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ORIGINAL ARTICLE

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Hepatic amino-acid metabolism in liver cirrhosis and in the long-term course after liver transplantation

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Abstract The aim of this study was to investigate the impact of orthotopic liver transplantation (OLT) on plasma levels and splanchnic turnover of key amino acids for muscular (branched-chain amino acids: BCAAs) and hepatic metabolism (aromatic amino acids (AAAs) and methionine) in 48 patients with cirrhosis, 14 patients after OLT, and 46 controls. Also, hepatic amino-acid supply and resting energy expenditure were measured. BCAA levels (no hepatic uptake) decreased in cirrhosis ($P < 0.001$) and were improved, although not normalized, after OLT ($P < 0.001$). AAA and methionine levels were raised in cirrhosis ($P < 0.001$) and normalized after OLT ($P < 0.001$). Hepatic supply of these amino acids increased in patients graded Child B and C and decreased significantly after OLT. Splanchnic uptake of AAAs and methionine increased significantly in Child-B and decreased in Child-C patients. After OLT, splanchnic extraction of AAAs and methionine was as in Child A. Circulating AAAs and methionine correlated with indocyanine-green half-life ($r = 0.71$, $P < 0.001$) and resting energy expenditure ($r = 0.50$, $P < 0.001$), indicating that levels of circulating AAAs and methionine in cirrhosis are determined by hepatic and extrahepatic metabolic factors. This study demonstrates persistent changes in muscular metabolism of BCAAs after OLT, while the hepatic amino-acid metabolism is normalized due to (1) a significant reduction in the rate of peripheral proteolysis, and (2) improved liver function compared with that in patients with cirrhosis.

Keywords Liver transplantation · Cirrhosis · Amino acids · Hepatic metabolism · Aromatic amino acids · Branched-chain amino acids · Methionine

Introduction

Levels of circulating amino-acids mainly reflect the balance between muscular and hepatic metabolism [13, 15, 25]: in the post-absorptive state, amino acids are primarily released by muscle tissue, while the liver is the key organ in amino-acid clearance. This metabolic function of the liver is illustrated by a steep rise in the plasma levels of almost all amino acids in fulminant hepatic failure and after hepatectomy [36].

In acute and chronic liver diseases, characteristic alterations in the profile of circulating amino acids have been described [18, 41, 42]. In cirrhosis, the plasma levels of methionine and the aromatic amino acids (AAAs) tyrosine and phenylalanine are elevated, while the plasma concentrations of the branched-chain amino acids (BCAAs) valine, leucine, and isoleucine are decreased [23, 27, 28]. There is a high hepatic clearance of AAAs in healthy controls [7, 8, 13]. Therefore, the elevation of AAAs in liver disease may reflect impaired hepatic

clearance. On the other hand, since BCAAs escape hepatic uptake, the decrease of BCAAs was attributed to changes in muscular metabolism [7, 10]. However, the pathophysiology of these alterations is still poorly understood [15, 16]. In particular, studies investigating the hepatic amino-acid turnover are lacking.

A variety of metabolic derangement occurs in patients with chronic liver disease. The cirrhotic patient is characterized by protein catabolism and a hypermetabolic state, metabolic parameters that have been recognized to impact on the prognosis of the patient after orthotopic liver transplantation (OLT) [29, 31]. In addition, muscle wasting, impaired production of albumin and clotting factors, as well as hepatic encephalopathy, have been related to an impaired amino-acid turnover [12, 16, 20]. The majority of these metabolic parameters are normalized after OLT. However, studies reporting plasma amino-acid levels after OLT have been performed in only the early postoperative period, in a situation before stable graft function is established, and parenteral nutrition and pre-existing malnutrition may impact on the results [6, 9, 11, 32, 37, 38]. It is thus not clear whether levels of circulating amino-acids as well as hepatic amino-acid metabolism are normalized in the clinically stable long-term course after liver transplantation. The aim of this study was therefore to investigate circulating levels and hepatic turnover of key amino acids in patients with end-stage liver disease and in the long-term course after successful liver transplantation.

Materials and methods

Patients

Three groups of patients were studied: 48 patients with biopsy-proven liver cirrhosis, 14 patients more than 6 months after OLT, and 46 controls without any liver or metabolic disease. Detailed clinical data of patients and controls are given in Table 1.

Patients with cirrhosis were graded according to the Child-Pugh classification [35]: Child A = 7 (14%), Child B = 21 (44%), and Child C = 20 (42%). Thirteen (27%) patients suffered from alcoholic liver disease, 19 (40%) had virus-induced cirrhosis (hepatitis-B virus, hepatitis-C virus), 14 (29%) suffered from biliary cirrhosis (primary biliary cirrhosis, primary sclerosing cholangitis), and in two (4%), liver disease was cryptogenic. The cirrhotic patients were studied while they were in hospital being assessed for liver transplantation. All had been following a weight-maintaining diet containing 80 g of protein daily for at least 1 week.

The OLT patients were studied during routine check-ups. The time since transplantation varied between 6 and 112 months (mean 35 months). All patients had been transplanted because of end-stage chronic liver failure. They were in a stable clinical condition with normal liver-function test results at the time of this study. No evidence of fibrosis or cirrhosis of the graft had been found in biopsies taken no more than 120 days before the study. A daily protein intake of 80 g was established for at least 1 week before the study. The immunosuppressive medication consisted of cyclosporin A, adjusted to serum levels between 80 and 120 ng/ml, and prednisone at under 7.5 mg per day.

Patients with suspected coronary artery disease who were undergoing diagnostic coronary angiography served as controls for the arterial amino-acid levels. None of them had a history of hepatic disease, all had completely normal liver function, normal ultrasound of the liver and biliary system, and negative serological findings for viral and autoimmune liver disease. In the controls, the daily oral protein intake was 80 g for at least 3 days before the examination.

Patients with proteinuria, suspected infections, clinically overt diabetes mellitus, thyroid dysfunction, or any other endocrine disorder, were excluded from the study. No hormone or thyroid regulatory medication was administered. Patency of portal vein and hepatic artery was documented in patients and controls by Doppler ultrasound before they were entered into the study.

All patients were thoroughly informed about the rationale and the possible risks of all investigational procedures and gave written consent before entering the study. The study protocol was approved by the ethics committee of the Medizinische Hochschule Hannover.

Assessment of splanchnic hemodynamics

After the patients had fasted overnight, we performed hepatic vein catheterization for the collection of hepatic venous blood samples, using a balloon catheter as described [2, 17]. Arterial blood was drawn from a line placed in the right femoral artery. No complications were encountered during or after the procedure. Quantitative hepatic blood flow was determined by the indocyanine-green (ICG, Cardio-Green, Paesel & Lorei, Frankfurt/Main, Germany) steady-state infusion technique according to a previ-

Table 1 Clinical details of controls, patients with liver cirrhosis, and OLT patients. Data are presented as mean ± SEM (*BMI* body mass index, *REE* resting energy expenditure)

Parameter	Controls	Cirrhosis	OLT
n	46	48	14
Gender ratio (M:F)	28:18	30:19	8:6
Age (years)	52 ± 3	49 ± 2	46 ± 3
BMI (kg/m^2)	25.0 ± 1.0	23.1 ± 0.5	25.2 ± 1.0
Fat mass (%)	–	23.2 ± 0.9	25.7 ± 1.1*
Body cell mass (%)	–	35.9 ± 1.2	38.5 ± 0.8*
Extracellular mass (%)	–	39.8 ± 1.0	35.7 ± 0.7*
REE (kcal/d)	–	1,781 ± 48	1,482 ± 52*
Daily protein intake (g/kg BW)	1.10 ± 0.06	1.16 ± 0.07	1.11 ± 0.07
Bilirubin (μmol/l)	10 ± 4*	66 ± 10	12 ± 5*
Albumin (g/l)	42 ± 1*	30 ± 1	40 ± 1*
Prothrombin time (%)	97 ± 2*	62 ± 2	98 ± 2*

*$P < 0.05$ or less, results significantly different from cirrhosis

ously published protocol [39]. Briefly, on the day prior to hepatic venous catheterization, individual ICG half-life ($ICG_{t1/2}$), as a measure of effective hepatic blood flow, was determined by ICG bolus injection [39]. From these data the individual ICG infusion rate was calculated according to the formula [39]: $I_{ICG} = \ln_2/ICG_{t1/2} \times 60$, with I_{ICG} representing the individual ICG infusion rate (mg/h), and $ICG_{t1/2}$ representing the $ICG_{t1/2}$(min). ICG was measured spectrophotometrically at the 800-nm wavelength (DU6 Beckmann photometer, Beckmann Instruments, Munich, Germany).

Patients received an intravenous loading dose of 0.3 mg ICG/kg body weight, followed by a constant infusion of ICG through a forearm cannula at the infusion rate calculated according to the formula above. After steady-state conditions had been achieved, hepatic blood flow (HBF) was calculated as: $HBF = I_{ICG}/(ICG_a - ICG_{hv})/(1-hct)$, with I_{ICG} representing the individual ICG infusion rate (mg/min), ICG_a representing the arterial ICG concentration (mg/l), ICG_{hv} representing the hepatic venous ICG concentration (mg/l), and hct representing the hematocrit. If the arteriohepatic venous ICG concentration difference was below 0.1 mg/l, no HBF calculation was performed [4]. If no stable steady-state could be achieved, a correction calculation was applied as described [39].

Blood sampling and measurement of amino acids

All blood samples were immediately placed on crushed ice and processed without delay. ICG was measured spectrophotometrically at the 800-nm wavelength (DU6 Beckmann photometer). For amino-acid analysis, plasma was deproteinized with 5% sulphosalicylic acid. Aliquots were stored at −80 °C and analyzed by automated ion-exchange chromatography on an automated amino-acid analyzer (Liquimat 5001, Biotronic, Maintal, Germany). For this study we measured methionine, the AAAs tyrosine and phenylalanine, and the BCAAs valine, leucine, and isoleucine. We calculated hepatic substrate supply (HSS) for the different groups of amino acids by multiplying HBF with the respective arterial amino-acid levels. We calculated hepatic amino-acid production/extraction rates by multiplying the respective arteriohepatic venous concentration differences by the HBF. Strictly speaking, what is referred to as hepatic production/extraction rates in this study represents splanchnic production/extraction rates since the contribution of the portal vein was not directly measured. Direct blood sampling from the portal vein is not possible due to ethical considerations. However, in the post-absorptive state, the measurement of splanchnic production/extraction reliably reflects the actual hepatic production/extraction of substrates.

Measurement of resting energy expenditure

We assessed resting energy expenditure by indirect calorimetry, using a ventilated open hood as described (Deltatrac Metabolic Monitor, Datex Instruments, Helsinki, Finland) [31].

Statistics

Statistical analysis was performed with the statistical package for social sciences (SPSS). Data are expressed as mean ± SEM. Non-parametric statistical tests were used. Kruskal-Wallis analysis of variance was used to compare values of three or more different groups. Using the Mann-Whitney *U*-test, we then compared the values that showed significant inter-group differences. Spearman's rank correlation coefficient was used to assess possible associations between different parameters. *P* values lower than 0.05 were considered statistically significant.

Results

Elevated levels of circulating AAAs and methionine in cirrhosis normalized after OLT, while BCAAs remained decreased

The arterial levels of the amino acids that were studied are summarized in Table 2. BCAA levels in patients with cirrhosis were significantly decreased, compared with controls (289 ± 10 μmol/l vs 465 ± 14 μmol/l, respectively, $P < 0.001$). This decrease occurred independent of the clinical stage of cirrhosis. However, in the clinically stable long-term course after OLT circulating BCAAs remained decreased (379 ± 14 μmol/l, $P < 0.001$ compared with controls), although significantly improved, compared with patients with liver cirrhosis ($P < 0.001$).

On the other hand, AAA levels were significantly elevated in patients with liver cirrhosis, compared with controls (211 ± 12 μmol/l vs 107 ± 4 μmol/l, respectively, $P < 0.001$). Levels increased significantly with clinical progression of the liver disease (Child A compared with Child B ($P < 0.001$) and Child C ($P < 0.01$); Fig. 1a). After OLT, circulating plasma AAAs were normalized (110 ± 5 μmol/l; Table 2 and Fig. 1a). Levels of circulating methionine were altered in the same fashion. In patients with cirrhosis, plasma methionine was significantly increased, compared with controls (59 ± 10 μmol/l vs 21 ± 1 μmol/l, respectively, $P < 0.001$), increasing with advancing Child stage (Child C: $P < 0.05$, Child B: $P < 0.01$, each compared with Child A; Fig. 2a). In patients after OLT, levels of circulating methionine were normal (20 ± 1 μmol/l; Table 2 and Fig. 2a).

Hepatic AAA and methionine clearance in cirrhosis depended on hepatic amino-acid supply and functional metabolic reserves of the liver

Neither in patients with cirrhosis nor in OLT patients was a significant hepatic extraction or production of

Table 2 Circulating amino acids in controls, patients with liver cirrhosis, and OLT patients. Values (μmol/l) are means ± SEM

Amino acid	Controls	Cirrhosis	OLT
BCAAs	465 ± 14[a]	289 ± 10[b]	379 ± 14[a,b]
Valine	244 ± 8[a]	156 ± 6[b]	201 ± 7[a,b]
Leucine	147 ± 5[a]	85 ± 3[b]	118 ± 5[a,b]
Isoleucine	74 ± 3[a]	48 ± 2[b]	60 ± 3[a,b]
AAAs	107 ± 4[a]	211 ± 12[b]	110 ± 5[a]
Tyrosine	56 ± 2[a]	132 ± 8[b]	57 ± 4[a]
Phenylalanine	51 ± 2[a]	79 ± 4[b]	53 ± 2[a]
Methionine	21 ± 1[a]	59 ± 10[b]	20 ± 1[a]

[a] $P < 0.05$ or less, results significantly different from cirrhosis
[b] $P < 0.05$ or less, results significantly different from controls

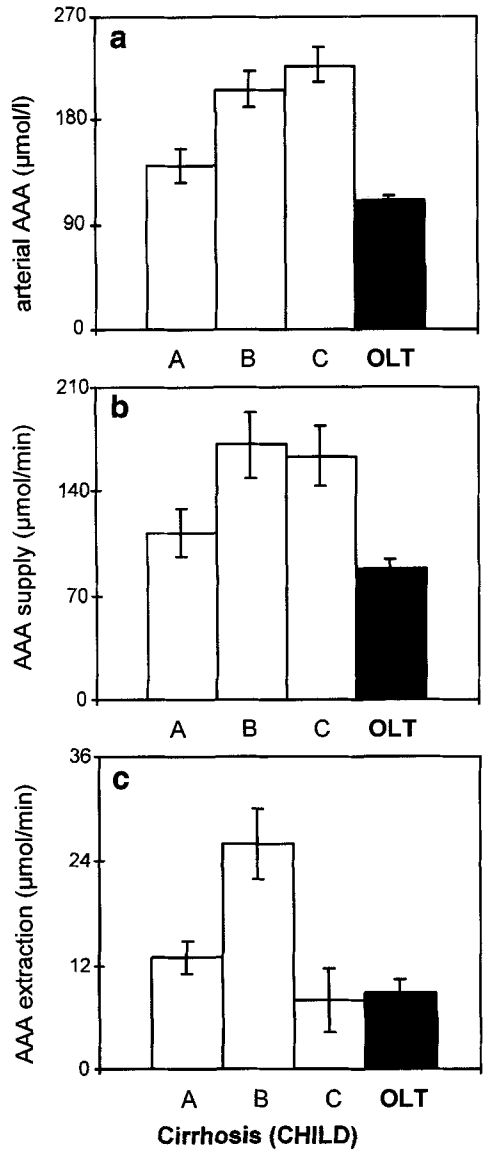

Fig. 1 Metabolism of AAAs in patients with liver cirrhosis and after OLT. **a** Levels of circulating AAAs, **b** HSS calculated as levels of arterial AAAs multiplied by splanchnic blood flow, **c** hepatic AAA extraction determined as difference in concentrations of arteriohepatic venous AAAs multiplied by splanchnic blood flow. Data represent mean ± SEM

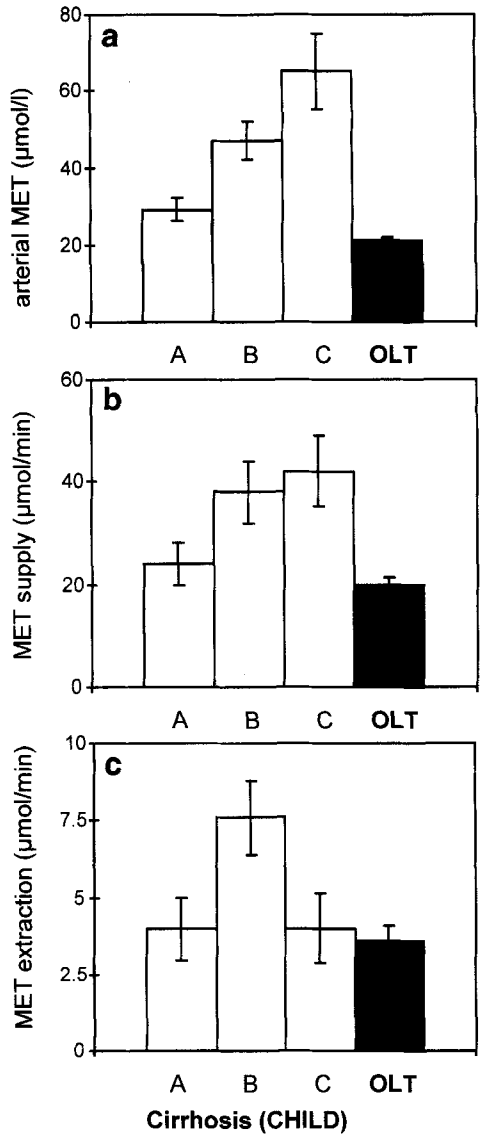

Fig. 2 Metabolism of methionine (*MET*) in patients with liver cirrhosis and after OLT. **a** Levels of circulating methionine, **b** HSS calculated as levels of arterial methionine multiplied by splanchnic blood flow, **c** hepatic methionine extraction determined as difference in concentrations of arteriohepatic venous methionine multiplied by splanchnic blood flow. Data represent mean ± SEM

BCAAs observed, which is consistent with previous reports [7]. Therefore, we focussed on the hepatic clearance of AAAs and methionine in more detail.

No statistically significant differences were observed between the groups of patients with cirrhosis and OLT patients for the hepatic extraction of AAAs (15.1 ± 5 µmol/min vs 8.8 ± 1.5 µmol/min, respectively) and methionine (5.6 ± 0.9 µmol/min vs 3.6 ± 0.5 µmol/min, respectively). Looking at patients in different clinical stages of cirrhosis, we found striking differences: patients graded Child A had a hepatic extraction rate of AAAs of 13 ± 2 µmol/min (Fig. 1c). Interestingly, in Child-B patients hepatic AAA extraction was doubled (26 ± 4 µmol/min, $P < 0.01$ compared with Child A), while in Child-C patients hepatic AAA extraction was significantly decreased, with 8 ± 4 µmol/min (NS compared with Child A, $P < 0.01$ compared with Child B). Hepatic AAA supply, on the other hand, was low in Child-A patients (112 ± 16 µmol/min; Fig. 1b). However, in Child-B and -C patients there was a steep rise in HSS of AAAs (173 ± 22 µmol/min, 161 ± 20 µmol/min, respectively, $P < 0.01$ compared with Child A). After

OLT, HSS of AAAs was even lower than in Child-A patients (88 ± 6 μmol/min; Fig. 1b).

Hepatic metabolism of methionine changed in a similar fashion. Hepatic extraction in Child-A patients was 4.0 ± 1.0 μmol/min (Fig. 2c). In Child-B patients hepatic methionine extraction was almost doubled (7.6 ± 1.2 μmol/min, $P < 0.05$ compared with Child-A; Fig. 2c) and decreased steeply in Child-C patients (4.0 ● 1.1 μmol/min, $P < 0.05$ compared with Child-B; Fig. 2c). HSS of methionine was 24 ± 4 μmol/min in Child-A patients (Fig. 2b), was almost doubled in the Child-B stage (38 ± 6 μmol/min, $P < 0.05$ compared with Child-A; Fig. 2b) and remained high in Child-C patients (42 ± 7 μmol/min, $P < 0.05$ compared with Child-A; Fig. 2b). In patients after OLT the HSS of methionine was 20 ± 1.5 μmol/min (Fig. 2b).

These data demonstrate that the hepatic extraction of AAAs and methionine depends on the HSS and the functional metabolic reserve capacity of the liver. In early stages, HSS is low and the hepatic extraction consequently is also low. While in advanced stages of cirrhosis the Child-B liver is able to respond partially to the increased HSS by increasing the extraction; the Child-C liver fails to do so.

Levels of circulating AAAs and methionine rose with decreasing effective hepatic blood flow and increasing resting energy expenditure

Next we assessed the association between arterial AAA and methionine levels and (1) $ICG_{t1/2}$ after single-dose bolus injection, a parameter of effective hepatic blood flow, and (2) resting energy expenditure as a parameter of whole-body metabolic activity. Arterial AAAs and methionine increased significantly with decreasing effective hepatic blood flow, reflected by an increasing $ICG_{t1/2}$ ($r = 0.65$, $P < 0.001$; $r = 0.71$, $P < 0.001$, respectively; Fig. 3). On the one hand, an increasing resting energy expenditure was significantly correlated with increasing arterial concentrations of AAAs and methionine ($r = 0.42$, $P = 0.002$; $r = 0.50$, $P < 0.001$, respectively; Fig. 4). On the other hand, however, although resting energy expenditure was significantly lower in the OLT group (see Table 1), no correlation with levels of circulating BCAAs was found. These results demonstrate that the levels of circulating AAAs and methionine are determined by hepatic as well as extra-hepatic factors.

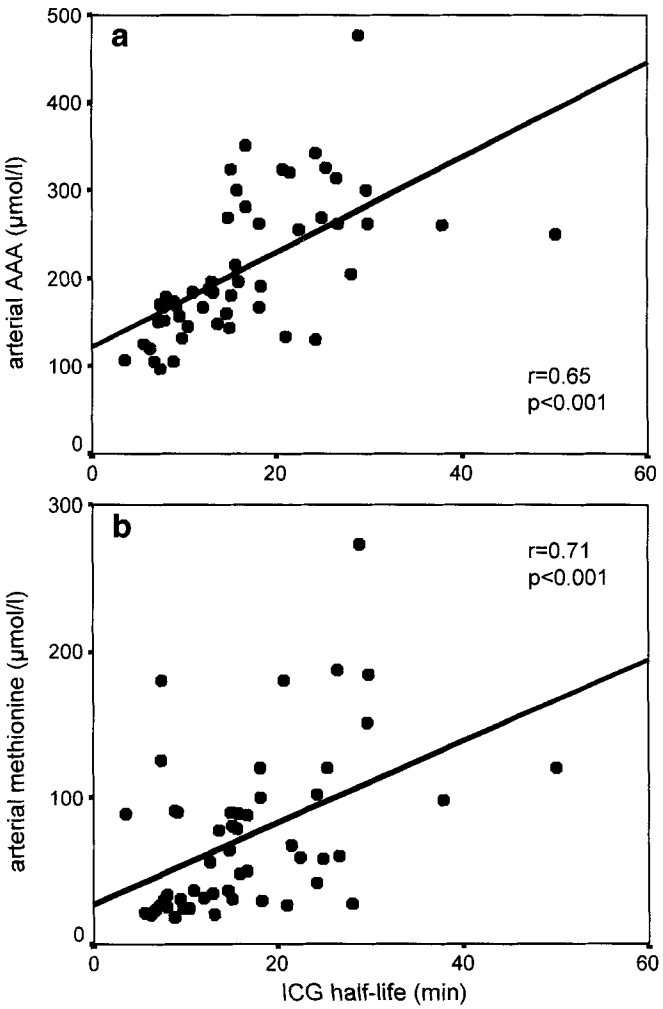

Fig. 3 Correlation between $ICG_{t1/2}$ as a measure of effective hepatic blood flow and levels of arterial **a** AAA and **b** methionine in patients with liver cirrhosis

Discussion

Circulating amino acids are mainly determined by hepatic and muscular metabolism, in the fasting state primarily reflecting the balance between amino-acid release from muscle protein stores and amino-acid uptake by the liver [12, 13, 16]. This study focuses on the hepatic metabolism of key amino acids in cirrhosis and after OLT: on the one hand we investigated BCAAs that are known to escape hepatic extraction and have a primary muscular uptake [10, 16], on the other hand we looked at amino acids with a high hepatic clearance: AAAs and methionine [7, 16]. The results demonstrated that (1) circulating BCAAs are decreased in cirrhosis and remain decreased, though improved, after OLT, indicating persisting disturbances of muscular metabolism in the long-term course after OLT; (2) increased plasma AAAs and methionine in cirrhosis normalize after OLT; (3) AAAs and methionine plasma levels depend on (a) HSS, i.e., amino-acid release by peripheral tissues, as well as (b) the remaining functional hepatic metabolic clearance capacity of the diseased liver.

BCAA levels are reduced early in the course of liver cirrhosis [1, 23, 26, 27, 40, 43] and a significant reduction

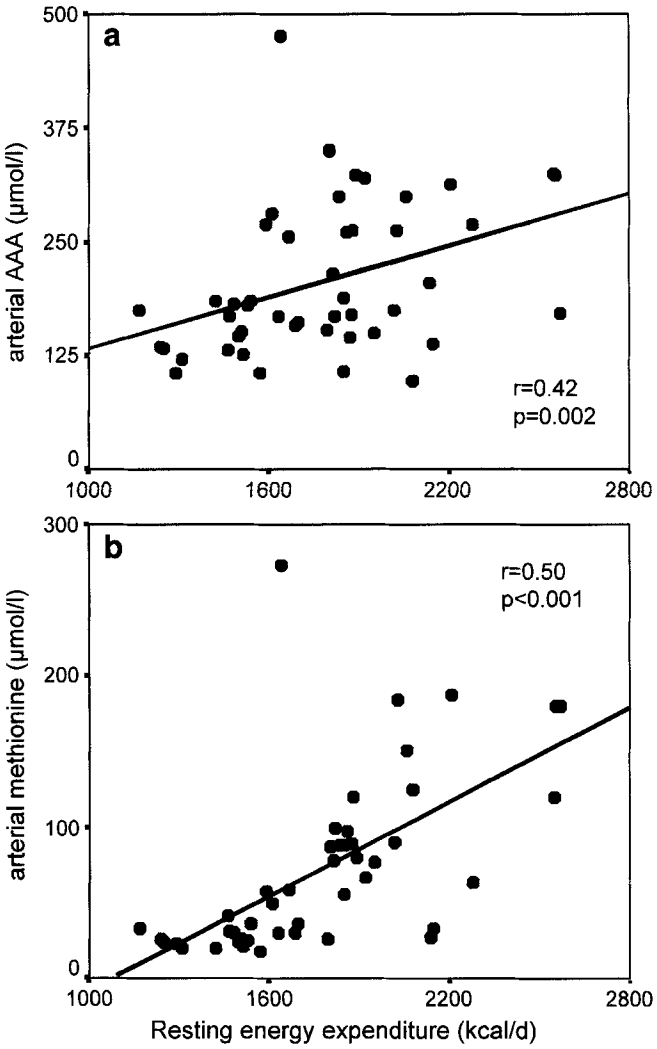

Fig. 4 Correlation between resting energy expenditure assessed by indirect calorimetry and levels of arterial **a** AAA and **b** methionine in patients with liver cirrhosis

in circulating BCAAs has been reported, even in patients with mild, possibly reversible liver disease [28]. In addition, no further decrease is seen once cirrhosis develops [28]. Our data are consistent with this observation, since the patients with cirrhosis who were investigated in our study had reduced levels of circulating BCAAs, independent of the clinical stage. The underlying alterations of muscular amino-acid metabolism in cirrhosis are yet unclear. Also, the functional significance of lowered plasma BCAA levels in cirrhosis remains to be determined, since muscular levels of BCAAs are comparable between patients with cirrhosis and controls [27]. After OLT, BCAA levels were improved, but not normalized. This finding is surprising, since we investigated patients in the clinically stable long-term course after OLT who had normal liver function test results. A few studies conducted early after OLT have shown a significant rise in levels of circulating BCAAs, and normalization was predicted for the long-term course [9, 32, 37]. However, in a recent study, leucine levels were followed up to 26 months after OLT, and the authors reported a persistent decrease, although in this study no cirrhotic patients were included for comparison [24]. As reported for healthy controls [7, 8], also in the patients with liver cirrhosis and after OLT whom we investigated, there was no significant hepatic extraction or production of BCAAs.

AAAs and methionine are amino acids with a high hepatic clearance [7, 10, 16]. Our data demonstrate that the plasma levels of these increase gradually with decreasing liver function and decreasing effective hepatic blood flow. Elevated levels have been reported in established cirrhosis [1, 23, 27, 40, 43]. In the early postoperative period of liver transplantation, levels of circulating AAAs and methionine decrease significantly [9, 32, 37]. Our data show that plasma levels of AAAs and methionine are also normalized in the long-term course after OLT when liver function and hepatic hemodynamics are restored to normal.

Although diminished plasma clearance of intravenously administered AAAs [14, 19, 22] and methionine [3] has been noted in patients with advanced cirrhosis, to our knowledge no direct measurement of hepatic AAA and methionine uptake has been reported in patients with liver cirrhosis or after OLT. Our data demonstrate that the increase of AAA and methionine plasma levels in cirrhosis has two components: HSS of these amino acids and hepatic clearance. Patients with liver cirrhosis are characterized by increased protein catabolism that may occur early in the course of liver disease [21, 25, 29]. Increased resting energy expenditure has been identified as being indicative of wasting and protein catabolism [30, 31]. In this study we show a significant association between the degree of hypermetabolism and circulating AAA and methionine levels. In cirrhosis, an increase in amino-acid liberation from endogenous protein stores within the muscle has been noted that increased with the severity of cirrhosis [33, 34]. In addition, when indirect methods to assess hepatic protein synthesis were employed, maximal stimulation of hepatic protein synthesis was reported in patients with cirrhosis [5]. After OLT, basal proteolysis was normalized [24]. These data are confirmed by our study. We demonstrated a significant increase in HSS for AAAs and methionine occurring in Child-B and C patients. The livers of patients graded Child-B are able to respond, although insufficiently, to increased substrate supply with an increase in amino-acid extraction. Thus, our data suggest a maximally stimulated hepatic amino-acid uptake in these patients. With progression of cirrhosis to the Child-C stage, however, the increase in substrate supply cannot be compensated for. Hepatic extraction rates decrease, although HSS remains high, and consequently, the

circulating plasma levels increase even further. In the long-term course after OLT, HSS decreases significantly and hepatic extraction rates return to basal levels. Consequently, circulating plasma levels of amino acids with a high and primary hepatic extraction normalize after OLT.

In conclusion, our results demonstrate that in the clinically stable long-term course after OLT only a partial normalization of the deranged plasma amino-acid profile seen in patients with liver cirrhosis is achieved. After OLT, BCAA levels are improved, but remain significantly lower than in controls, indicating persisting alterations of muscular metabolism, while AAA levels return to normal with normalization of liver function and normalization of HSS as indicator of the basal rate of proteolysis.

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