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Serum neutral amino acid concentrations in cirrhotic patients with impaired carbohydrate metabolism.

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Abstract

Serum neutral amino acid levels in cirrhotic patients with abnormal oral glucose tolerance test patterns were not different from those of subjects without impaired carbohydrate metabolism. However, the characteristic features of serum aminograms in the patients, that is, increased levels of tyrosine, decreased levels of valine and leucine and the diminished ratio of branched chain amino acids to phenylalanine and tyrosine levels, were less pronounced in those treated with insulin. This finding is clinically important for evaluating the serum aminogram of cirrhotic patients under insulin therapy.

KEYWORDS: amino acid, cirrhotics, carbohydrate metabolism, insulin, glucose tolerance test

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— BRIEF NOTE —

SERUM NEUTRAL AMINO ACID CONCENTRATIONS IN CIRRHOTIC PATIENTS WITH IMPAIRED CARBOHYDRATE METABOLISM

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Abstract. Serum neutral amino acid levels in cirrhotic patients with abnormal oral glucose tolerance test patterns were not different from those of subjects without impaired carbohydrate metabolism. However, the characteristic features of serum aminograms in the patients, that is, increased levels of tyrosine, decreased levels of valine and leucine and the diminished ratio of branched chain amino acids to phenylalanine and tyrosine levels, were less pronounced in those treated with insulin. This finding is clinically important for evaluating the serum aminogram of cirrhotic patients under insulin therapy.

Key words : amino acid, cirrhotics, carbohydrate metabolism, insulin, glucose tolerance test.

The plasma amino acid imbalance in patients with liver cirrhosis is due not only from the impaired amino acid metabolism in the injured liver but also the different dietary condition and the altered excretion of pancreatic hormones. Changes in the metabolism of branched chain amino acids (BCAA), especially in the muscle, may develop from higher plasma insulin and glucagon levels frequently observed in cirrhotic patients (1). Insulin is known to be a major regulator of protein metabolism, and its deficiency results in marked protein catabolism leading to protein-calorie malnutrition. These considerations led us to investigate how the plasma amino acid imbalance in cirrhotic patients is affected by the associated carbohydrate metabolism abnormality. This relationship is important for evaluating the abnormal serum aminogram of cirrhotics with various complications such as diabetes mellitus, hepatocellular carcinoma and protein-calorie malnutrition.

Nineteen patients with liver cirrhosis and 3 control subjects without hepatobiliary or gastrointestinal disease, who were admitted to Okayama University Hospital, were adopted as clinical subjects for this study. The cirrhotic patients were well compensated, and the diagnosis was made exclusively by peritoneoscopy and histological observation of the liver. All the subjects ate regularly a special diet (1800 kcal, protein 80 g and fat 45 g/day) ; they were neither obese nor lean. The subjects were free of acute and chronic infectious diseases and renal failure.

Patients having a long-term history of diabetes mellitus before the onset of liver disease and alcoholic patients were excluded from this study. The oral glucose tolerance test (OGTT) was performed with 100 g glucose, and the OGTT patterns were classified into three categories according to the criteria of Japanease Society of Diabetes Mellitus : normal, borderline and diabetic. The OGTT patterns and clinical data of the cirrhotic patients are summarized in Table 1. The major liver function tests were similar among the three groups. Three diabetic patients with cirrhosis were on treatment with one daily injection of a long-acting insulin preparation. These patients and seven other cirrhotics, who had the diabetic OGTT pattern but were not under insulin therapy, were under good metabolic and hormonal control according to the early morning, normal fasting blood sugar level. Serum amino acid concentrations were determined with a Hitachi liquid chromatograph as described previously (2).

Plasma valine and leucine levels and the ratio of BCAA/aromatic amino acids (AAA) (serum levels of valine, leucine and isoleucine to those of phenylalanine and tyrosine) were significantly lower, and the tyrosine level significantly higher, in the 19 patients with cirrhosis than in the 3 control subjects. There were no essential differences in the serum neutral amino acid levels between two cirrhotic groups, one with the blood sugar level higher and the other with it lower than 100 mg/dl. The best correlation between the level of a neutral amino acid and the blood sugar level was that in the case of methionine ($r=0.56$, $0.1<p<0.20$). However, this type of analysis is very limited in its accuracy, since the blood sugar levels in the patients varied only within the range of 80 to 150 mg/dl. The elevated phenylalanine and tyrosine levels and decrease in the BCAA/AAA ratio observed in the cirrhotics were less pronounced in patients with the diabetic OGTT

TABLE 1. OGTT PATTERNS AND LIVER FUNCTIONS OF 19 PATIENTS WITH LIVER CIRRHOSIS

	Pattern of glucose tolerance test			
	Normal	Borderline	Diabetes mellitus	
			Without insulin	With insulin
No. of patients	3	6	7	3
Age	32–64 (54)	31–75 (55)	40–75 (55)	48–76 (58)
Deviation from ideal body weight (%)	110±11	110±8	105±13	104±13
Dietary intake (kcal/day)	1680	1740±320	1700±95	1600
Fasting blood sugar (mg/dl)	81	108±29	114±2	104±2
Serum total bilirubin (mg/dl)	2.0±0.5	1.5±0.7	2.2±0.4	0.9±0.4
Serum albumin (g/dl)	3.1±0.3	3.2±1.1	3.0±0.4	3.5±0.8
Blood NH_3 (μg/dl)	90±8	122±37	128±41	100
Serum GPT (IU)	31±2	70±21	45±14	67±54

Results are shown as the Mean±S.D.
( )=Average.

TABLE 2. OGTT PATTERN AND SERUM NEUTRAL AMINO ACID LEVELS IN CONTROL SUBJECTS AND PATIENTS WITH LIVER CIRRHOSIS

	Control subject	Patients with liver cirrhosis		
		Normal OGTT	Abnormal OGTT	
			Without insulin	With insulin
	(3)	(3)	(7)	(3)
		(μmoles/l)		
Valine	228± 46	132± 24*	128± 41*	115± 79
Leucine	134± 21	65± 11*	72± 20	76± 47
Isoleucine	73± 14	40± 8	43± 11	44± 19
Phenylalanine	54± 22	100± 31*	77± 21	52± 9 #
Tyrosine	53± 22	148± 43*	119± 24	76± 10
Methionine	24± 15	69± 14*	54± 5*	22± 8 #
BCAA/AAA	4.1± 0.6	0.9± 0.5*	1.2± 0.6*	2.1± 0.7

Significant correlation ($p < 0.05$) between control subjects and cirrhotic patients (*) and between normal OGTT and abnormal OGTT (#). No. of patients = ( ).

pattern, especially in patients treated with insulin. A nearly normal pattern of neutral amino acid levels was observed in the insulin-treated patients even though they had liver cirrhosis (Table 2).

Before disscussing the correlation of the serum amino acid imbalance to the impaired carbohydrate metabolism in patients with liver cirrhosis, the metabolism of pancreatic hormones, especially insulin, which directly affect the amino acid metabolism in various tissues, should be considered. Furthermore, serum aminograms in patients with diabetes mellitus, but not having liver disease, should be referred to. A glucose tolerance abnormality together with raised peripheral blood concentrations of insulin and glucagon has often been recorded in patients with liver cirrhosis. The peripheral hyperinsulinism is due solely to the decreased hepatic insulin degradation, and the hyperglucagonemia results from pancreatic glucagon hypersecretion, though a direct relationship between amino acid metabolism and glucagon has been also suggested (3). Selective alterations in the glucagon receptors in the cirrhotic liver may lead to the weakening of the hormonal action of glucagon often detected in cirrhotic patients by the changes in the blood glucose, amino acid and cyclic nucleotide levels.

Berger *et al.* (4) have measured the amino acid levels in the two extreme conditions of insulin excess and insulin deficiency. The blood BCAA levels were high only in patients with diabetic ketosis and low in the cases of insulinoma. BCAA levels were significantly correlated to the blood glucose levels. The particular sensitivity of the blood BCAA levels to insulin has previously been demonstrated in man by infusion of exogenous insulin and by stimulating the secretion of endogenous insulin with intravenous glucose administration (5). However, these data were obtained exclusively with subjects without severe liver disease.

The plasma insulin in the cirrhotic patients does not reflect the biologic effectiveness at the tissues, since there are varying degrees of peripheral insulin resistance. Therefore, it is unreasonable to expect a direct correlation between the serum insulin and BCAA concentrations. That there is no significant relationship between these two parameters in patients with liver cirrhosis has already been reported (6). We have investigated the effect of insulin and glucagon administrations to patients with liver cirrhosis on their serum amino acid levels (7). The administration of insulin in a glucose solution may induce accelerated secretion of endogenous glucagon from the pancreas. BCAA levels increased slightly only 3 h after the end of the insulin infusion. The lowering of plasma BCAA and other amino acid levels following the intake of glucose is assumed to be mediated by the stimulated insulin secretion.

An increase in the phenylalanine and tyrosine levels and the BCAA/AAA ratio have been correlated to the extent of liver dysfunction (6). The major liver function test results were similarly abnormal among the cirrhotics examined in this study (Table 1). Therefore, the nearly normal aminograms observed in the insulin-treated cirrhotics may be misleading as to the prognosis and the estimation of encephalopathy during the clinical course. Our previous report (8) also indicated that the serum aminograms of cirrhotic patients with hepatocellular carcinoma were only slightly abnormal.

REFERENCES

1. Soeters, P.B. and Fischer, J.E.: Insulin, glucagon, amino acid imbalance and hepatic encephalopathy. *Lancet* **2**, 880-882, 1976.
2. Watanabe, A., Higashi, T. and Nagashima, H.: An approach to nutritional therapy of hepatic encephalopathy by normalization of deranged amino acid patterns in serum. *Acta Med.* Okayama **32**, 427-440, 1978.
3. Landau, R.L., and Lugibihl, K.: Effect of glucagon on concentration of several free amino acids in plasma. *Metabolism* **18**, 265-276, 1969.
4. Berger, M., Zimmermann-Telschow, H., Berchtold, P., Drost, H., Muller, W.A., Gries, A. and Zimmermann, H.: Blood amino acid levels in patients with insulin excess (functioning insulinoma) and insulin excess (diabetic ketosis). *Metabolism* **27**, 793-799, 1978.
5. Zinnemann, H.H., Nutall, F.Q. and Goetz, F.C.: Effect of endogenous insulin on human amino acid metabolism. *Diabetes* **15**, 5-8, 1966.
6. Murakami, H.: Studies of plasma amino acids in patients with hepatic encephalopathy. Part I. Plasma amino acids in patients with acute and chronic hepatic failure. *Jpn. J. Gastroenterol.* **78**, 205-213, 1981.
7. Watanabe, A., Higashi, T., Hayashi, S., Obata, T., Sakata, T., Takei, N., Shiota, T. and Nagashima, H.: Effects of insulin and glucagon on serum amino acid concentrations in liver disease. *Acta Med. Okayama* (in press).
8. Higashi, T., Watanabe, A., Hayashi, S., Obata, T. and Nagashima, H.: Clinical and experimental studies on characteristic features of serum aminograms in cirrhotic patients with primary hepatoma and in rats with ethionine-induced hepatoma. *Acta Hep. Jpn.* **21** : 1196-1204, 1980,