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Vitamin Response Inherited Metabolic Disorders

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Editorial

The requirement of vitamin prescribed by RDA generally represents the quantities needed for normal health by majority of individuals in the population. Vitamins usually interact with many biomolecules before they reach the site where they function following absorption, transport and metabolism. The active cellular form must also interact with one or more proteins to carry out its biological function. This generates many potential sites for genetic disruption of vitamin metabolism and function. Due to mutation in an intestinal transport protein, for example, a vitamin may be inadequately absorbed. Mutation of a particular enzyme may raise the value of Km for a cofactor derived from a vitamin result in relative deficiency of activity when the vitamin is present at normal concentration. Although such type of diseases cannot yet be cured, the clinical signs and symptoms can sometimes be relieved by administration of a very large oral or parental dose of the appropriate vitamin. In these patients megadose vitamin therapy has a basis in human biochemistry and differs from indiscriminate self-medication for diseases which has no established relation to the vitamins used.

Few inherited disorders, however, respond to mega doses of a particular vitamin which is not directly related to the defective protein. The enzyme pyruvate carboxylase deficiency leads to encephalomyelopathy where there is lactic and pyruvic academia. Pyruvate carboxylase requires biotin and converts pyruvate to oxaloacetate for Krebs cycle or for neoglucogenesis. A major metabolic pathway for pyruvate is oxidative decarboxylation to acetyl CoA, catalyzed by pyruvate dehydrogenase complex. Some patients have been reported to show clinical improvement when treated with lipoic acid. Others have responded to thiamine. Lipoic acid and thiamine participate in the pyruvate dehydrogenase complex. Probably they reduce the concentrations of pyruvate and lactate by increasing the flux through the pyruvate dehydrogenase complex. Other examples include the use of vitamin E to reduce haemolysis in some patients with deficiency of glutathione synthetase or Glucose-6-phosphate dehydrogenase; folic acid cholin or betain in some cases of homocystinuria due to cystathionine β-synthase deficiency and pyridoxine in some cases of primary hyperoxaluria due to deficiency of soluble glyoxalate α-ketoglutarate carboligase. As in the case of pyruvate carboxylase deficiency, the effect might be due to enhancement of alternative metabolic pathways that bypass the defective enzyme.

Not all patients who show the similar clinical data respond to vitamin therapy. Thus if the structural gene for an apoenzyme or transport molecule is completely absent due to gene deletion, no amount of vitamin or cofactor will correct the defect. If the mutation interacts substrate rather than cofactor binding, the pathway will be blocked and cannot be relieved by increased concentration of cofactor. So far six mutations have been identified that cause methylmalonic aciduria, but not all respond to large doses of cyanocobalamine. Similarly, only some patients with homocystinuria due to deficiency of N^5N^{10}-methylenetetrahydrofolate reductase respond to treatment with folic acid.

Near about 24 inherited diseases have been found to respond to pharmacological doses of a vitamin. Although most are very rare, their study has contributed much to knowledge of metabolism in the human body. Some are, however, heterogeneous in symptoms and in responsiveness to therapy, suggesting genetic heterogeneity.

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