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Arginase
argininosuccinate synthetase
homocitrullinuria

hyperammonemia
hyperlysinemia

Periodic Hyperammonemia, Hyperlysinemia, and Homocitrullinuria Associated with Decreased Argininosuccinate Synthetase and Arginase Activities

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Summary

An 18-year-old mentally and physically retarded male with periodic hyperammonemia is described. Levels of lysine and citrulline in his serum and those of blood ammonia were elevated and daily excretions of homocitrulline in his urine were strikingly high on an ordinary diet. With a decrease in protein intake to 1.5 g/kg body weight/day, only urinary homocitrulline excretion remained about 10 times higher than the normal values whereas the other amino acids in his serum and urine appeared to be within the normal range. After an oral load of lysine on a normal protein intake, several abnormal findings were observed. That is, clinically he had episodes of irritability, vomiting, and coma caused by ammonia intoxication. Biochemically, levels of citrulline and arginine in his serum and the urinary homocitrulline excretion rate continued to increase and arginase in the blood cells was markedly depressed. Blood cell arginase, which showed lower activity than that of control subjects, particularly on a normal protein intake, was extremely inhibited by lysine in the in vitro experiment. The citrulline tolerance curve after the load of L-citrulline was found to be normal on a low protein intake. Lysine:NAD-oxidoreductase activity in the liver was near the lower limits of the control values. The activity of argininosuccinate synthetase (ArgSS) was reduced to 22% of the control values. Arginase activity was also reduced.

Speculation

Hyperlysinemia, hypercitrullinemia, and massive homocitrullinuria found in our patient may be due to a partial defect of ArgSS, which has affinity for both citrulline and homocitrulline. We speculate that impairment of ammonia disposal participates in the deficiency of ArgSS as well as arginase.

A case of congenital lysine intolerance with periodic ammonia intoxication was first reported by Colombo et al. (8) in 1964. The patient, a 3-month-old girl, had been suffering from episodes of vomiting, coma, convulsions, and failure to thrive since birth. In another report (7), these authors postulated that the cause of hyperlysinemia was an impairment in the degradation of lysine due to a partial defect of lysine:NAD-oxidoreductase in the liver and that ammonia detoxication was impaired by hyperlysinemia which acts as a competitive inhibitor on arginase. The activities of the urea cycle enzyme in the liver of the patient were normal. No other case has since been reported during the past 10 years.

Recently we (17) reported an 18-year-old mentally and physically retarded boy, suffering from anorexia and vomiting from 2 months of age. Our case closely resembles Colombo's, but the specific findings of the former were abnormally high concentra-

tions of serum citrulline and urinary homocitrulline and de-creased ArgSS activity.

The purpose of this report is to investigate the etiology of our patient with discussion of the metabolic error in reference to the lysine-urea cycle.

CASE REPORT

The patient was born in May 1956, after an uncomplicated pregnancy and delivery. The parents were not related and his father, mentally retarded, died of lung cancer at the age of 63 years. He has four normal siblings and a brother who died of an unknown disease with convulsion attacks. We had no clue to a detailed family history, for his family had been scattered. He had been asymptomatic until 2 months after birth. At that point he had episodes of anorexia and vomiting and was admitted to a local hospital because of malnutrition. During admission, he suf-fered from anorexia and vomiting without episodes of coma or convulsions. At 9 years of age he weighed only 15 kg and was apparently mentally retarded. With advance in age, attacks of coma and convulsions increased in frequency, to about once a week. He recovered from these symptoms with a low protein intake and intravenous glucose infusion within a week. He was hospitalized as a mentally retarded child until 18 years old, when he was first seen at the university hospital to undergo a complete medical examination, since a thin layer chromatographic screen-ing test for urinary amino acids revealed abnormal amounts of lysine and homocitrulline. His height was 126 cm (normal, 165.4 cm) and weight 18 kg (normal, 57.0 kg). His physique was poorly developed. The patient required assistance in walking be-cause of lordosis of the spine and atrophy and weakness of mus-cles. He had no apparent abnormality of the cardiovascular and respiratory systems. The liver and the spleen were not palpable. No abnormal tendon reflexes were found. IQ (Suzuki-Benett test) was 39. Relevant laboratory data were: red blood cell count, 416 × 10⁴/mm³; hemoglobin concentration, 13.7 g/100 ml; white blood cell count, 4200/mm³; serum alanine aminotrans-ferase (GPT), 29.5 Karmen units (normal, 5–35); serum aspar-tate aminotransferase (GOT), 65 Karmen units (normal, 5–40); blood pyruvic acid, 0.247 M; blood lactic acid, 8.017 M; arterial pH, 7.498; serum CO_2, 24.8 mM/liter. Serum protein electro-phoresis disclosed an increase in the γ-globulin fraction (26 g/100 ml). Blood ammonia levels under an ordinary diet were in the range of 250–900 μg/100 ml (normal range, 100–150), which was normalized with a low protein intake. X-ray survey of the skeletal system revealed osteoporosis.

MATERIALS AND METHODS

Quantitative analyses of amino acids in serum and urine were performed by means of the automatic amino acid analyzer (JCL-6AH type, Jeol Co.). Blood ammonia was determined according to the method of Okuda and Fujii (16). Lysine loading tests were performed by oral administration of 150 or 300 mg L-lysine-HCl/kg body weight after an overnight fast. Arginase in blood cells was measured by the method of Tomlinson and West-all (23). The activity was expressed as micromoles per 60 min per g hemoglobin. Inhibition tests on blood cell arginase by ly-sine in vitro were carried out, using arginine solution (0.23 M, pH 9.5), added to different concentrations of L-lysine in each study: 0.23 M, 0.5 × 0.23 M, 0.25 × 0.23 M, and no lysine. Urea cycle enzymes in open biopsy of the liver from the patient were assayed by the method of Brown and Cohen (2). L-Ly-sine:NAD-oxidoreductase activity in the liver was measured by the method of Bürgi et al. (3). In brief, the medium contained 0.4 ml L-lysine in 0.05 M Tris buffer (pH 8.8), 0.05 ml 0.06 M NAD solution, 0.02 ml 0.05 M cysteine, and 0.3 ml 1:50 liver homogenate. Enzyme activities were expressed in micromoles lysine metabolized per min by measuring the formation of $NADH_2$ in a photometer at a wavelength of 360 nm at 37°.

RESULTS

AMINO ACIDS IN SERUM AND URINE

The patient's serum levels of lysine and citrulline on a normal protein intake were elevated as compared to control values whereas the levels of the other amino acids remained within normal range. The patient had lysinuria, argininuria, and mas-sive homocitrullinuria. On a low protein diet or a protein intake of 1.0–1.5 g/kg body weight/day, serum levels of citrulline were still higher than the upper limits of the control range, whereas lysine was at the lower limit. Urinary amino acid excretion was within normal limits except for the still increased homocitrulline (Tables 1, 2).

ORAL LOADING TESTS OF L-LYSINE

His serum levels of lysine, arginine, and citrulline increased 4 hr after the load compared with levels in control subjects (Table 3). The urinary excretion rate of lysine, homocitrulline, argi-nine, and ornithine increased greatly after the load (Table 2). During the loading tests, blood cell arginase was measured. The activity of our patient was markedly depressed and elevation of blood ammonia ranged from 168–340 μg/100 ml 4 hr after the load. Nevertheless, one a low protein intake the extent of argi-nase depression by the lysine load showed almost the same tendency as control subjects (Fig. 1).

INHIBITION TESTS OF ARGINASE IN BLOOD CELLS BY L-LYSINE IN VITRO

Arginase in blood cells in our patient measured using 0.23 M arginine solution without lysine was relatively reduced and it was markedly depressed by the addition 0.23 M lysine to 0.23 M arginine solution. On a low protein intake arginase was almost equal to normal values and the extent of arginase inhibition by lysine was not more remarkable than that of the control subjects (Fig. 2).

ORAL LOADING TEST OF CITRULLINE

An oral loading test of L-citrulline on a low protein intake revealed normal serum response; no change in serum concentra-tion of lysine was observed in the patient (Table 4).

Table 1. Serum concentrations of amino acids

Amino acids, μmol/liter	Patient		Control subjects, mean ± SD
	UND[1]	ULPD[2]	
Alanine	229.0, 223.4	160.0	389.7 ± 95.1
Arginine	86.1, 87.3	96.0	96.8 ± 19.2
Citrulline	178.5	70.0	32.2 ± 11.2
Cystine	59.9, 62.4	42.7	81.9 ± 16.3
Glutamic acid	188.4	166.0	225.9 ± 84.8
Glutamine	202.8,	192.7	483.1 ± 93.2
Glycine	201.1, 151.8	144.9	262.2 ± 38.4
Histidine	51.5, 120.5	63.2	76.9 ± 14.0
Isoleucine	28.2, 37.3	46.0	50.9 ± 12.0
Leucine	66.3, 86.1	70.2	105.4 ± 20.0
Lysine	458.3, 248.3	136.0	168.8 ± 34.0
Methionine	18.7, 17.4	34.2	17.5 ± 5.8
Phenylalanine	52.7, 61.7	45.6	48.4 ± 8.9
Proline	100.8	153.8	234.5 ± 76.8
Serine	138.8, 134.2	87.1	143.2 ± 38.7
Threonine	225.8, 151.3	337.1	145.5 ± 40.3
Tyrosine	28.7, 34.2	45.3	63.8 ± 15.9
Valine	130.7, 131.5	126.0	219.5 ± 38.9

[1] Under a normal diet.

[2] Under a low protein diet.

Table 2. *Urinary excretion rates of amino acids before and after 6-hr oral loading tests of L-lysine-HCl[1]*

Amino acids, μmol/g creatinine	Patient		Control subjects (mean ± SD)	
	Before	After	Before	After
Cystine	259	168	150.8 ± 57.8	133.8 ± 50.4
Lysine	4,849	·20,000	853.4 ± 704.0	1,546.0 ± 977.0
Ornithine	131	202	52.4 ± 30.5	57.6 ± 32.2
Arginine	704	1,789	30.6 ± 18.3	34.9 ± 21.2
Homocitrulline	3,613	4,270	30[,2] 31[2]	22[2] 58[2]

[1] One hundred fifty milligrams per kg body weight.
[2] Two control subjects.

Table 3. *Serum concentrations of lysine, citrulline, and arginine before and after oral load of L-lysine-HCl (300 mg/kg body wt) under a low protein diet[1]*

	Amino acids, μmol/liter			
	Before	After 60 min	After 120 min	After 240 min
Lysine	198 (170, 116)	431 (630, 532)	950 (620, 610)	1,100 (470, 136)
Citrulline	70 (n.d.)		363 (n.d.)	420 (n.d.)
Arginine	140 (90, 86)	188 (100, 84)	259 (90, 95)	260 (90, 89)

[1] n.d.: not detected. Numbers in parentheses indicate control values.

Concentrations of Arginine and Lysine

Fig. 2. Inhibition test of blood cell arginase by L-lysine in the *in vitro* experiment in the patient (●) and control subjects (○). The dotted line indicates the loading test under a low protein intake. (I), (II), (III), and (IV) indicate the concentrations of arginine solution (0.23 M, pH 9.5) that contain L-lysine of zero, 0.25 × 0.23 M, 0.5 × 0.23 M, and 0.23 M, respectively.

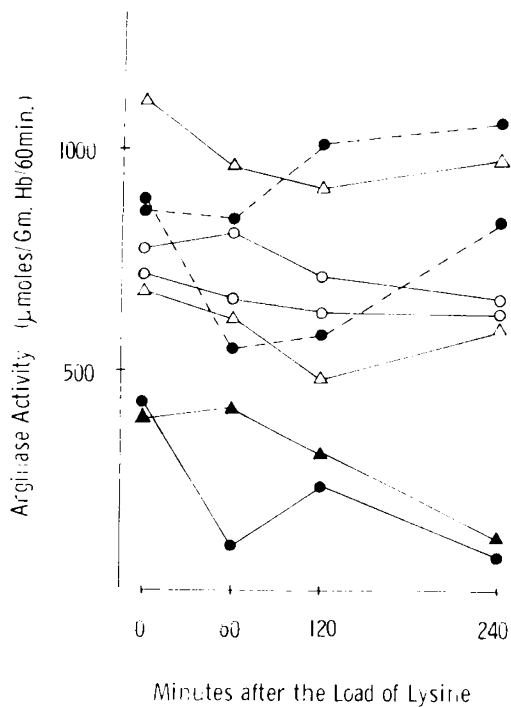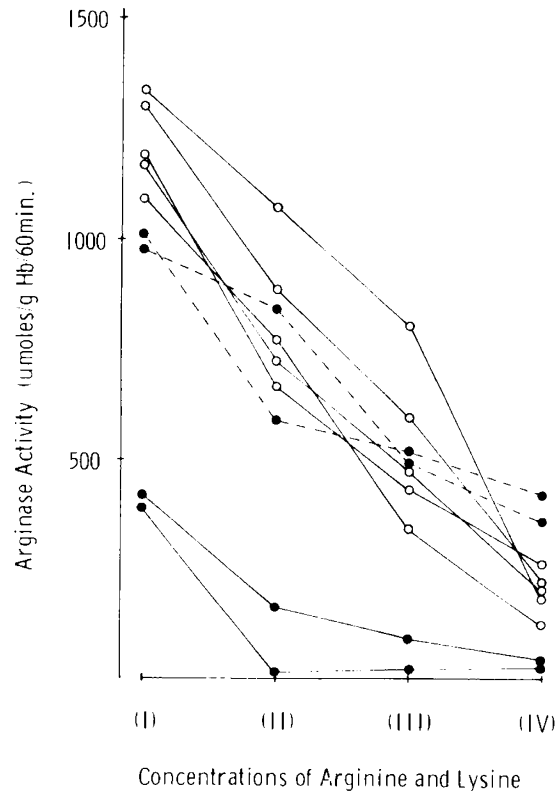Minutes after the Load of Lysine

Fig. 1. Blood cell arginase activity after the oral load of L-lysine-HCl in the patient (●, ▲) and control subjects (○, △). Circles and triangles indicate lysine loading tests of 150 mg/kg and 300 mg/kg, respectively. The dotted line (- - -) indicates the loading test under a low protein intake.

Table 4. *Serum concentrations of citrulline and lysine before and after oral load of L-citrulline (100 mg/kg body wt)[1]*

	Amino acids, μmol/liter			
	Before	After 60 min	After 120 min	After 240 min
Citrulline	80 (20)	1070 (740)	110 (170)	170 (160)
Lysine	140 (130)	130 (130)	140 (140)	120 (100)

[1] Numbers in parentheses indicate control values.

those of ArgSS and arginase were reduced to 22% and 29% of normal values, respectively. L-Lysine:NAD-oxidoreductase activity was 64% of the average values for controls (Table 5).

ENZYME ACTIVITIES IN THE LIVER

Activities of ornithine carbamyl transferase (OCT) and the argininosuccinate cleaving enzyme were within normal limits but

HISTOLOGY OF LIVER TISSUE

There was slight fatty infiltration of the hepatocytes without any other specific findings.

Table 5. *Enzyme activities in liver*

		Urea cycle enzyme, μmol/g of wet weight/hr	
		Controls ($n = 5$)	
	Patient	Mean	Range
Ornithine transcarbamylase	5280	3618	(3000–4280)
Argininosuccinic acid synthetase	9.4	43.4	(33.6–51.4)
Argininosuccinase	208	249	(208–284)
Arginase	2410	8384	(6000–9600)
L-Lysine:NAD-oxidoreductase (μmol/liter homogenate/min)	13.2	20.7	(16.7–25.7)

DISCUSSION

The diseases associated with hyperlysinemia have been designated as persistent hyperlysinemia, saccharopinuria, and periodic hyperlysinemia. In three cases with persistent hyperlysinemia reported by Woody *et al.* (24, 25), the levels of lysine in serum were approximately 10 times normal values. Dancis *et al.* (10) demonstrated that lysine ketoglutarate reductase activity was considerably reduced in the skin fibroblasts grown from these three cases and that the enzyme defect was essential etiology in this disease. They established the saccharopine pathway as the major degradative pathway for lysine in humans. In other cases with persistent hyperlysinemia reported by Armstrong *et al.* (1) and Ghadimi *et al.* (12), the plasma concentrations of lysine were not so high as those of Woody's cases and etiology in their patients is unknown as yet. In order to differentiate strictly our case from Woody's cases, enzyme assay for main pathway of lysine degradation would appear to be necessary. However, clinical manifestations and biochemical data in the patients with persistent hyperlysinemia were different from those of our patient since they did not have hyperammonemia and since the increased lysine levels in their serum remained unchanged even under a low protein diet. Abnormal saccharopine excretion in the urine of our patient was not found as it was in the case of saccharopinuria (4). Therefore, the disease of our patient does not seem to belong to the same category of persistent hyperlysinemia or saccharopinuria. Some of disorders of branched chain amino acid metabolism or hyperglycinemia with ketosis due to a defect in isoleucine metabolism (14), propionic acidemia (15), or methylmalonic acidemia (9, 13), have been recognized to be associated also with hyperammonemia or protein intolerance. However, these patients can be differentiated from our case by marked metabolic acidosis or hyperglycinemia, which are characteristic biochemical features. On the other hand, Colombo's case is remarkably similar to our case from both clinical and biochemical viewpoints. Colombo *et al.* (7) believed that L-lysine:NAD-oxidoreductase deficiency in his patient showed that lysine is one of the potent substrates which inhibit arginase. As we also have indicated, arginase in blood cells was inhibited by lysine in the *in vitro* experiments and it was extremely depressed after an oral lysine load on a normal diet. However, it is not easy to speculate that an excess of lysine inhibits arginase, for persistent hyperlysinemic patients have had no episodes of ammonia intoxication after an oral load of lysine. This arginase deficiency of blood cells or the liver may play a part in the cause of hyperammonemia. As Ghadimi (11) suggested that the ability of blood cell of Colombo's case to concentrate amino acids might be abnormal, high intracellular concentrations of lysine or some lysine metabolites in our patient also may inhibit arginase. In the case of our patient L-lysine:NAD-oxidoreductase activity in the liver was nearly at the lower limits of the control values.

Since it has now been recognized that the pipecolic acid pathway involving lysine:NAD-oxidoreductase reaction at the initial step is not the major degradative pathway of lysine metabolism in man, we have some doubt that a partial defect of this enzyme produces the cause of the hyperlysinemia as Colombo concluded. Furthermore, some facts not reported by Colombo *et al.* (7, 8) were found as follows. First, ArgSS activity in the liver was considerably reduced compared to the control values. Second, the homocitrullinuria of our patient was far greater in order of magnitude than that of Colombo's case (6). Third, the oral lysine load caused the levels of citrulline as well as arginine in serum and urinary homocitrulline excretion rate to increase 4 hr after the load. Here it is necessary to discuss the importance of ArgSS deficiency in our case.

In 1972 Scott-Emuakpor *et al.* (21) reported on a 33-year-old mentally retarded male with citrullinemia apparently due to ArgSS deficiency, who had raised plasma and urine levels of lysine, homocitrulline, and homoarginine, and who could synthesize normal amounts of urea under ordinary dietary conditions without significant ammonia intoxication. They postulated that the patient was synthesizing urea by a late developing cycle whose intermediates were the homologs of the ordinary urea cycle. Cathelineau *et al.* (5) also believed the hypothesis that lysine and homocitrulline were, respectively, substrates of ordinary OCT and ArgSS because hyperlysinemia had been a constant factor in OCT deficiency and because the accumulation of lysine and homocitrulline had been observed in ArgSS deficiency. Several investigators (19, 20, 22) have speculated about its existence. Rochovansky and Ratner (18) have obtained 10% bovine ArgSS activity with homocitrulline as substrate. In our patient, when L-lysine was orally administered, serum concentrations of citrulline were strikingly elevated and urinary excretion rates of homocitrulline were greatly elevated. These experimental data stand to reason in speculating that they result from ArgSS deficiency. On the other hand, oral loading tests of L-citrulline showed normal tolerance curve and no change in serum lysine was observed in either the patient or the control subjects. Consequently, ArgSS deficiency itself is not essential etiology in our case, but it participates in the metabolic disturbance which appears conspicuously after the loads of protein or lysine. From these facts the partial defect of ArgSS as well as reduced arginase in the liver of the patient may play an important role in the etiology of the disease.

CONCLUSION

Periodic hyperammonemia, hyperlysinemia, and homocitrullinuria were observed in an 18-year-old male with mental and physical retardation. The cause of his abnormal biochemical features may be due to a partial defect of ArgSS as well as reduced arginase in the liver.

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Cholesterol
familial hypertriglyceridemia
triglyceride

type IV diet
type IV hyperlipoproteinemia

Familial Hypertriglyceridemia in Children: Dietary Management

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Summary

This study was designed to evaluate prospectively the continuing effects of dietary management in 44 children with familial hypertriglyceridemia. For obese children, weight reduction programs were instituted by metabolic dietitians. For nonobese children, for obese children with successful weight reduction (or for those who could not lose weight but would follow an altered diet), a modification of the National Institutes of Health (NIH) type IV diet was provided. Adherence to the diet program was monitored by monthly reassessment for 6 months in the outpatient clinic. In 43 children whose average age was 13 years at the time of diagnosis, mean ± SE plasma triglycerides were reduced after 6 months of weight reduction-NIH type IV diet from 253 ± 33 to 116 ± 8 mg/dl, $P < 0.01$. After 6 months on diet, the group mean decrement in weight (1 ± 1 kg) was not significant, and decrements in weight failed to correlate with decrements in plasma triglycerides, $r = 0.131$. Despite this failure to reduce weight appreciably, after 6 months on diet plasma triglyceride levels were reduced to normal (< 140 mg/dl) in 32 of the 43 children. At 8 months' follow-up in 13 children, mean plasma triglyceride was 170 ± 31 mg/dl, having been 290 ± 86 at time of diagnosis, $P < 0.01$. Plasma triglyceride levels at 8 months were normal in 5 of the 13 children. Plasma triglycerides were normal in 4 of 5 children with evaluation at 1 year, in 3 of 7 at 18 months, and in 4 of 14 at 22–26 months. When weight gain was proportionately greater than accretion of height, and where no attention to either caloric intake or composition was given, triglycerides remained elevated, whereas dietary adherence was generally accompanied by reduced or normal triglycerides. Amelioration of familial hypertriglyceridemia on the NIH type IV diet is a realizable goal in children, but requires persistent, repetitive reexamination and reinstruction.

Speculation

Dietary management of pediatric familial hypertriglyceridemia may be important as a primary, longitudinal approach to reduction of the increased atherosclerotic risk attendant to familial hypertriglyceridemia.

Primary hypertriglyceridemia occurs in 20% of children (under age 21) born to parents with familial hypertriglyceridemia (10). Substantial obesity is associated with the pediatric expression of familial hypertriglyceridemia in 30–60% of affected children (9, 10). Unlike pediatric familial hypercholesterolemia (7, 11), where dietary intervention provides only limited lipid lowering, most children with familial hypertriglyceridemia will normalize their triglycerides on a weight reducing/type IV (5) diet (9, 10). Amelioration of pediatric hypertriglyceridemia on diet may be important as a primary, longitudinal approach to reduction of increased atherosclerotic risk reported in some (2, 3), but not all adults (1) with familial hypertriglyceridemia.