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Alteration of Regional Cerebral Metabolism in Patients with Cirrhosis in Positron Emission Tomography

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Abstract To evaluate the alteration of cerebral blood flow and oxygen metabolism in cirrhosis, we measured regional cerebral blood flow (rCBF), cerebral metabolic rate for oxygen ($rCMRO_2$), and oxygen extraction fraction (rOEF) in twelve patients with cirrhosis (six with a history of hepatic encephalopathy and six without) and six age-matched controls using positron emission tomography. Regional CBF in whole brain was not different in cirrhotic patients from that in controls. In six cirrhotic patients with a history of hepatic encephalopathy, $rCMRO_2$ was significantly lower in the frontal, temporal, parietal and occipital cortices, hippocampus, thalamus, cerebellum and brain stem, than that in each region of controls. On the other hand, $rCMRO_2$ in six cirrhotic patients without a history of hepatic encephalopathy did not differ from the controls in all regions except for the frontal cortex. Regional OEF in cirrhotic patients without a history of hepatic encephalopathy was higher in the hippocampus and striatum than that in each region of controls. Among twelve cirrhotic patients, $rCMRO_2$ in the occipital cortex and striatum correlated directly with plasma leucine levels, and $rCMRO_2$ in the striatum directly correlated with plasma valine levels. Regional $CMRO_2$ in the frontal cortex, temporal cortex, parietal cortex, white matter as well as brain stem correlated inversely with plasma phenylalanine levels, and $rCMRO_2$ in the occipital cortex correlated inversely with plasma tyrosine levels. Brain oxygen metabolism is impaired in cirrhotic patients with a history of hepatic encephalopathy, but preserved in those without a history or in the early stage of cirrhosis. Reduced oxygen metabolism is related with altered amino acid metabolism.

Key words: Positron emission tomography, Hepatic encephalopathy, Cirrhosis

Introduction

It has been reported that cerebral blood flow and oxygen metabolism is impaired in patients with hepatic cirrhosis[1)6)9)12)16)17)]. Recently, positron emission tomography has made possible the examination of abnormalities in regional cerebral blood flow (rCBF), cerebral metabolic rate for oxygen ($rCMRO_2$) and oxygen extraction fraction (rOEF) in human. We, therefore, measured rCBF, $rCMRO_2$ and rOEF using positron emission tomography in cirrhotic patients with and without a clinical history of hepatic encephalopathy, and compared with six control subjects. Furthermore, we examined correlations between $rCMRO_2$ and plasma concentrations of branched chain amino acids or aromatic amino acids.

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Materials and Methods

Patients

Twelve patients with cirrhosis, 5 men and 7 women, aged 45 to 69 years with an average of 60.3 years were studied. All patients were admitted to our clinic for the evaluation of liver disease. The patients were divided into two groups according to the presence of a history of hepatic encephalopathy. Six patients [Child Pugh severity score A (n=2) and B (n=4)] had a history of hepatic encephalopathy; three in clinical grade II, two in grade III, one in grade IV. This clinical grading is based on deterioration in mental and psychometric functions[4]. The other six patients had no history of previous hepatic encephalopathy. We compared the variables in 12 cirrhotic patients with those in six age-matched controls, transient global amnesia (n=3), transient ischemic attack (n=2) and pulmonary tuberculosis (n=1), free from liver disease. None of the controls had neurological abnormalities at the time of positron emission tomography scanning.

Liver function tests: serum total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, prothrombin time, ammonia and indocyanine green retention at 15 minutes were determined. Plasma concentrations of amino acids such as branched chain amino acids (isoleucine, leucine, valine) and aromatic amino acids (tyrosine, phenylalanine) were measured using high performance liquid chromatography. Neuropsychological tests including Wechsler Adult Intelligence Scale or Mini-Mental State Examination were performed in 11 of the 12 patients with cirrhosis. Conventional or digital subtraction angiography of head and neck was performed and was normal in all control subjects. Neurological examination, electroencephalogram and brain computed tomography (CT; TCT 60 A, Toshiba Inc., Tokyo, Japan) were performed in all patients. Brain magnetic resonance imaging (MRI; Sigmasystem, GE Medical System, Milwaukee, Wisconsin, U.S.A.) was also obtained in all patients with cirrhosis.

Positron emission tomography

Positron emission tomography studies were performed in all patients of the three groups. Regional CBF, $rCMRO_2$ and rOEF were measured by $H_2{}^{15}O$ continuous infusion and $^{15}O_2$ continuous inhalation according to the ^{15}O steady state technique described by Frackowiak et al.[5] Regions of interest (18 × 14 mm) were set on the bilateral cerebral cortical areas (frontal, temporal, parietal and occipital cortices), hippocampus, white matter (centrum semiovale), deep gray matter (striatum and thalamus), cerebellar cortex, and brain stem. The right and left values of each region of interest were averaged, and compared with the mean of the six control subjects. Among twelve cirrhotic patients, correlations of $rCMRO_2$ values to branched chain amino acids and aromatic amino acids were determined.

Statistical analysis

Regional CBF, $rCMRO_2$ and rOEF were compared among three groups by Student's t-test. Liver function, neuroradiological findings and psychometric tests were also compared between the cirrhotic groups with and without a history of hepatic encephalopathy by Student's t-test. Linear regression analyses were employed to evaluate the significance between $rCMRO_2$ and plasma concentration of aromatic amino acids as well as branched chain amino acids.

Results

The clinical and laboratory findings of 12 patients with cirrhosis, six with history of he-

patic encephalopathy (group A) and six without (group B), and six control patients (group C) are summarized in Tables 1 and 2. There were no significant differences in the age and sex distributions between cirrhotic patients and controls. Brain CT and MRI demonstrated no abnormal findings except for mild brain atrophy in five of group A, two of group B and three of group C. Slightly abnormal electroencephalogram (EEG) showing a low voltage symmetrical alpha rhythm and diffuse slow waves was observed in four patients in groups A and two in group B. Borderline EEG was noted in one each in group A and B, and normal EEG was found in only one in group A and two in group B. Controls showed normal EEG in all five cases studied. Wechsler Adult Intelligence Scale scores tended to be lower in group A than in group B, but the difference was not statistically significant. Mini-Mental State Examination scores were within normal ranges in all cirrhotic patients. Albumin concentrations were significantly decreased in group A and B, and levels of AST, ALT and total bilirubin were significantly increased compared with those in the control group. Laboratory data indicated more severe liver dysfunction in group A than in group B, but the difference in mean values of the two groups was only statistically significant in the measure of indocyanine green retention at 15

Table 1 Clinical and neuroradiological findings in cirrhotic patients and controls

No.	Age	Sex	Brain atrophy on CT, MRI	EEG change	Neuropsychology WAIS	MMSE
Cirrhosis with hepatic encephalopathy (group A, n=6)						
1	58	M	+	2	86	ND
2	69	F	+	2	97	28
3	57	M	+	1	99	29
4	68	F	+	2	90	28
5	45	F	−	0	ND	ND
6	52	M	+	2	102	30
Cirrhosis without hepatic encephalopathy (group B, n=6)						
7	67	F	+	1	68	ND
8	64	F	+	0	114	28
9	57	M	−	2	120	30
10	55	F	−	2	90	30
11	54	F	−	0	104	29
12	57	M	−	ND	109	30
Controls (group C, n=6)						
13	65	M	+	0		
14	62	M	+	0		
15	53	M	−	0		
16	66	M	+	ND		
17	59	F	−	0		
18	62	F	−	0		

Brain atrophy was detected using computed tomography (CT) or magnetic resonance imaging (MRI). EEG, electroencephalogram; 0, normal; 1, borderline; 2, slightly abnormal. WAIS, Wechsler Adult Intelligence Scale. MMSE, Mini-Mental State Examination. ND, not determined.

Table 2 Laboratory findings in cirrhotic patients and controls

Group	A (Cirrhosis)	B (Cirrhosis)	C (Controls)
History of HE	(+)	(−)	(−)
No. of cases	6	6	6
Total bilirubin (mg/dl)	2.3±1.6[d]	2.0±0.8[d]	0.6±0.2
AST (U/L)	75±24[e]	126±52[d]	20.2±8.7
ALT (U/L)	55±20[c]	116±90[b]	19.6±12.5
Albumin (g/dl)	2.9±0.3[e]	2.8±1.1[e]	4.0±0.2
Prothrombin time (%)	48±25	81±41	
ICG retention, 15 min. (%)	63±14[a]	36±16	
Fisher quotinent	1.0±0.4	1.5±0.7	
Ammonia (μg/dl)	69±15	61±48	

Data given as mean±SD.
HE, hepatic encephalopathy. AST, aspartate aminotransferase. ALT, alanine aminotransferase. ICG, indocyanine green. Fisher quotinent = (isoleucine + leucine + valine)/(tyrosine + phenylalanine)
[a] $p<0.05$ vs. group B. [b] $p<0.05$, [c] $p<0.01$, [d] $p<0.005$, [e] $p<0.001$ vs. controls.

minutes.

Mean values of rCBF in the cerebral cortical areas including frontal, temporal, parietal and occipital cortices were 29.0±6.4 mg/100g/min in group A, 31.9±3.6 mg/100g/min in group B and 33.6±5.0 mg/100g/min in control group. Mean values of rCBF in cirrhotic patients (group A and B) were lower than in controls in almost all regions, but the differences were not significant. Regional CBF tended to be higher in group B than in the control group in the regions of striatum, thalamus and white matter. Among the patients, rCBF in group A was lower than that in group B in these regions, although changes were not significant. Mean values of $rCMRO_2$ in group A were significantly lower than those in controls in the frontal, temporal, parietal and occipital cortices, hippocampus, thalamus, cerebellum and brain stem (Fig. 1). Group A patients had significantly lower $rCMRO_2$ than did group B patients in the frontal, temporal, parietal and occipital cortices, hippocampus and thalamus. Mean value of $rCMRO_2$ in the frontal cortex was significantly lower in group B than in controls. However, in the striatum and white matter, mean $rCMRO_2$ values were higher in group B than in controls. Mean values of rOEF in the cerebral cortical areas were 44.0±5.6% in cirrhotic patients and 40.7±3.6% in controls. The mean values of rOEF in cirrhotic patients were elevated in comparison with controls, but the differences were not significant in all regions except for the striatum and hippocampus where the mean rOEF in group B was significantly increased over that of controls.

A correlation between $rCMRO_2$ values and the plasma concentrations of amino acids (isoleucine, leucine, valine, phenylalanine and tyrosine) was analyzed in 12 cirrhotic patients (Fig. 2). An increase in plasma leucine concentration correlated with an increase of $rCMRO_2$ in the occipital cortex ($r=0.674$, $p<0.05$) and striatum ($r=0.786$, $p<0.005$), and an increase in plasma valine concentration correlated with an increase in $rCMRO_2$ of the striatum ($r=0.581$,

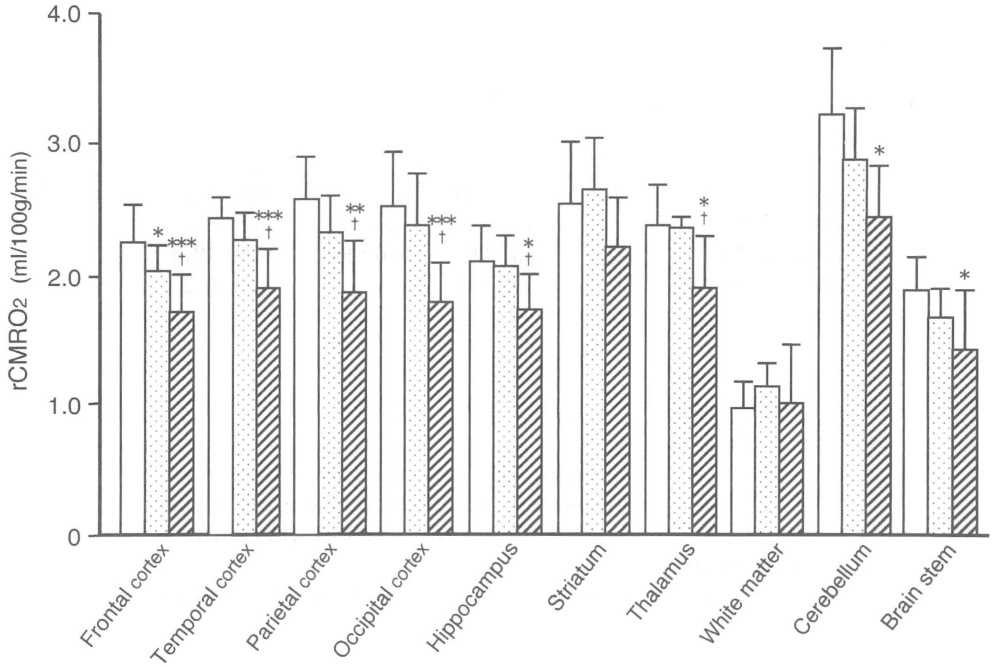


Fig. 1 Regional cerebral metabolic rate for oxygen ($rCMRO_2$) values in cirrhotic patients with (▨, group A) or without (⬚, group B) hepatic encephalopathy and controls (□, group C). Values represent mean±SD. * $p<0.05$, ** $p<0.01$, *** $p<0.005$ vs. Group C controls. † $p<0.05$ vs. cirrhotic patients without hepatic encephalopathy.

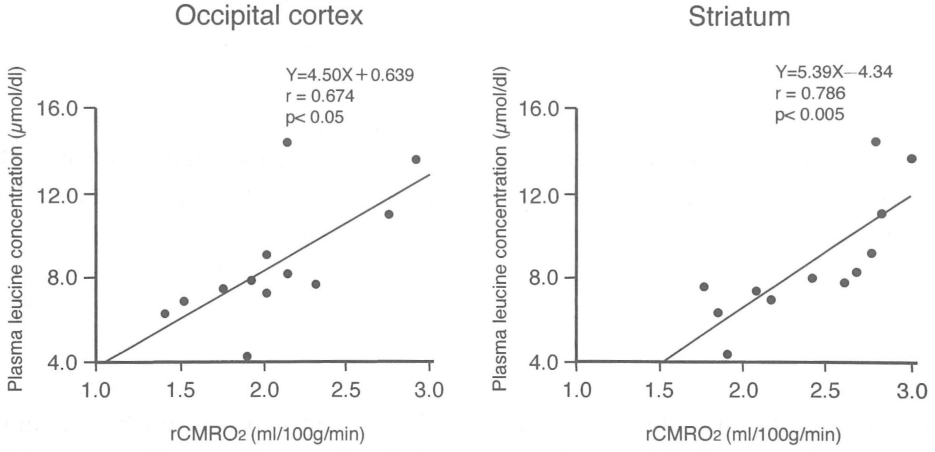
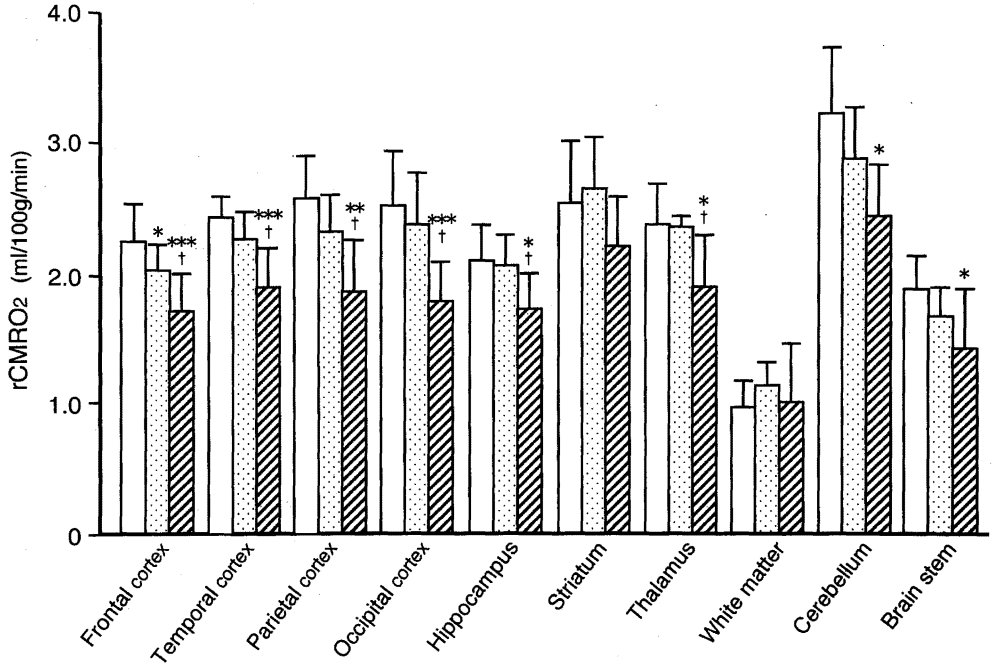


Fig. 2 Correlation between plasma leucine concentration and $rCMRO_2$ values in the occipital cortex and striatum.

$p<0.05$). An increase in plasma phenylalanine concentration correlated with a decrease in $rCMRO_2$ of the frontal cortex ($r=-0.584$, $p<0.05$), temporal cortex ($r=-0.606$, $p<0.05$), parietal cortex ($r=-0.628$, $p<0.05$), white matter ($r=-0.641$, $p<0.05$) and brain stem ($r=-0.628$, $p<0.05$). An increase in plasma tyrosine concentration correlated with a decrease in $rCMRO_2$ of the occipital cortex ($r=-0.626$, $p<0.05$). Each $rCMRO_2$ values was not correlated



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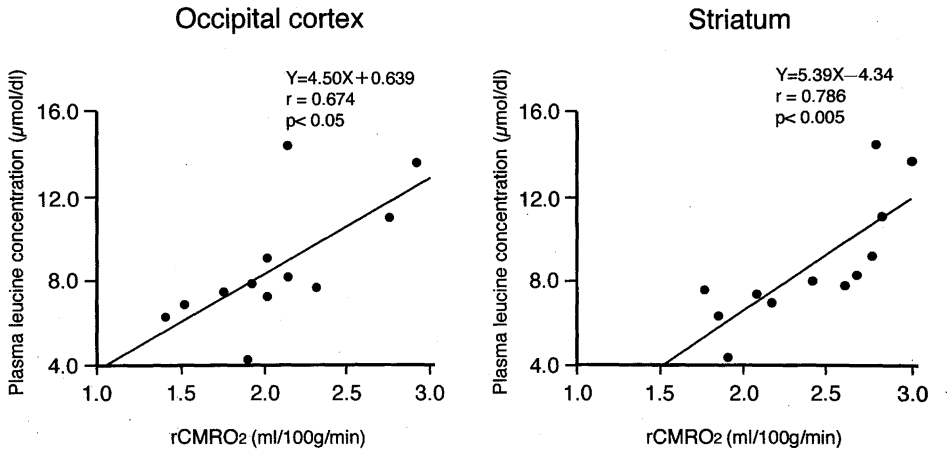

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with plasma ammonia, indocyanine green retention, prothrombin time and other laboratory data, and was not correlated with Wechsler Adult Intelligence Scale and Mini-Mental State Examination.

Discussion

The present study demonstrated a trend of decreased rCBF in cirrhotic patients in comparison with age-matched controls, a significant decrease in global $rCMRO_2$ in the patients with a history of hepatic encephalopathy. The $rCMRO_2$ reduction was detectable in the frontal, temporal, parietal and occipital cortices, hippocampus, thalamus, cerebellum and brain stem.

Most of previous studies showed that CBF in cirrhotic patients with hepatic encephalopathy is reduced[6)7)12)14)]. Posner et al.[14)] reported that CBF increased in patients without encephalopathy, but decreased in patients with severe encephalopathy. Rodriguez et al.[16)] also reported that CBF was reduced in cirrhotic patients with subclinical hepatic encephalopathy. In contrast, Fazekas and colleagues[6)], who measured CBF and $CMRO_2$ of whole brain using Kety-Schmidt's method, found that in patients with cirrhosis both CBF and $CMRO_2$ were decreased compared with those in age-matched controls, and also that $CMRO_2$ further decreased in patients with clinically apparent encephalopathy. Our results obtained in cirrhotic patients with a history of hepatic encephalopathy were similar to the previous studies. Lockwood and colleagues[8)] have measured cerebral glucose metabolism in rats after portacaval shunt-induced hyperammonemia, and concluded that glucose metabolism was increased in the caudate-putamen, thalamus, and other subcortical gray matter regions, relative to those measured in various cortical regions. They also reported positron emission tomography study in patients with liver disease and minimal hepatic encephalopathy, that the regional cerebral metabolic rate for glucose (rCMRGl) was increased in the caudate, thalamus, and cerebellum, and decreased in the cerebral cortices[9)], which being similar to the pattern of glucose metabolism redistribution in the rat experiment[8)]. The present study together with other studies indicated that, in the early stage of cirrhosis without history of hepatic encephalopathy, rCBF and $rCMRO_2$ or rCMRGl increase in the subcortical gray matter and thalamus, but decrease in cerebral cortices. In advanced cirrhosis, however, these values decrease in almost all the regions of the brain.

It is well accepted that hepatic encephalopathy is related to the imbalance of plasma concentrations of amino acids. Marcelle et al.[10)] measured the concentrations of branched chain amino acids and aromatic amino acids in the brain tissue obtained from autopsied cirrhotic patients who died of hepatic encephalopathy. They inferred that alterations in the concentration of aromatic amino acids might lead to disturbances of monoamine neurotransmitters in the brain. Our data showed that plasma leucine concentration correlated directly with $rCMRO_2$ in the occipital cortex and striatum, and plasma valine concentration directly correlated with $rCMRO_2$ in the striatum. Furthermore, present study showed that plasma phenylalanine concentration correlated inversely with $rCMRO_2$ in the frontal, temporal, parietal cortices, white matter and brain stem, and plasma tyrosine concentration inversely correlated with $rCMRO_2$ in the occipital cortex. In the brain, branched chain amino acids are reactive to α-ketoglutaric acid, and glutamic acid is synthesized. This combined with ammonia to glutamine. In result, a

decrease in branched chain amino acids gives rise to increase in ammonia, and brain function may be depressed. This fact may be related to the direct correlation between plasma leucine concentration and $rCMRO_2$. Phenylalanine and tyrosine are the precursors of dopamine and the increases lead to elevation of pseudoneurotransmitters including octopamine and tyramine, and to depression of the nervous system function. This may be related to the reduction of $rCMRO_2$ in the patients with encephalopathy.

There is a strong correlation between plasma leucine concentration and $rCMRO_2$ in the striatum. It has been reported that the basal ganglia, which is composed of the striatum and other parts, plays a role as central motor nervous system and participates in the cognitive function[3], so the metabolic impairment of the basal ganglia may contribute to the symptom of hepatic encephalopathy. Ocarroll et al.[13] who measured rCBF in patients with chronic liver disease using positron emission tomography, demonstrated that the degree of cognitive impairments was directly correlated with functional abnormality in the basal ganglia. They inferred from their results that motor sequelae in patients with hepatic encephalopathy might also relate to the pathological changes in the basal ganglia. Bernthal et al.[2] reported that the caudate nucleus diminished its size in diameter, which was significantly correlated with the result of psychometric tests in patients with chronic liver disease. Furthermore, Pujol and colleagues[15] have found the degeneration of the globus pallidus on MRI in patients with advanced liver disease. Maria et al.[11] also reported the similar results, suggesting a relationship between pathological changes and hepatic encephalopathy.

The present results suggest that cirrhosis, regardless of the history of hepatic encephalopathy, is associated with metabolic derangements of several regions of the brain including the basal ganglia. Furthermore, plasma concentrations of branched chain amino acids and aromatic amino acids appear to influence $CMRO_2$.

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(和文抄録)

肝硬変患者における局所脳代謝（PET）の変動

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肝硬変における脳血流および脳酸素代謝の変動を検討するために，肝硬変患者12例(肝性脳症の既往を認める6例および既往を認めない6例）および対照者6例の局所脳血流量（rCBF)，局所脳酸素代謝率（$rCMRO_2$）および局所脳酸素摂取率（rOEF）をpositron emission tomographyを用いて測定した．局所脳血流量は肝硬変患者および対照者の間で全ての脳の領域において差がみられなかった．局所脳酸素代謝率は肝性脳症の既往を認める肝硬変患者において前頭葉，側頭葉，頭頂葉および後頭葉の各皮質，海馬，視床，小脳および脳幹で対照者に比べ有意の低下が認められた．一方，肝性脳症の既往のない肝硬変患者においては，前頭葉において低下がみられた以外，局所脳酸素代謝率は対照者との間に差はみられなかった．また，局所脳酸素摂取率は肝性脳症の既往のない肝硬変患者において海馬および線条体で対照者に比べ上昇が認められた．肝硬変患者12例において脳酸素代謝率および血漿アミノ酸濃度の関連について検討し，後頭葉および線条体の脳酸素代謝率は血漿ロイシン濃度と，線条体の脳酸素代謝率は血漿バリン濃度と正の相関を認めた．また，前頭葉，側頭葉，頭頂葉，白質および脳幹の脳酸素代謝率は血漿フェニルアラニン濃度と，後頭葉の脳酸素代謝率はチロシン濃度と負の相関を認めた．肝硬変患者において脳酸素代謝は肝性脳症の既往のあるものに低下が認められたが，早期の肝硬変あるいは肝性脳症の既往がない肝硬変では保たれており，脳酸素代謝と脳内アミノ酸代謝との関連が示唆された．