A New Transport Interaction of Dibasic Amino Acids and Citrulline in Human Kidney

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OYANAGI, K., SOGAWA, H., MINAMI, R., NAKAO, T., KARUBE, K. and TSUGAWA, S. *A New Transport Interaction of Dibasic Amino Acids and Citrulline in Human Kidney.* Tohoku J. exp. Med., 1981, 134 (1), 55-58 — The oral loading tests of lysine in 9 healthy men and the intravenous loading tests of lysine, ornithine and arginine in 3 healthy men were carried out. The results indicated that the membrane transport system of citrulline in the human kidney was clearly inhibited by dibasic amino acids, lysine, ornithine, and arginine. ——— dibasic amino acids; citrulline; membrane transport

Cystinuria is a well-known transport disorder of cystine and the dibasic amino acids, lysine, ornithine, and arginine. Dent and Rose (1951) first postulated that reabsorption of these four amino acids in the renal tubule cell is defective in cystinuric patients. Recent studies (Rosenberg et al. 1962; Fox et al. 1964; Segal et al. 1977) using both rat and human kidney cortex slices revealed that dibasic amino acids shared a common transport system, but that cystine uptake was controlled by an independent mechanism.

Several clinical observations, of hyperdibasicaminoaciduria without cystinuria (Oyanagi et al. 1970; Whelan and Scriver 1968) and cystinuria without hyperdibasicaminoaciduria (Brodehl et al. 1967), support separate membrane transport systems for cystine and dibasic amino acids.

The purpose of the present study is to describe the transport interaction of dibasic amino acids and citrulline which was hitherto unrecognized in the human kidney.

SUBJECTS AND METHODS

Nine healthy colleagues of our Department participated in the following experiments.

Oral loading tests of L-lysine. After overnight fasting, 150 mg of L-lysine per kg of body weight were administered orally. Urine specimens were collected before and after the loading for 4 hr. Quantitative analyses of amino acids were performed by a Technicon Amino-Acid Auto Analyzer.

Constant infusion tests with L-lysine, L-ornithine, and L-arginine. 12 ml/kg body weight/hr of 20 mM, 40 mM, and 80 mM L-lysine, L-ornithine, and L-arginine solutions were constantly infused for 90 min on separate days, and blood samples were taken before

and just after the load. Urine specimens were collected for 30 min during the final 30 min of the load. Amino acids in serum and urine were measured by means of an automatic amino acid analyzer (Hitachi, KLA 5).

RESULTS

The results obtained are shown in Tables 1, 2 and 3. The urinary excretion rates of lysine after the oral loading of L-lysine increased 1.5 times as compared with those before the loading, whereas cystine and other dibasic amino acids were unchanged. On the other hand, the urinary excretion rates of citrulline after the loading were clearly elevated, with these findings being observed in all urine specimens tested. However, the urinary excretion rates of other neutral amino acids after the loading were slightly decreased (Table 1).

The urinary excretion rates of citrulline during constant infusion of dibasic amino acids were gradually increased according to the concentration of infused amino acids as were those of cystine and dibasic amino acids (Table 2). On the

TABLE 1. *Urinary excretion rates of amino acids before and after loading of lysine, 150 mg/kg*

Amino acid	Before loading (n=9)		After loading (n=9)	
	Mean	Range	Mean	Range
Threonine	291	120- 483	250	147- 484
Serine	509	345- 754	442	279- 660
Glutamic acid	169	87- 325	156	88- 246
Glycine	1335	554-2640	1059	388-1952
Alanine	318	115- 579	304	121- 640
Valine	54	36- 90	33	25- 48
Cystine	148	65- 283	120	73- 247
Methionine	27	trace- 46	20	2- 40
Citrulline	19	trace- 43	101	63- 165
Isoleucine	47	17- 127	33	21- 52
Leucine	55	31- 90	56	43- 91
Tyrosine	104	62- 192	96	57- 141
Phenylalanine	66	39- 131	55	35- 76
Ornithine	39	17- 66	38	19- 72
Lysine	942	231-1741	1418	184-3220
Histidine	1095	675-1775	1014	638-1313
Arginine	28	12- 56	31	13- 83

Values are expressed as $\mu\text{moles/g creatinine}$.

TABLE 3. *Serum concentrations*

	Lysine infusion				Ornithine
	Before	20 mM	30 mM	80 mM	Before
Serum citrulline ($\mu\text{moles/liter}$)					
Case 1	13	9	9	9	6
Case 2	24	12	16	12	13
Case 3	21	14	14	11	6

TABLE 2. *Urinary excretion rates of dibasic amino acids, cystine and citrulline before and after constant infusion*

Amino acids		Lysine infusion			Ornithine infusion			Arginine infusion		
		Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3
Lysine	Before	53	82	83	435	126	37	976	457	140
	20 mM	18800	13700	5041	4585	2429	1870	7949	4493	4071
	40 mM	134300	94300	92940	12115	11600	9564	9194	9892	19236
	80 mM	421000	404700	410000	20330	22120	22375	14370	16970	26500
Ornithine	Before	53	66	169	21	49	102	81	202	95
	20 mM	336	173	70	5894	1271	1607	7205	578	657
	40 mM	2167	977	1210	65920	33670	46180	34730	6432	23444
	80 mM	3618	2753	3567	270790	214650	420750	121500	28250	82738
Arginine	Before	5	29	6	5	6	5	12	202	2
	20 mM	451	236	77	380	143	115	3881	1671	1086
	40 mM	4286	2081	2559	4098	3084	3282	31980	32160	93819
	80 mM	17590	8414	11027	4829	11060	12663	168300	207720	447280
Cystine	Before	85	72	41	121	44	75	271	195	51
	20 mM	316	297	25	606	129	261	1898	694	1286
	40 mM	1126	904	1108	1738	1216	1346	2484	3027	4347
	80 mM	3090	2897	2395	2842	2831	3500	3493	4277	5430
Citrulline	Before	3	9	7	8	6	6	16	28	9
	20 mM	25	37	10	56	343	149	119	144	128
	40 mM	154	193	320	262	463	603	210	865	500
	80 mM	554	1069	1407	868	857	1575	880	1295	2075

Values are expressed as μ moles/g creatinine.

other hand, the serum concentrations of citrulline during infusion were unchanged (Table 3).

DISCUSSION

Citrulline is one of the neutral amino acids and it is generally believed that amino acid groups in the human kidney, such as neutral amino acid, acidic amino acid, cystine and dibasic amino acids, glycine and imino acids, and β -amino acids, apparently share a common transport system (Rosenberg et al. 1962; Wilson and Scriver 1967; Scriver and Wilson 1967). The inborn errors of amino acid transport support the separate membrane transport systems.

The present study, the oral loading tests and constant infusion tests of dibasic amino acids in healthy men, revealed the existence of a transport interaction in

of citrulline during constant infusion

infusion			Arginine infusion			
20 mM	40 mM	80 mM	Before	20 mM	40 mM	80 mM
6	6	5	4	4	4	7
40	18	4	5	5	5	4
6	6	5	5	5	5	4

the human kidney between dibasic amino acids and citrulline which is not as yet recognized.

It is difficult to explain the existence of this transport system, but it may be speculated that citrulline has a structural resemblance to dibasic amino acids.

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