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Deficiency of Carnitine in Non-Ruminant Animals

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ABSTRACT

Under most conditions for the majority of species, carnitine would not be considered a vitamin as it is adequately synthesized in body tissues. However, the need for supplemental carnitine has been demonstrated in mammals in circumstances in which the biosynthesis is limited by nutritional deprivation of the precursor amino acids lysine and methionine. Dietary carnitine is essential for some insect species, including beetles of the family Tenebrionidai (mealworms), the beetle Oryza- ephilus surinamensis, and the fly Drosophila melanogaster. For these species it is appropriate to refer to carnitine as a vitamin.

INTRODUCTION

Vitamins are defined as a group of complex organic compounds present in minute amounts in natural foodstuffs that are essential to normal mal metabolism and lack of which in the diet causes deficiency diseases. Vitamins consist of a mixed group of chemical compounds and are not related to each other as are proteins, carbohydrates, and fats. Their classification together depends not on chemical characteristics but on function. Vitamins are differentiated from the trace elements, also present in the diet in small quantities, by their organic nature.

Vitamins are required in trace amounts (micrograms to milligrams per day) in the diet for health, growth, and reproduction. Omission of a single vitamin from the diet of a species that requires it will produce deficiency signs and symptoms. Many of the vitamins function as coenzymes (metabolic catalysts); others have no such role, but perform certain essential functions. Some vitamins deviate from the preceding definition in that they do not always need to be constituents of food. Certain substances that are considered to be vitamins are synthesized by intestinal tract bacteria in quantities that are often adequate for body needs. However, a clear distinction is made between vitamins and substances that are synthesized in tissues of the body. Ascorbic acid, for example, can be synthesized by most species of animals, except when they are young or under stress conditions. Likewise, in most species, niacin can be synthesized from the amino acid tryptophan and vitamin D from action of ultraviolet light on precursor compounds in the skin. Thus, under certain conditions and for specific species, vitamin C, niacin, and vitamin D would not always fit the classic definition of a vitamin.

Classically, vitamins have been divided into two groups based on their solubility's in fat solvents or in water. Thus, fat-soluble vitamins include A, D, E, and K, while vitamins of the B-complex and C are classified water soluble. Fat-soluble vitamins are found in foodstuffs in association with lipids. The fat-soluble vitamins are absorbed along with dietary fats, apparently by mechanisms similar to those involved in fat absorption. Conditions favorable to fat absorption, such as adequate bile flow and good micelle formation, also favor absorption of the fat-soluble vitamins [10, 15].

Water-soluble vitamins are not associated with fats, and alterations in fat absorption do not affect their absorption. Three of the four fat-soluble vitamins (vitamins A, D, and E) are well stored in appreciable amounts in the animal body. Except for vitamin B_{12}, water-soluble vitamins are not well stored, and excesses are rapidly excreted. A continual dietary supply of the water-soluble vitamins and vitamin K is needed to avoid deficiencies. Fat-soluble vitamins are excreted primarily in the feces via the bile, whereas water-soluble vitamins are excreted mainly in the urine. Water-soluble vitamins are relatively nontoxic, but excesses of fat-soluble vitamins A and D can cause serious problems. Fat-soluble vitamins consist only of carbon, hydrogen, and oxygen, whereas some of the water-soluble vitamins also contain nitrogen, sulfur, or cobalt.

METABOLISM

Under normal conditions in omnivores, about 70 to 80% of dietary carnitine is absorbed [15, 29].

Carnitine appears to be absorbed across the proximal small intestine by an active process dependent on Na^+ as well as by a passive diffusion, which may be important for the absorption of large doses of the factor. The uptake of carnitine from the intestinal lumen into the mucosa is rapid, and about one-half of the carnitine taken up is acetylated in that tissue. Carnitine is not carried in blood in any tightly bound forms, in contrast to many water-soluble vitamins. Tissues such as cardiac and skeletal muscle re quire carnitine for normal fuel metabolism but cannot synthesize carnitine and are totally dependent on the transport of carnitine from other tissues.

Cantrell and Borum [7] reported that carnitine uptake by the heart is facilitated by a cardiac carnitine-binding protein.

Carnitine is synthesized in liver and kidney and stored in skeletal muscle; free carnitine is excreted mainly in the urine [15, 19].

The product is trimethylamine oxide [21, 15]. Carnitine is highly conserved by the human kidney, which reabsorbs more than 90% of filtered carnitine, thus playing an important role in the regulation of carnitine concentration in blood.

Carnitine synthesis depends on two precursors, L-lysine and methionine, as well as ascorbic acid, nicotinamide, vitamin B_6, and iron [15, 25].

Deficiency in any cofactor will cause L-carnitine deficiency. In rats, total acid-soluble carnitine and free carnitine in plasma and tissues were reduced in a vitamin B_6 deficiency but increased when vitamin B_6 was provided in a repletion diet [11, 15].

It has been suggested that early features of scurvy may be attributed to carnitine deficiency. Vitamin C is a cofactor for two α-ketoglutarate-requiring dioxygenase reactions in the pathway of carnitine biosynthesis. Carnitine concentrations are variably low in some tissues of vitamin C-deficient guinea pigs. The results of studies of enzyme preparations and perfused liver *in vitro*, and of scorbutic guinea pigs *in vivo*, provide compelling evidence for participation of ascorbic acid in carnitine biosynthesis [3, 15].

Results reported by Ha et al. [13] suggest that ascorbic acid is specifically required for the hydroxylation of γ-butyrobetaine and, furthermore, that ascorbic acid can regulate carnitine synthesis in primary cultured liver cells from guinea pigs.

Choline has also been shown to affect carnitine homeostasis in humans and guinea pigs [15, 27].

Choline supplementation resulted in decreased urinary excretion of carnitine in young adult women, and choline resulted in a conservation of carnitine in guinea pigs. In choline-deficient rats, a single injection of choline raised the con- centration of liver carnitine within 1.5 hours [9, 15].

This suggests that choline was capable of facilitating carnitine release from some storage pool, as de novo synthesis would require more time.

In the rat, about 1/15 to 1/20 of the body pool turns over each day, consistent with the slow rate of turnover in muscle, where most of the body carnitine is stored [1, 15].

For the dog, 95 to 98% of the carnitine body pool is in skeletal muscle and heart [25, 28 and 15].

Borum [5] reported that the small intestine in rats is a considerable and previously unrecognized proportion of the carnitine pool of suckling animals.

DEFICIENCY

In carnitine deficiency, fatty acid oxidation is reduced, and fatty acids are diverted into triglyceride synthesis, particularly in the liver. Mitochondrial failure develops in carnitine deficiency when there is insufficient tissue carnitine available to buffer toxic acyl-coenzyme metabolites. Toxic amounts of acyl-CoA impair the citrate cycle, gluconeogenesis, the urea cycle, and fatty acid oxidation. Carnitine replacement treatment is safe and induces excretion of toxic acyl groups in the urine [33].

If carnitine deficiency involves the liver, the supply of ketones and the utilization of long-chain fatty acids during starvation are cut off; all tissues become glucose dependent. When liver carnitine is depleted, starvation tends to cause nonketotic, insulinopenic hypoglycemia. Because liver hepatocytes depend on fatty acids for their energy requirements during fasting, carnitine depletion may also cause clinical liver dysfunction, shown by hyperammonemia, encephalopathy, and hyperbilirubinemia [1, 35].

Skeletal muscles are generally involved, with weakness, lipid myopathy, and myoglobinuria often aggravated or precipitated by fasting or exercise. The heart, like skeletal muscle, is dependent on fatty acids for energy during fasting, and heart failure and arrhythmias are frequent manifestations of systemic carnitine deficiency. The heart derives approximately 60% of its ATP supply from β-oxidation of fatty acids. Carnitine concentrations in the heart are normally very high in many species [25].

Swine

The capacity of swine to synthesize carnitine hasn't been directly examined. Plasma and tissue concentrations of carnitine are reduced in neonatal pigs reared on formulas devoid of carnitine [34].

Supplementation by carnitine in 4-kg mini-pigs during total parenteral nutrition was shown to increase their energy gain from exogenous fat and to increase their nitrogen retention fourfold [9, 35].

Supplemental carnitine resulted in increased growth rate at moderately high lysine intakes, but tended to depress growth rate when lysine levels were near, below, or in considerable excess of published requirements [8].

it was found that pigs that were lightweight at weaning were more likely to have a positive growth response to supplemental carnitine over the 4-week nursery period than heavier pigs. No benefit from supplemental L-carnitine to young pigs. Likewise, addition of L-carnitine to the lactation diet had little effect on the performance of the first parity sow. However, decreased feed intake during the first week of lactation and a tendency toward fewer days to estrus were observed [30].

Dietary L-carnitine has been found to improve the gain: feed ratio and reduces carcass lipid accretion in early weaned pigs fed 1,000 ppm of L-carnitine [34].

In newborn pigs, medium-chain fatty acid (MCFA) oxidation accounted for 40% of the MCFA infused, and carnitine, independent of the level, increased the fatty acid oxidation by as much as 20% if the energy provided as MCFA exceeded 50% of the metabolic needs of the pig. From results of trials with finishing pigs, there was a curvilinear response in growth rate for the first 14 days, and in back-fat thickness at slaughter weight, due to carnitine intake. Growth rate and back fat were both increased at higher carnitine intakes. There was a differential response due to sex, by female pigs responding to a much greater degree than male castrates [12, 32].

Poultry

The increases in plasma and hepatic acylcarnitines in broilers fed 0.5% L-carnitine indicated supplementary carnitine lessens the load of free acyl groups in the liver by eventual oxidation or excretion [5]. In another study, carnitine intake (0, 50, and 100 mg/kg) didn't affect body weight, feed con version efficiency, or proximate composition at 21 days in turkeys and at 45 days in broilers. L-Carnitine significantly increased cholesterol in egg yolk when added with or without nicotinic acid at 500 mg/kg. With 50 and 100 mg/kg in the feed of layer hens, hatchability increased by 4 and 2.9%, respectively [15, 29 and 35].

Horses

Working by horses in combined training, the animals were tested in exercise trials and were given 5g/day of L-carnitine with oats. It was found that carnitine didn't improve performance, but there was a lower increase of lactate in the carnitine group during exercise and a lower increase of enzyme activity of lactate dehydrogenase. It was concluded that carnitine, besides its function in mitochondria energy-linked processes, also improves membrane stability [20]. In brood mares supplemented with 10 g/day of L-carnitine, it was found that the decline in milk carnitine after foaling was reversed in supplemented animals but not in unsupplemented ones. The drop in foal plasma carnitine was also reversed in foals from supplemented mares, and there were no apparent side effects of carnitine supplementation [11, 17].

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