

REVIEW ARTICLE

Carnitine: A Review

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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 B₁₂, 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.

CHEMICAL STRUCTURE

Carnitine is a quaternary amine, β -hydroxy- γ -trimethylaminobutyrate (Fig.1). It is a very hygroscopic compound, easily soluble in water, and has a molecular weight of 161.2. Carnitine is found in biological samples both as the free carnitine and as the ester of a wide variety of acyl compounds. Of the two types of carnitine, L- and D-carnitine, only L-carnitine is biologically active.

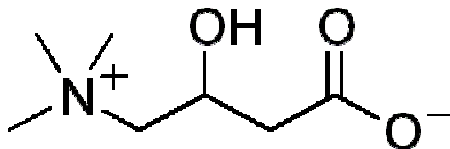


Fig1: Chemical structure of carnitine. www.Wikipedia.com, 2001.

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 require 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 B₆, 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 B₆ deficiency but increased when vitamin B₆ 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 (ϵ -N-trimethyllysine hydroxylase and γ -butyrobetaine hydroxylase) 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 concentration 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.

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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.

FUNCTIONS

Carnitine is an important cofactor for normal cellular metabolism. Optimal utilization of fuel substrates for adenosine triphosphate (ATP) generation by skeletal muscle during exercise is dependent on adequate carnitine stores. Carnitine is required for transport of long-chain fatty acids into the matrix compartment of mitochondria from cytoplasm for subsequent oxidation by the fatty acid oxidase complex for energy production. The oxidation of long-chain fatty acids in animal tissues is dependent on carnitine because it allows long-chain acyl-CoA esters to cross the mitochondrial membrane, which is otherwise impermeable to CoA compounds. Carnitine facilitates the β -oxidation of long-chain fatty acids in the mitochondria by transporting the substrate into the mitochondria. Carnitine acyltransferase is the enzyme responsible for this shuttle mechanism. It exists in two forms, carnitine acyltransferase I and carnitine acyltransferase II. After the long-chain fatty acid is activated to acyl-CoA, it is converted to acylcarnitine by the enzyme carnitine acyltransferase I and crosses to the matrix side of the inner mitochondrial membrane. Carnitine acyltransferase II then releases carnitine and the acyl-CoA into the mitochondrial matrix. Acyl-CoA is then catabolized via β -oxidation [6, 7 and 15]. Thus, utilization of long-chain fatty acids as a fuel source depends on adequate concentrations of carnitine.

The role of carnitine in the transport of long-chain fatty acids across the inner mitochondrial membrane is known. However, liver medium-chain fatty acid (MCFA) metabolism has been considered carnitine independent because of their passive diffusion through the inner mitochondrial membrane and intramitochondrial activation [13, 15].

However, evidence suggests that MCFA metabolism may be affected by supplemental carnitine [15, 20 and 31].

Another role of carnitine may be to protect cells against toxic accumulation of acyl-CoA compounds of either endogenous or exogenous origin by trapping acyl groups such as carnitine esters, which may then be transported to the liver for catabolism or to the kidney for excretion in the urine. It has been reported that nicotinamide and L-carnitine protect human cells from oxygen free radical-induced damage and that this makes these compounds possible antiaging substances [15, 32].

Carnitine also has functions in other physiological processes critical to survival, such as lipolysis, thermogenesis, ketogenesis, and possibly regulation of certain aspects of nitrogen metabolism [15, 26].

Carnitine administration has significant benefits in patients with disorders of ammonia metabolism, including urea cycle defects, chronic valproic acid therapy, liver failure, organic acidemias, and Reye's syndrome [3, 15].

Carnitine plays a role in ammonia detoxification [15, 30].

Propionyl-L-carnitine protects the ischemic heart from reperfusion injury, perhaps by scavenging free radicals or preventing their formation by chelating iron necessary for generation of hydroxyl radicals. Its function as an antiarrhythmic agent for the heart has been reported [15, 22].

An additional function of carnitine is as a memory- and alertness-enhancing agent in Alzheimer's disease [12, 15].

EFFECT OF DIETARY

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 (acyl-CoA) 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 [8, 15].

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 [4, 15].

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 [15, 16 and 17].

Ruminants

Research conducted with both steers and heifers fed high-roughage diets supplemented with soybean meal resulted in increased weight gains when supplemented with carnitine, while other studies have showed no effect [15, 23].

Diets high in forage or roughage content generally shift the ruminal volatile fatty acid profile in the direction of more acetate production and less propionate production, and carnitine is reported to be important in the regulation of liver and blood acetate levels.

Feeding veal male Holstein calves from 140 days with or without supplement of 1, 3, or 5 g/day of L-carnitine resulted in mean daily weight gains of 1.12, 1.14, 1.19, and 1.23 kg, while carcass yield was 64.1, 64.7, 65.5, and 66.4%, respectively. The auxinic effect of carnitine is attributed to its hyperglycemic activity and favorable effect on lipid metabolism [18, 15].

Intravenous L-carnitine significantly lowered plasma ammonia N levels in ewes given oral urea [15, 20 and 24].

Addition of L-carnitine to ruminant feeds could alleviate hyper-ammonemia experienced by ruminants that consume a high level of non- protein N.

The most popular topic of carnitine research in ruminants has been that dealing with ketonemia, an economically important problem commonly known as pregnancy toxemia in sheep, and ketosis, acetonemia, and ketoacidosis in cattle. Ketosis occurs when body reserves are mobilized for productive functions; the condition is exacerbated by restriction of energy or protein intake. It is hypothesized that ketosis is the result of the derepression of carnitine acyltransferase, which allows large, uncontrolled amounts of fatty acids to enter the liver mitochondria, where they are metabolized to acetoacetate and subsequently form β -hydroxybutyrate, both of which accumulate.

In lactating dairy cows, carnitine supplementation increased concentrations of carnitine in plasma and liver and improved lipid digestibility [15, 21].

However, in three dairy cattle experiments, supplemental carnitine (6 to 12 g/day) did not benefit milk yield or milk composition but was effective at increasing the concentrations of carnitine in liver, plasma, and milk of dairy cows during early lactation [14, 31, 15].

Humans

It was formerly assumed that because humans have the ability to synthesize carnitine, this compound is not an essential nutrient. However, since 1973 it has been described as "conditionally essential" because it was discovered that certain segments of the human population—mainly preterm infants, normal infants, adults on total parenteral nutrition, and adults and children with a variety of genetic, infectious, and injury-related illnesses—have a need for carnitine.

Borum [5] presented evidence that newborns have a critical need for carnitine since they have not attained the full biosynthetic capacity for carnitine, and their plasma and tissue concentrations are low. Newborn infants depend heavily on lipids as a concentrated source of fuel to achieve rapid growth during the first months of life [28, 15]. It has been estimated that the amount of carnitine in skeletal muscle of very premature infants, indexed to whole-body weight, is about 10 times less than that of adults.

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In premature infants, Helms et al. [14] observed increased nitrogen balance and weight gain in intravenously fed infants supplemented with carnitine.

Bremer et al. [6] concluded that very low birth weight infants requiring prolonged parenteral nutrition have carnitine deficiency with impaired ketogenesis. Parenteral administration of carnitine appears to alleviate this metabolic disturbance. In low birth weight infants, lowered plasma-free carnitine produced higher blood ammonia.

Human carnitine deficiency can be hereditary or acquired. Hereditary carnitine deficiency can be grouped into three clinical entities: myopathic carnitine deficiency, systemic carnitine deficiency, and organic acidurias. Acquired carnitine deficiency is due to inadequate intake, increased requirement, and increased loss of carnitine [10, 15].

Myopathic and systemic abnormalities are classified as autosomal recessive disorders. A defective transport system for carnitine uptake has been proposed as the cause of the myopathic disorder [5, 7 and 15].

It is not known what biochemical defect causes the systemic disorder. In both cases, the muscle is infiltrated with fat, and there is general weakness. The organic acidemias are inborn errors of metabolism in which fatty and organic acids accumulate, causing growth retardation, muscle hypotonia, protein intolerance, hyperammonemia, and ketoacidosis. Metabolic improvement has been observed with oral L-carnitine [22, 15].

REFERENCES

1. Bonner, C.M., DeBrie, K.L., Hug, G., Landrigan, E., and Taylor, B.J. (1995). *J. Pediatr.* 126,287.
2. Bonomi, A., Quantarelli, A., Sabbioni, A., Mazzali, I., Cabassi, E., Corradi, A., and Cantoni, A.M. (1991). *Riv. Soc. Ital. Sci. Alim.* 20, 401.
3. Borum, P.R. (1981). *Nutr. Rev.* 39, 385.
4. Borum, P.R. (1985). *Can. J. Physiol. Pharmacol.* 63, 571.
5. Borum, P.R. (1991). In *Handbook of Vitamins (L.J. Machlin, ed.)*, p. 557. Marcel Dekker, New York.
6. Bremer, J. (1990). *J. Clin. Chem. Clin. Biochem.* 28, 297.
7. Cantrell, C.R., and Borum, P.R. (1982). *J. Biol. Chem.* 257, 10599.
8. Carter, A.L., and Frenkel, R. (1978). *J. Nutr.* 108, 1748.
9. Chan, M.M. (1984). In *Handbook of Vitamins (L.J. Machlin, ed.)*, p. 549. Marcel Dekker, New York.
10. Chapa, A.M., Fernandez, J.M., White, T.W., Bunting, L.D., Gentry, L.R., Ward, T.L., and Blum, S.A. (1998). *J. Anim. Sci.* 76, 2930.
11. Goa, K.L., and Brogden, R.N. (1987). *Drugs*, 34, 1.
12. Golper, T.A., and Ahmad, S. (1992). *Semin. Dialysis*, 5, 94.
13. Grandjean, D., Valette, J.P., Jouglu, M., Gabillard, C., Barque, H., Bene, M., and Guillaud, J.P. (1993). *Recueil de Medecine Veterinaire*, 169, 543.
14. Ha, T.Y., Otsuka, M., and Arakawa, N. (1991). *J. Nutr. Sci. Vitaminol.* 37, 371.
15. Ha, T.Y., Otsuka, M., and Arakawa, N. (1994). *J. Nutr.* 124, 732.
16. Helms, R.A., Mauer, E.C., Hay, W.W., Christensen, M.L., and Storm, M.C. (1990). *JPEN* 14, 448.
17. McDowell, L. R. (2001).
18. Rebouche, C.J. (1991). *Am. J. Clin. Nutr.* 54(6 Suppl.), 1147S. Rebouche, C.J. (1992). *FASEB J.* 6, 379.
19. Rebouche, C.J., and Chenard, C.A. (1991). *J. Nutr.* 121, 539.
20. Rebouche, C.J., and Engel, A.G. (1983). *Arch. Biochem. Biophys.* 220, 60. Rebouche, C.J., and Paulson, D.J. *Ann. Rev. Nutr.* 6, 41.
21. Rebouche, C.J., Panagides, D.D., and Nelson, S.E. (1990). *Am. J. Clin. Nutr.* 52, 820.
22. Reznic, A.Z., Kagan, V.E., Ramsey, R., Tsuchiya, M., Khwaja, S., Serbinova, E.A., and Packer, L. (1992). *Arch. Biochem. Biophys.* 296, 394.
23. Roe, C.R., and Bohan, T.P. (1982). *Lancet* 1, 1411.
24. Rossle, C., Kohse, K.P., Franz, H.E., and Furst, P. (1985). *Clinica Chimica Acta*, 149, 263.
25. Sakemi, K., Hayasaka, K., Tahara, M., Sanada, Y., and Takada, G. (1992). *Tohoku J. Exp. Med.* 167, 89.
26. Santulli, A., and D'Amelio, V. (1986). *Aquaculture* 59, 177.
27. Santulli, A., Modica, A., Curatolo, A., and D'Amelio, V. (1988). *Aquaculture* 68, 345.
28. Spagnoli, A., Lucca, U., Menasce, G., and Bandera, L. (1991). *Neurology* 41, 1726.
29. Stumpf, D.A., Parker, W.D., and Angelini, C. (1985). *Neurology* 35, 1041.
30. Sugiyama, N., Suzuki, K., and Wada, Y. (1984). *Jpn. Pediatr. Soc.* 88, 1968.
31. Tanphaichitr, V., and Leelahagul, P. (1993). *Nutrition* 9, 246.
32. Torreele, E., Van Der Sluisgen, A., and Verreth, J. (1993). *Br. J. Nutr.* 69, 289.
33. Tuan, S., and Chou, C.C. (1995). *J. Chi. Nutr. Soc.* 20, 73.
34. Van Kempen, T., and Odle, J. (1993). *J. Nutr.* 123, 1531.
35. Van Kempen, T., and Odle, J. (1995). *J. Nutr.* 125, 238.
36. Waber, I.J., Valle, D., Neill, C., Dimauro, S., and Shug, A. (1982). *J. Pediatr.* 191(5), 700.
37. Weaver, L.T., Rosenthal, S.R., Gladstone, W., and Winter, H.S. (1992). *Acta Pediatr.* 81, 79.
38. www.Wikipedia.com, 2011.