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Effects of Dietary Histidine and Methionine Loading in Rats With a Portacaval Shunt

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IMURA, K., S. KAMATA, S. HATA, A. OKADA, T. WATANABE AND H. WADA. *Effects of dietary histidine and methionine loading in rats with a portacaval shunt.* PHARMACOL BIOCHEM BEHAV **24**(5) 1323–1328, 1986.—To elucidate disturbances of brain amine metabolism in hepatic coma, the effects of dietary histidine and methionine loading on the brain levels of amino acids and transmitter amines and on behavior were examined in rats with a portacaval shunt (PCS rats). Surgical construction of a portacaval shunt exaggerated the increase in brain histamine caused by dietary histidine loading 4 weeks after operation. Although the marked increase in the brain level of methionine itself did not affect on the brain levels of catecholamines, serotonin, and histamine, brain level of 5-HIAA was decreased in PCS rats on methionine-enriched diet. Diminished spontaneous activity was observed in PCS rats on either diet, which could not be related to the disturbance of brain amine metabolism caused by excess histidine and methionine. These results indicated that histamine was involved in the derangement of brain amine metabolism in PCS rats, and that direct effect of dietary methionine loading on the brain levels of transmitter amines was not observed in PCS rats. The etiological relation of these substances to hepatic coma should be further investigated.

Histidine Methionine Histamine Catecholamine Serotonin Portacaval shunt Rat brain

IMPAIRED amine metabolism has been suggested to be involved in the pathogenesis of hepatic coma [1, 4, 7, 8, 12]. Increased brain levels of tryptophan, serotonin and 5-hydroxyindole acetic acid (5-HIAA), and tyrosine and octopamine have been observed in rats with a portacaval shunt (PCS rats), a model of liver failure [1,3]. The infusion of specially formulated amino acid mixture containing large amounts of branched-chain amino acids has been shown to cause normalization of the plasma amino acid pattern and simultaneously to restore consciousness in patients with hepatic coma [9,24]. Although infusion of glucose and branched-chain amino acids has been reported to normalize brain content of tryptophan, phenylalanine, and tyrosine in PCS rats [19], little is known about the mechanism of action of branched-chain amino acids and the relationship between hepatic coma and disturbances of amine metabolism.

Previously, we reported that surgical construction of a portacaval shunt in rats caused an increase in brain amino acids, including glutamine, methionine, cystathionine, phenylalanine, tyrosine, tryptophan and histidine, and that dietary amino acids greatly affected the brain levels of aromatic amino acids in PCS rats that are precursors of neurotransmitters [13]. Dietary overloading of phenylalanine, tyrosine, and tryptophan, respectively, failed to induce comatose state in PCS rats though it provoked considerable alterations of brain levels of catecholamines, serotonin, and trace amines [14]. These results suggested that the interaction of these amines and aminergic neuron may not play a key role in inducing hepatic coma. As a continuation of these studies; we tested the effects of dietary histidine and methionine loading on the brain levels of amino acids and transmitter amines and on behavior in PCS rats.

ABBREVIATIONS

PCS	portacaval shunt
dopamine or DA	3,4-dihydroxyphenylethylamine
NA	noradrenaline
5-HT	5-hydroxytryptamine or serotonin
5-HIAA	5-hydroxyindole acetic acid
HA	histamine
OD	ordinary diet
His-R	histidine-enriched diet
Met-R	methionine-enriched diet

METHOD

Surgical Procedures

Adult, male Wistar rats weighing about 400 g were used.

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TABLE 1

AMINO ACID COMPOSITIONS OF RAT DIETS

	OD	His-R	Met-R
Asp	2.26	2.00	2.00
Glu	4.00	0.50	0.50
Pro	1.33	1.00	1.00
Gly	1.32	1.00	1.00
Ala	1.34	2.00	2.00
Ser	1.08	2.00	2.00
Thr	0.94	0.50	0.50
Cys	0.30	—	—
Met	0.28	0.20	5.20
Val	1.19	0.70	0.70
Leu	1.93	0.90	0.90
Ile	0.97	0.50	0.50
Phe	1.06	1.00	1.00
Tyr	0.57	—	—
Trp	0.15	0.20	0.20
His	0.57	5.50	0.50
Lys	1.47	1.00	1.00
Arg	1.52	1.00	1.00
Total	20.00	20.00	20.00

Values are given as grams per 100 g of diet.

TABLE 2

FOOD INTAKE AND CHANGE OF BODY WEIGHT

	OD		His-R		Met-R	
	Sham (8)	PCS (5)	Sham (9)	PCS (7)	Sham (9)	PCS (8)
Food Intake[a]	17.3 ± 2.6	15.2 ± 2.2	16.0 ± 3.1	14.8 ± 0.5	9.2 ± 1.0§	9.1 ± 0.8§
Change of Body Weight[b]						
Week 1	−8 ± 18	−36 ± 25*	−39 ± 12§	−41 ± 16§	−67 ± 16§	−74 ± 25§
Week 2–4	18 ± 10	5 ± 37	−6 ± 35	1 ± 11	−36 ± 17§	−66 ± 24*§#

Numbers of animals are shown in parentheses under the operations. [a]Results are given as means ± S.D. in grams per day. [b]Results are given as means ± S.D. in grams. *$p<0.05$, †$p<0.01$: Significant difference from the value for sham-operated rats on the same diet. ‡$p<0.05$, §$p<0.01$: Significant difference from the value for sham-operated rats on OD. ¶$p<0.05$, #$p<0.01$: Significant difference from the value for PCS rats on OD.

An end-to-side portacaval anastomosis was made by the suture technique under anesthesia with intraperitoneal injection of ketamine [13]. Postoperatively, PCS rats and weight-matched sham-operated controls (laparotomy only) were housed in groups with lighting between 8:00 and 20:00, and were given specially prepared diets and water ad lib for 4 weeks. Then they were decapitated between 10:00 and 12:00. Blood was collected from the neck, and the brain was quickly removed and weighed. These materials were stored at −80°C until use.

Preparation of Diets

Diets with 3 different amino acid compositions, ordinary diet (OD), histidine-enriched diet (His-R), and methionine-enriched diet (Met-R), were prepared (Table 1). The indicated amino acids were blended thoroughly into a mixture of corn starch (60%), α-starch (10%), powdered filter paper (8%), salad oil (6%), mineral salt (7%), granulated sugar (6%), and vitamins (2%).

Activity Study

An animex D.S.E. activity meter with a sensitivity of 25 μA and tuning set of 40 μA was used. In week 4 after operation, each rat was transferred to a plastic cage in an adjacent measurement-room and kept in the activity meter for 24 hr to allow it to become acclimatized. Then activity was measured for a 24 hr period, and the number of counts per hr was recorded.

TABLE 3

PLASMA AMINO ACIDS IN SHAM-OPERATED AND PCS RATS 4 WEEKS AFTER OPERATION

	OD		His-R		Met-R	
	Sham (8)	PCS (5)	Sham (9)	PCS (7)	Sham (9)	PCS (7)
Phe	77 ± 10	123 ± 38*	67 ± 20	122 ± 35†‡	69 ± 14	120 ± 47†§
Tyr	99 ± 24	122 ± 29	66 ± 21	81 ± 28#	77 ± 15	80 ± 32#
His	72 ± 13	122 ± 39*	1607 ± 692§	3951 ± 1422†§#	116 ± 37	141 ± 21
Met	64 ± 15	73 ± 31	55 ± 12	54 ± 12	1998 ± 1006§	1784 ± 495§#
Val	197 ± 36	171 ± 54	153 ± 58	169 ± 31	101 ± 32§	97 ± 49§
Leu	153 ± 25	134 ± 41	107 ± 26§	98 ± 19§	64 ± 15§	52 ± 38§#
Ile	92 ± 17	80 ± 29	64 ± 15§	58 ± 14§	37 ± 9§	44 ± 31§¶

Values are shown as means ± S.D. in nmoles/ml. Other explanations are as for Table 2.

TABLE 4

BRAIN AMINO ACIDS IN SHAM-OPERATED AND PCS RATS 4 WEEKS AFTER OPERATION

	OD		His-R		Met-R	
	Sham (8)	PCS (5)	Sham (9)	PCS (7)	Sham (9)	PCS (8)
Phe	63 ± 10	170 ± 45†	76 ± 16	126 ± 26†§#	69 ± 13	111 ± 26†§#
Tyr	69 ± 13	187 ± 20†	77 ± 22	111 ± 38‡#	59 ± 16	105 ± 34†‡#
His	89 ± 19	203 ± 36†	2097 ± 1303§	4855 ± 1466†§#	124 ± 36‡	187 ± 72§
Met	43 ± 15	71 ± 51	47 ± 32	51 ± 20	1114 ± 402§	1302 ± 420§#
Val	66 ± 12	65 ± 21	79 ± 19	61 ± 12	40 ± 7§	33 ± 10§#
Leu	70 ± 15	87 ± 12	68 ± 14	67 ± 19	55 ± 11	70 ± 49
Ile	36 ± 5	31 ± 3	31 ± 12	30 ± 9	22 ± 6§	22 ± 3§

Figures are shown as means ± S.D. in nmoles/g wet weight. Other explanations are as for Table 2.

Biochemical Determinations

Plasma and brain amino acids in deproteinized samples were analyzed with a Hitachi amino acid analyzer (Model 835). Noradrenaline, dopamine, serotonin, and 5-HIAA were determined simultaneously as described previously [13]. Briefly, 3% perchloric acid extracts of brain were chromatographed sequentially on columns of Amberlite CG-50 and a Sephadex G-10, and the amine fractions were each analyzed; noradrenaline and dopamine were measured by the ethylenediamine condensation method [23], and serotonin and 5-HIAA by the acidic *o*-phthalaldehyde method [18]. Brain histamine was separated by Dowex-50 and measured by the alkaline *o*-phthalaldehyde method of Shore *et al.* [32] as modified by Yamatodani *et al.* [39,40].

Statistical Analysis

Statistical analysis of data was performed by use of an ANOVA and Newman Keuls multiple comparison test.

RESULTS

Food Intake and Change of Body Weight

The amounts of food intake were similar in sham-operated and PCS rats, but the intake of Met-R were less than those of the other two diets (Table 2). Sham-operated rats on OD lost weight during the first week after operation and then gained weight (Table 2). PCS rats on OD lost more weight than sham-operated rats in the first week after operation. Both groups of rats lost more weight on His-R and Met-R than sham-operated rats on OD during this period. Both groups of rats on Met-R subsequently continued to lose weight. Weight loss was greater in PCS rats than that in sham-operated rats on Met-R in the last 3 weeks.

Plasma Levels of Amino Acids

Comparison with the plasma levels of amino acids in sham-operated rats on OD revealed an increase in the levels of phenylalanine and histidine in PCS rats on OD (Table 3). A marked increase in the plasma level of histidine and a mild reduction in the levels of leucine and isoleucine were observed in sham-operated rats on His-R compared to those in sham-operated rats on OD. PCS rats on His-R also showed an increase in the levels of phenylalanine and histidine compared to those in sham-operated rats on His-R. A marked increase in the level of methionine and a decrease in the levels of branched-chain amino acids were noted in sham-operated rats on Met-R. PCS rats on Met-R showed an increase in the level of phenylalanine compared to that in sham-operated rats on Met-R.

TABLE 5

BRAIN TRANSMITTER AMINES AND METABOLITE IN SHAM-OPERATED AND PCS RATS 4 WEEKS AFTER OPERATION

	OD		His-R		Met-R	
	Sham (8)	PCS (5)	Sham (9)	PCS (7)	Sham (9)	PCS (8)
NA	1.95 ± 0.13	1.79 ± 0.30	1.87 ± 0.22	2.04 ± 0.36	1.91 ± 0.25	1.70 ± 0.25
DA	4.11 ± 0.34	4.13 ± 0.50	4.70 ± 0.71	4.61 ± 1.01	4.24 ± 0.62	3.83 ± 0.53
5-HT	1.85 ± 0.16	1.72 ± 0.31	1.64 ± 0.36	1.58 ± 0.38	1.63 ± 0.34	1.58 ± 0.25
5-HIAA	1.35 ± 0.25	2.66 ± 0.73†	1.60 ± 0.35	2.03 ± 0.56¶	1.79 ± 0.54	1.86 ± 0.53¶
HA	0.334 ± 0.088	0.752 ± 0.318	2.49 ± 0.78§	3.06 ± 0.84*§#	0.406 ± 0.206	0.674 ± 0.137

Figures are shown as means ± S.D. in nmoles/g wet weight. Other explanations are as for Table 2.

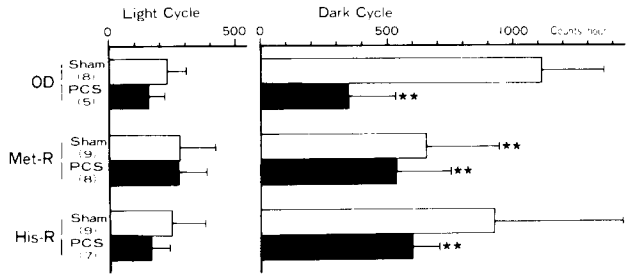

FIG. 1. Spontaneous activity in sham-operated and PCS rats in week 4 after operation. Numbers of animals are shown in parentheses under the operations. Results are given as means±S.D. of counts per hour. $^{**}p<0.01$: Significant difference from the value for sham-operated rats on OD.

Brain Levels of Amino Acids

Comparison with the brain levels of amino acids in sham-operated rats on OD revealed an increase in the levels of phenylalanine, tyrosine, and histidine in PCS rats on OD (Table 4). A marked increase in the level of histidine was observed in sham-operated rats on His-R. PCS rats on His-R also showed an increase in the levels of three aromatic amino acids compared to those in sham-operated rats on His-R. A marked increase in the level of methionine was noted in sham-operated rats on Met-R along with a mild increase in the brain level of histidine and a decrease in the levels of branched-chain amino acids. PCS rats on Met-R showed an increase in the levels of phenylalanine and tyrosine compared to those in sham-operated rats on Met-R.

Brain Levels of Transmitter Amines

Comparison with the brain levels of transmitter amines in sham-operated rats on OD revealed an increase in the level of 5-HIAA in PCS rats on OD (Table 5). A marked increase in the level of histamine was observed in sham-operated rats on His-R compared to those in sham-operated rats on OD. PCS rats on His-R showed a further increase in the level of histamine. No significant difference was observed between the brain levels of transmitter amines in sham-operated rats on OD and both groups of rats on Met-R. PCS rats on Met-R and His-R showed a decrease in the level of 5-HIAA compared to those in PCS rats on OD.

Spontaneous Activities and Behavior

When monitored with an Animex activity meter, average spontaneous activities in the dark cycle were lower for PCS rats on all diets than for sham-operated rats on OD (Fig. 1). Sham-operated rats on Met-R diet also showed decreased average spontaneous activity in the dark cycle. All animals survived the experiment and showed no obvious encephalopathic signs.

DISCUSSION

Excess methionine has been reported to have toxic effects on metabolism in the liver of experimental animals including rats [10]. Klain *et al.* [16] reported that administration of a 15% casein diet supplemented with 4.0% DL-methionine to rats resulted in a marked reduction in food intake and weight loss together with a marked increase in urinary excretion of a number of amino acids, indicating severe disorder of nitrogen metabolism. Consistent with these observations, we observed the decreased food intake and the marked weight loss in sham-operated and PCS rats on Met-R containing 5% L-methionine (Tables 1 and 2).

In spite of the decreased food intake, a marked increase in the plasma and brain levels of histidine and methionine was observed in rats on His-R and Met-R, respectively (Tables 3 and 4). These rats also showed a decrease in the plasma levels of branched-chain amino acids (Table 3), which may be caused by small amounts of branched-chain amino acids in both diets (Table 1). In addition, nitrogen catabolism seen in rats on Met-R may be another reason for a decrease in the plasma and brain levels of branched-chain amino acids, for increased metabolism of branched-chain amino acids has been suggested in protein-calorie malnutrition [28]. Although a decrease in the plasma levels of branched-chain amino acids may increase an entrance of histidine and methionine into brain, which has been reported to compete with branched-chain amino acids [26], a marked increase in the brain levels of histidine and methionine (Table 4) may be due to dietary overloading of histidine and methionine.

Brain levels of aromatic amino acids, such as phenylalanine, tyrosine, and histidine, were elevated in PCS rats on all diets (Table 4). In addition of elevated plasma levels (Table 3), an increased entrance of aromatic amino acids into brain has been reported [12]. Brain levels of catecholamines and serotonin were not significantly affected by the dietary overloading of histidine and methionine, though a mild decrease in the brain level of 5-HIAA was observed in

PCS rats on His-R and Met-R compared to that in PCS rats on OD (Table 5).

Brain level of histamine was increased according to an increase in the brain level of histidine (Tables 4 and 5). Dietary overloading of histidine brought about a marked increase in the brain level of histamine as previously reported [2, 17, 30, 35]. Surgical creation of portacaval shunt resulted in the further increase in the brain levels of histidine and histamine. Although protein malnutrition has also been reported to cause an elevation in the brain levels of histidine and histamine [5], only a mild elevation in the brain level of histidine was observed in sham-operated rats on Met-R presenting nitrogen catabolism.

It is difficult to detect encephalopathic signs in PCS rats by usual observation. However, a variety of behavioral alterations have been reported, including diminished spontaneous activity, decreased responses to electric shock, and decreased startle responses to both tactile and auditory stimuli [36,37]. To detect behavioral abnormalities, we measured spontaneous activity, which decreased in PCS rats on OD (Fig. 1). Although Martin *et al.* [20,21] reported that no major alteration in behavioral parameters was observed in PCS rats manifesting increased turnover of brain serotonin, our previous work [14] revealed that diminished spontaneous activity in PCS rats was restored by the administration of phenylalanine-, tyrosine-, and branched-chain amino acids-enriched diet, suggesting that this abnormality may be intimately related to the increased turnover of brain serotonin. No decrease in spontaneous activity in sham-operated rats on His-R (Fig. 1) suggests that the increased level of brain histamine may have no effect on the spontaneous activity. Diminished spontaneous activity in PCS rats on His-R (Fig. 1) may be rather due to the increased turnover of serotonin, which was suggested by the mild increase in the brain level of 5-HIAA (Table 5). The diminished spontaneous activity in rats on Met-R (Fig. 1) may suggest a specific action of methionine toxicity on locomotor activity. However, the possible effect of severe malnutrition should also be considered as a possible explanation in these rats.

Brain histamine has been suggested as a possible neurotransmitter in mammals [11, 31, 34]. Recently, the histaminergic neuron system was demonstrated in rat brain by fluorescent immunohistochemistry using antibody raised against L-histidine decarboxylase [38]. Although several kinds of brain neurotransmitter amines have been suggested to be involved in the pathogenesis of hepatic coma, little attention has been paid to histamine. Plasma level of histidine has been reported to be raised in patients with hepatic coma due to chronic liver dysfunction and acute liver failure [9,25]. The increased levels of brain histidine and histamine in PCS rats (Tables 4 and 5) revealed the involvement of histamine in the derrangement of brain amine metabolism in severe liver dysfunction. However, even a marked increase in brain histamine did not bring about diminished locomotor activity and alterations in the brain levels of catecholamine and serotonin. Administration of cimetidine, an H2 antagonist, has frequently been observed to induce encephalopathy in patients with severe liver dysfunction [15]. This observation suggests that the increased activity of histaminergic neuron might act protective to hepatic coma. Increased brain histamine has also been observed in uremic rats [29] and protein-malnourished rats [6], and it has been suggested to be associated with the abnormal behaviors, such as water consumption, continuous avoidance, self-stimulation, and thermal regulation [5]. Further investigation is needed to clarify the specific etiological significance of brain histamine in hepatic coma and other disorders.

Methionine has also been suspected of inducing hepatic coma. Oral administration of methionine induced hepatic coma in patients with liver cirrhosis [27] and brought about a comatose state in dogs with a portacaval shunt in the presence of elevated ammonia level [22]. In addition, the toxic effects of methionine have been proposed to be mediated through mercaptans [20,41], ATP depletion [10], and taurine [33]. However, the role of methionine in hepatic coma is still controversial, and effect of methionine on brain amine metabolism has not been clear. Present study revealed no significant effect of methionine on brain levels of transmitter amines, and that spontaneous activity was decreased in rats on Met-R. Rosen *et al.* [28] reported that nitrogen catabolism may increase brain levels of tyrosine and octopamine in PCS rats. However, only a mild increase in the brain level of tyrosine was seen in PCS rats on Met-R (Table 4), which also showed malnutrition (Table 2). These results require further investigation on the etiological role of methionine in inducing hepatic coma.

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