Is Carnitine an Essential Nutrient for Humans?

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At the time that lysine was shown to be the precursor of the four-carbon chain of carnitine in mammals, Broquist and colleagues (1) noted that this amino acid and carnitine shared the same precursor–product relationship as tryptophan and niacin. Clearly both carnitine and niacin are synthesized from their essential amino acid precursors in humans. Why, then, has carnitine not achieved the same "vitamin" status as niacin? Perhaps the answer to this question is that, with the exception of two isolated cases of questionable etiology, no *nutritional* deficiency of carnitine has been described in humans. Certainly there has been no epidemic of carnitine deficiency to parallel the outbreaks of pellagra in the southern United States in the early part of this century.

Because carnitine is plentiful in most Western diets (it is abundant in meat and dairy products), there has been little opportunity to, or interest for, study of nutritional carnitine deficiency in adult populations. It is generally accepted that human adults are able to synthesize sufficient carnitine to supply the needs of the body. Surprisingly little evidence is available to support this generalization. Studies of rural Asian populations with diets high in cereal grains, and of patients maintained on long-term total parenteral nutrition (TPN) have provided modest documentation. Tanphaichitr and co-workers (2) determined plasma carnitine levels in Thai residents of Bangkok (well nourished, with diets including meat, fish and rice) and Ubol (a rural province in Northeast Thailand; diets consisting mainly of rice and raw, fermented fish). Mean (± SEM) plasma carnitine levels in these two populations were 56.6 ± 1.8 μM (n = 111) and 50.3 ± 1.7 μM (n = 87), respectively. Although the difference between the two groups is statistically significant, biologically, that difference probably is not meaningful. In a normal U.S. population the range of plasma total carnitine concentrations was 37–89 μM, with means (± SD) for males and females of 59.3 ± 11.9 μM (n = 40) and 51.5 ± 11.6 μM (n = 45), respectively (3). The relatively small difference in mean plasma carnitine concentrations in Bangkok and Ubol residents may be attributed to the overall nutritional state of the study participants. The authors noted that for Ubol adults, urinary creatinine excretion, serum albumin and hematocrit all were lower than for participants from Bangkok. These differences may stem from the predominantly cereal (rice) diets consumed by Ubol residents, which contained little carnitine and were limiting in lysine, the essential amino acid precursor of carnitine.

In a second study normal Indian men from middle- and low-income groups were shown to have normal plasma carnitine levels (4). The study participants consumed primarily cereal grain diets. Daily intake of carnitine was estimated to be 9–15 mg, or approximately 15% of the intake from an average Western diet.

Hahn and co-workers (5) studied 47 North American adult surgical patients maintained on carnitine-free TPN. Nineteen of these patients were followed for more than 30 d after the start of TPN. Total carnitine levels in plasma were normal at the start of TPN, and on the whole, remained unchanged up to the 15th d of infusion. Subsequently the levels began to fall and by d 40 had fallen an average of 33%. When TPN was interrupted and oral feeding had started, plasma carnitine levels increased within 2–3 d. The results imply that carnitine synthesis in adults was sufficient to maintain normal carnitine concentrations for 20–30 d, but beyond that length

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of time endogenous production became inadequate.

Although the studies cited above are useful, the populations of subjects studied fail to meet one or both of two essential criteria: *1*) The experimental groups of subjects must be normal, i.e., they should be well-nourished and free of genetic or acquired disease. In the studies cited above, the Ubol population was malnourished, and the TPN patients suffered from a variety of serious ailments. 2) The diets of experimental subjects should include no carnitine. The participants in both the Thai and Indian studies received at least small amounts of carnitine in their diets.

For study of the essentiality of carnitine, perhaps an appropriate subject population would be strict vegetarians. Plant products provide only minute amounts of dietary carnitine. In general, many vegetarians maintain a normal, healthy existence. A systematic study of this group may reveal that dietary carnitine is not required for maintenance of good health in adults. This study should include indices not only of plasma carnitine concentration (which may not reflect whole-body carnitine status), but also of metabolic response to fasting, and, if possible, skeletal muscle carnitine concentration and rate of fatty acid oxidation. For carnitine to be considered an essential nutrient, it is not sufficient to demonstrate low carnitine concentrations in body fluids or tissues; a functional impairment of a normal metabolic process must be documented. Although it appears reasonable to assume that carnitine is not required in the diet of human adults, from a scientific viewpoint, such a conclusion lacks experimental or epidemiologic justification.

The picture in the human infant is somewhat different. Results of several studies have shown that newborn infants fed carnitine-free enteral formulas or TPN solutions develop markedly reduced plasma carnitine levels (see ref. 5 for a review). Infants consuming carnitine-free formula diets over several months from birth may have plasma carnitine concentrations as low as 5–15 μM (compared with normal level of 30–60 μM). Several investigators have attributed this decline to "reduced capacity" for or "deficient" carnitine biosynthesis. This argument is most often based on the observation that in human infants hepatic γ-butyrobetaine hydroxylase (the last enzyme in the carnitine biosynthetic pathway) activity is only about 12% of that in adults. However, recent studies in rats indicate that γ-butyrobetaine hydroxylase, even at levels found in human infants, is not rate-limiting for carnitine biosynthesis (see ref. 5 for a review). The possibility that infants do indeed have a "reduced capacity" for carnitine biosynthesis has not been excluded and should be given serious consideration. However, another argument, which has not received attention in the literature, may also explain decreased plasma carnitine concentrations in infants. By viture of rapid growth, infants are adding new tissue, particularly muscle, which must be supplied de novo with carnitine. If the rate of carnitine biosynthesis is marginal for maintenance of steady-state levels in a nongrowing individual (i.e., an adult), then infants likely will not have the synthetic capacity to provide carnitine to new tissue. As carnitine in existing tissues and fluids is redistributed to new tissue, a relative deficiency in all tissues (and fluids) would ensue.

The possible functional consequences of reduced plasma carnitine levels in infants have been explored, both in normal-term infants fed carnitine-free formulas and in premature infants fed by TPN (see ref. 5 for a review). Small differences in plasma free fatty acids, β-hydroxybutyrate and the free fatty acid/β-hydroxybutyrate ratio were noted, but no pathological significance could be attributed to these changes. These studies have not determined if clinical signs of carnitine deficiency would manifest during periods of fasting. By analogy to genetically determined forms of systemic carnitine deficiency, periods of fasting in some of these individuals provoked hypoglycemia, acute encephalopathic attacks and dicarboxylic aciduria. However, ethical considerations preclude study of the effects of fasting on human infants at risk for carnitine deficiency.

With respect to the human infant, two sides of the question of essentiality of dietary carnitine may be argued. On the one hand, many normal newborns have progressed through infancy while receiving no dietary

carnitine. On the other hand, short-term stress (i.e., fasting or infection) may provoke clinical sequelae due to carnitine deficiency (which may not occur in infants receiving dietary carnitine). Because in practice so little is known about these effects, they may go unrecognized. Clearly, further research and clinical observation will delineate answers to these questions. Until this information is available, it is inappropriate to include or exclude carnitine as an essential nutrient for the human infant.

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