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# Pathophysiology and treatment of citrin deficiency

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## ≡ Abstract ≡

Citrin is a mitochondrial aspartate-glutamate carrier predominantly expressed in the liver, which plays a role in various metabolic pathways, including aerobic glycolysis, gluconeogenesis, urea cycle, and protein and nucleotide synthesis. We found that human citrin deficiency causes adult-onset type II citrullinemia (CTLN2) and neonatal cholestatic hepatitis (NICCD). CTLN2 patients suffer from hyperammonemia which causes disorientation, unconsciousness, aberrant behavior, convulsion, coma and death. Hyperlipidemia, pancreatitis and hepatoma are often seen complications of CTLN2. NICCD patients suffer from cholestasis, jaundice, hypoproteinemia, hypoglycemia, galactosemia, and multiple aminoacidemias including citrulline, Thr, Met, Tyr, and Arg. We propose that metabolic disturbances in citrin deficiency mainly result from disturbance in hepatic cytosolicNADH management. This is because citrin is a member of malate-aspartate shuttle which plays a role in aerobic glycolysis through transport of NADH reducing equivalent from cytosol to mitochondria. In the absence of citrin, aspartate required for urea synthesis can not be supplied from mitochondria, but could be formed from glutamate and oxaloacetate catalyzed by cytosolic AST. To supply oxaloacetate for cAST, malate should be oxidized by cMDH, which yields NADH. If NADH is not converted back to oxidized NAD, hyperammonemia develops, because lack of aspartate stops argininosuccinate synthetase reaction. A large amount of carbohydrate intake or administration results in deterioration due to cytosolic NADH accumulation: Tamakawa et al. reported a case in which intravenous administration of high concentration of glucose

resulted in coma and hyperammonemia; Many CTLN2 patients died shortly after administration of glycerol and fructose solution; Individuals with citrin deficiency take much less carbohydrate; We found hyperammonemic and citrullinemic effect of carbohydrate intake to a patient with citrin deficiency We created a human citrin deficiency model mouse, which showed hyperammonemia and citrullinemia. Furthermore, oral administration of sucrose further increased blood ammonia. Those results indicate danger of carbohydrate and should be considered for the therapy.