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Letter to the Editor: Lysine Intolerance in Methylmalonic Acidemia

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There are two different metabolic pathways to synthesize urea; (*a*) Krebs-Henselite urea cycle; and (*b*) lysine-homocitrulline-homoarigine-urea cycle, although the latter is a minor pathway and supported by a few reports (5, 7, 8, 10). The first two steps of Krebs-Henselite cycle-carbamylphosphate synthesis and conversion from ornithine to citrulline are located at mitochondria in the liver, where a step of lysine to homocitrulline is also thought to be located (2).

The connections of hyperlysinemia and hyperammonemia in urea cycle disorders was reported in ornithine carbamyltransferase deficiency (4), citrullinemia (5, 8), hyperlysinemia (1), and hyperornithinemia (2). In methylmalonic acidemia, hyperlysinemia and hyperammonemia were also noted (6, 9). In earlier report, we used the lysine loading test in two patients with variant form of citrullinemia, in whom a higher elevation was found in blood lysine, ammonia, and urinary lysine as well as in urinary homocitrulline and homoarginine (5). These observations prompt us to perform the same loading test in a patient with methylmalonic acidemia. A patient diagnosed as having methylmalonyl CoA mutase deficiency in cultured lymphocytes and skin fibroblasts (5) was receiving lysine (100 mg/dl per os) at attack of the episode and under dietary control, where blood methylmalonic acid was 250 and below 10 μg/ml, respectively. In the former condition, serum lysine was elevated from 3.5 to 38.8 μmol/dl, blood ammonia was elevated from 184 to 290 μg/dl, and urine lysine was elevated from 113 to 986 mole/g creatinine [these increments were higher than those in control in our laboratory (6)], but no elevation was found in urinary homocitrulline and homoarginine. On the contrary, in the latter condition, serum lysine (5.1 μmole/dl) and blood ammonia (111 μg/dl) were essentially unchanged, and an increase in urine lysine from 120 to 540 mole/g creatine was within control range.

Loading test was repeated using a double amount of lysine at another attack of episode; urinary homocitrulline and homoargine were again not elevated.

Shapiro *et al.* (9) found decreased activities of all 5 enzymes in Krebs-Henselite urea cycle in an autopsied liver sample of methylmalonic acidemia. In rat and human liver homogenate, methylmalonyl CoA but not methylmalonic acid inhibited carbamylphosphate synthetase I (3).

If lysine-urea cycle is intact in our patient, urinary homocitrulline and homoarginine might be elevated as blood ammonia increased, like in citrullinemia (6, 8) and other Krebs-Henselite urea cycle disorders (4). Observed results may suggest that elevated blood methylmalonic acid or methymalonyl CoA has a toxic effect on lysine and ammonia metabolism, possibly on the stage of mitochondrial function.

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