min)

<table>
<thead>
<tr>
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<th>Cirrhotic Patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Meal</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.2 ± 0.2</td>
<td>7.1 ± 0.3*</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>102 ± 31</td>
<td>946 ± 133†</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>106 ± 12</td>
<td>115 ± 13*</td>
</tr>
<tr>
<td>Phenylalanine, μmol/l</td>
<td>66 ± 4</td>
<td>103 ± 8*†</td>
</tr>
<tr>
<td>Tyrosine, μmol/l</td>
<td>73 ± 9</td>
<td>128 ± 12†</td>
</tr>
<tr>
<td>Total AA, mmol/l</td>
<td>2.56 ± 0.11</td>
<td>3.40 ± 0.13*</td>
</tr>
<tr>
<td>Branched chain AA, μmol/l</td>
<td>508 ± 20</td>
<td>767 ± 30*</td>
</tr>
<tr>
<td>D3-Phe TTR</td>
<td>8.63 ± 0.57</td>
<td>6.20 ± 0.47*</td>
</tr>
<tr>
<td>D3-Tyr TTR</td>
<td>0.99 ± 0.12</td>
<td>0.80 ± 0.11*</td>
</tr>
<tr>
<td>D2-Tyr TTR</td>
<td>3.69 ± 0.27</td>
<td>2.46 ± 0.21†</td>
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</table>

Values are means ± SE. AA, amino acid; Phe, phenylalanine; Tyr, tyrosine; TTR, tracer-to-tracee ratio. *P < 0.01 or less vs. basal. †P < 0.05 or less, cirrhotic vs. control group.
Amino acid kinetics. Phenylalanine Ra, total tyrosine Ra, phenylalanine hydroxylation, and the dietary endogenous tyrosine Ra increased in both groups postprandially irrespective of the model used (Fig. 3). Tyrosine Ra and hydroxylation (using both models), as well as phenylalanine Ra (using the plasma model), were greater in the patients in both the fasted and the fed states (Table 3). In the cirrhotic group, the rate of NHPD (using the intracellular model) did not significantly change vs. baseline with meal ingestion (from 0.91 ± 0.04 to 1.03 ± 0.10 μmol·kg⁻¹·min⁻¹, P = not significant), whereas in controls NHPD increased mildly although significantly (from 0.86 ± 0.08 to 1.01 ± 0.07 μmol·kg⁻¹·min⁻¹, P < 0.05 by pair Wilcoxon’s test vs. baseline), reaching, however, similar values in both groups. Conversely, NHPD calculated with the plasma model increased significantly vs. baseline and to the same extent in the two groups (Fig. 3). By the intracellular model, phenylalanine clearance was slightly lower (−9%, −15%, P < 0.1) in the cirrhotic than in the control group, and it decreased in both groups with the meal (Fig. 3). However, phenylalanine clearance calculated via the plasma model was virtually identical in the cirrhotic and the control subjects, and it did not change in either group with the meal (Fig. 3). Tyrosine clearance was not different between the groups and it did not change vs. baseline in either group irrespective of the model used (Fig. 3).

DISCUSSION

The purpose of this study was to investigate the mechanism(s) of the increased tyrosine and phenylalanine concentrations in stable liver cirrhosis under both fasted and fed conditions. We report increased rates of tyrosine appearance in both conditions (irrespective of the model used), resulting from both increased total tyrosine production and from increased phenylalanine hydroxylation to tyrosine. Therefore, these alterations can account at least in part to the fasting and postprandial hypertyrosinemia usually found in cirrhosis.

As regards the hyperphenylalaninemia of the patients, more complex mechanisms are likely involved, possibly including both increased production and decreased disposal. In the cirrhotic subjects phenylalanine Ra was greater than in controls in the plasma model, whereas it was only modestly although insignificantly increased in the intracellular model (Table 3). These findings, in conjunction with the increased (endogenous) tyrosine Ra, are compatible with accelerated rates of protein breakdown, as previously reported in cirrhosis (25). Conversely, phenylalanine clearance tended to be (insignificantly) lower in the patients using the intracellular but not the plasma model (Fig. 3). The reason(s) for these inconsistencies between the two models are unknown, although they may depend on an altered equilibrium between intracellular and extracellular amino acid enrichments and pools in cirrhosis (13). The discussion of this complex issue may go beyond the scope of this study. At present, however, besides the leucine-KIC approach, no alternative method exists to estimate such a disequilibrium in vivo, with the exception of data arising from tissue biopsy. The latter, however, can be performed in vivo only under specific indications and in a limited number of accessible tissues. Therefore, given these limitation, we chose to present the kinetic data using both the plasma and the intracellular model.

We previously showed that the first-pass splanchnic uptake of dietary phenylalanine was decreased in cirrhosis (25). Although in the present study we did not administer any amino acid isotope with the meal, and therefore we could not substantiate this alteration, it is possible that also changes in the initial splanchnic handling of the dietary phenylalanine accounted for the postprandial hyperphenylalaninemia observed in the patients (25). Furthermore, should tyrosine splanchnic uptake mirror that of phenylalanine, a possibly decreased splanchnic uptake also of this aromatic amino acid could contribute to the postprandial hypertyrosinemia observed in cirrhosis.

The data of the normal subjects here reported (with the addition of one subject) are presented also as an amendment of the phenylalanine and tyrosine intracellular data of Table 2 of the referenced paper (30). Those published data were biased by a small calculation error recently discovered. Nevertheless, the correlations between various parameters and the general significance of the data reported in Ref. 28 remain the same.
Our data also suggest in the patients a mild impairment (using the intracellular model) of phenylalanine utilization for protein synthesis (NHPD), which did not increase significantly after the meal, at variance with a small albeit significant increase observed in the controls. Nevertheless, the magnitude of increase of NHPD was similar in the two groups. Therefore, we would conclude that there is no relevant reduction of the whole body rate of phenylalanine incorporation into protein(s) in compensated cirrhosis. This is at variance with the reduced rate of whole body leucine utilization for protein synthesis previously reported (29). The reason(s) for these partial discrepancies between these two model amino acids are unclear.

Table 3. Steady-state Phe and Tyr kinetics using either plasma or intracellular enrichments and/or pools (see METHODS)

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<tr>
<td></td>
<td>Basal</td>
<td>Meal</td>
</tr>
<tr>
<td><strong>Calculated using plasma pools</strong></td>
<td></td>
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</tr>
<tr>
<td>Phe Ra</td>
<td>0.89±0.05*</td>
<td>1.26±0.10†</td>
</tr>
<tr>
<td>Tyr Ra</td>
<td>0.83±0.05*</td>
<td>1.29±0.13†</td>
</tr>
<tr>
<td>Hy</td>
<td>0.098±0.016*</td>
<td>0.170±0.032†</td>
</tr>
<tr>
<td>% of Phe Ra to Hy</td>
<td>10.7±1.3*</td>
<td>13.7±2.7*</td>
</tr>
<tr>
<td>Hy as % Tyr Ra</td>
<td>11.6±1.7*</td>
<td>13.0±1.8*</td>
</tr>
<tr>
<td><strong>Calculated using intracellular pools</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phe Ra</td>
<td>1.03±0.06</td>
<td>1.20±0.10†</td>
</tr>
<tr>
<td>Tyr Ra</td>
<td>1.00±0.07*</td>
<td>1.42±0.14†</td>
</tr>
<tr>
<td>Hy</td>
<td>0.126±0.023*</td>
<td>0.171±0.033†</td>
</tr>
<tr>
<td>% of Phe Ra to Hy</td>
<td>11.9±1.6*</td>
<td>14.6±2.8*</td>
</tr>
<tr>
<td>Hy as % Tyr Ra</td>
<td>12.2±1.5</td>
<td>11.9±1.7</td>
</tr>
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</table>

Values are means ± SE. Rate of appearance (Ra) is calculated in μmol·kg LBM⁻¹·min⁻¹. NHPD, nonhydroxylative phenylalanine disposal; Hy, hydroxylation. *P < 0.025 or less, cirrhotic vs. control group. †P < 0.01 or less vs. basal, by ANOVA.

Our data also suggest in the patients a mild impairment (using the intracellular model) of phenylalanine utilization for protein synthesis (NHPD), which did not increase significantly after the meal, at variance with a small albeit significant increase observed in the controls. Nevertheless, the magnitude of increase of NHPD was similar in the two groups. Therefore, we would conclude that there is no relevant reduction of the whole body rate of phenylalanine incorporation into protein(s) in compensated cirrhosis. This is at variance with the reduced rate of whole body leucine utilization for protein synthesis previously reported (29). The reason(s) for these partial discrepancies between these two model amino acids are unclear.
and they may depend on the unavailability of a “direct” intracellular model of phenylalanine-tyrosine kinetics in cirrhosis. On the other hand, the finding of increased phenylalanine hydroxylation rates, both under fasted and fed conditions, indicates an increased loss through an irreversible catabolic step of this essential amino acid, which therefore becomes unavailable for protein synthesis. This is in agreement with previous observations showing the absence of either the meal-enhanced, or the amino acid plus insulin-stimulated increase, of leucine disposal for protein synthesis in cirrhosis (26, 29). A reduced albumin synthesis was also shown in these patients following a mixed meal (29). In addition, a decreased muscle protein synthesis was previously demonstrated in cirrhotic subjects (25). Taken together, an overall defect of protein synthesis may be suspected in liver cirrhosis, although not all measurements may agree.

In this study, we employed a previously published phenylalanine-tyrosine tracer method to estimate whole body protein synthesis in human subjects postprandially (30). The use of phenylalanine-tyrosine tracers is attractive, because the measurement of phenylalanine catabolism (i.e., hydroxylation), which is required for the calculation of whole body protein synthesis (33, 34), does not require expired air collection. Nevertheless, its validity also in patients with liver cirrhosis needs to be confirmed.

Our patients’ general nutritional state was only moderately altered, as shown by a ~8% decrease of the estimated contribution of LBM to body weight (see METHODS). Therefore, the subtle albeit measurable kinetic defects shown in the present as well as in previous studies (25, 26, 29) could contribute, in the long term, to the development of more marked nutritional alterations in these patients.

At least 50–60% of whole body phenylalanine hydroxylation takes place within the splanchnic area, likely in the liver under normal conditions (28). Despite the expected defect of hepatic metabolic function(s) in cirrhosis, surprisingly, hydroxylation was not decreased but rather increased in our patients. This observation suggests that the presence of liver disease, at least to the degree observed in these subjects, did not result in any impairment of this enzymatic activity. Alternatively, a compensatory role of other tissues and/or organs (mostly the kidney, which possesses a relevant hydroxylation capacity) (28) may occur. Conversely, it is possible that at more advanced disease states liver phenylalanine hydroxylation and other metabolic activities involving the aromatic amino acids are decreased, in analogy with the reduced tyrosine oxidation capacity reported in fulminant hepatic failure (17). In this study, we did not measure tyrosine oxidation, since the tyrosine tracer here infused was not carbon labeled. However, should tyrosine oxidation be decreased, such a defect combined with an increased tyrosine production could reinforce the observed plasma hypertyrosinemia.

An increased hydroxylation can be driven either by substrates, hormones, or other metabolic or regulatory conditions (1, 27). Hyperglucagonemia was shown to acutely increase hydroxylation (27). However, glucagon concentrations in our patients were normal in both the fasted and the fed states (Table 1), and we did not find any correlation between glucagon and hydroxylation in this study. Hyperphenylalaninemia, whatever the cause for it, could itself increase hydroxylation by a mass action (7, 35). The $K_m$ for liver hydroxylase ranges between 200 and 300 $\mu$M (4, 32), well within the circulating phenylalanine concentrations, whereas at increasing phenylalanine intakes both phenylalanine oxidation and its conversion to tyrosine were dose dependent and did not reach a plateau (35).

No correlation was found between protein synthesis and some of the measured variables (in particular, amino acid and insulin concentrations), in analogy with previously reported data (30). Thus the factors regulating the postprandial increase of whole body protein synthesis also in cirrhosis are probably more complex than that is currently believed, and only partially known.

We have expressed our data over LBM. Although data expression over body cell mass may be more meaningful in cirrhosis (12), LBM could represent a reasonable and simpler way to estimate the metabolically active mass (with respect to proteins) of the body.

In conclusion, this study demonstrates that an increased tyrosine production is a key mechanism for the hypertyrosinemia commonly found in cirrhosis. Despite the occurrence of liver disease, phenylalanine hydroxylation is also increased, suggesting both an increased amino acid catabolism of this essential amino acid and an intact hydroxylation activity at least at the whole body level. The hyperphenylalaninemia may be due either to increased production from proteolysis, to a mildly impaired protein synthesis, and/or to decreased amino acid clearance most likely at the splanchnic level. These observations may be useful in a better understanding of the pathophysiological mechanism(s) leading to the increased aromatic amino acid concentrations and protein wasting in liver cirrhosis. However, more studies are required, also in patients with an advanced disease state.

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POSTPRANDIAL TYROSINE KINETICS IN CIRRHOSIS


