Carnitine[1]

Carnitine (L-γ-trimethylamino-β-hydroxybutyrate) functions metabolically as a covalent molecular chaperone of acyl compounds esterified to its hydroxyl moiety (1,2). The quintessential metabolic function of L-carnitine is to shuttle long-chain FAs (LCFAs)[2] across the inner mitochondrial membrane to their primary site of β-oxidation within the mitochondrial matrix. The transfer of acyl compounds from CoA-esters to carnitine also serves to regenerate cellular-free CoA that is essential for intermediary metabolism. Synthesis of acylcarnitines is catalyzed by a family of carnitine *O*-acyltransferase enzymes (EC 2.3.1.21, EC 2.3.1.137, and EC 2.3.1.7) that transfer the acyl group from acyl-CoA to form acylcarnitine. The acylcarnitines can then be transported across cell-surface [organic cation transporter; solute carrier family 22 (organic cation/carnitine transporter), member A5 (*SLC22A5*), organic cation transporter number 2] and inner mitochondrial (carnitine–acylcarnitine translocase; *SLC25A20*) membranes via specific transporters.

Deficiencies

Mutations in the *SLC22A5* gene (often referred to as carnitine transporter deficiency) lead to a severe primary deficiency of carnitine in blood and tissues. Patients may be symptomatic as infants with hypoglycemia, hyperammonemia, hypotonia, myopathy, and/or cardiomyopathy. Identification of disease in older children and adults is usually based on skeletal myopathy (with or without lipid accumulation in muscle) and/or cardiomyopathy. Cardiac arrhythmias can be life threatening. Asymptomatic women have been identified postpartum on the basis of carnitine deficiency in their babies identified through newborn screening or symptoms. Primary carnitine deficiency is diagnosed by measuring free and total carnitine concentration in blood in which barely detectable amounts are present. It may also be identified in babies through newborn screening of dried blood spots by tandem MS. Because blood concentrations of carnitine are extremely low, urine measurements are unreliable unless a patient is already being supplemented. Secondary carnitine deficiency can develop in any condition that leads to carnitine loss in excess of intake or endogenous synthetic capacity. This situation is particularly common in inborn errors of FA or organic acid metabolism in which conjugation of carnitine to accumulating metabolic intermediates promotes renal excretion of potentially toxic compounds. Carnitine concentration may be low in strict vegans as a result of restricted intake of high carnitine containing animal protein. Carnitine concentration also is lower in pregnant women, leading to relatively low amounts in newborns, sometimes leading to diagnostic confusion with a primary deficiency in the baby or mother. Accordingly, infant formulas (especially soy-based formulas) are supplemented with carnitine to match concentrations normally found in breast milk.

Diet Recommendations

Currently, carnitine has no established dietary reference intakes. Carnitine can be classified as a conditionally essential nutrient, meaning that, although most individuals can synthesize enough to meet their metabolic needs, under some circumstances, endogenous synthesis is inadequate. In particular, developing neonates may require dietary carnitine, as may patients with selected inherited disorders, individuals on a strict vegan diet, and patients on dialysis. The pathway of de novo synthesis is limited by the release of trimethyl-lysine during protein turnover and involves several enzymatic reactions involving other essential nutrients, including vitamin C, iron, niacin, and vitamin B-6. Because the last step in the pathway (γ-butyrobetaine hydroxylase) is limited to liver, kidney, and brain, other tissues must obtain carnitine from circulation.

Food Sources

Carnitine is very high in red meat (up to 80 μg/100g), intermediate in dairy products, and low-to-nonexistent in vegetable foods. The L-isomer is synthesized commercially, and dietary supplements of high purity are available and are generally recognized as safe.

Clinical Uses

The only clinically validated use for carnitine is in the treatment of primary carnitine deficiency. Supplementation of symptomatic patients with carnitine (100–300 mg · kg^{-1} · d^{-1}) resolves the systemic manifestations of carnitine transporter defect and prevents additional episodes of metabolic decompensation. There is considerable controversy over the role of treatment in asymptomatic adults, because reports of sudden unexplained death in this population suggest some ongoing clinical pathophysiology. Its use in secondary carnitine deficiency seems logical, but formal data are lacking. Doses are usually lower than for carnitine transporter deficiency (50–100 mg · kg^{-1} · d^{-1}). Carnitine is frequently prescribed as a component of a variable cocktail of medications used in patients with inborn errors of the mitochondrial respiratory chain, but again there are no formal studies documenting efficacy. Two other carnitine derivatives have received some use in clinical and research situations. Propionylcarnitine has been proposed as a treatment for cardiac dysfunction, especially in the context of ischemia, chronic fatigue, and some neurologic conditions; however, results in all cases have been inconclusive or conflicting, and thus the compound should continue to be considered only as a research agent. Similarly, acetylcarnitine has been proposed to act as an antioxidant and has been used in mitochondrial respiratory chain deficiencies, neurodegenerative disorders, and to slow aging. Again, no conclusive evidence supports efficacy.

Toxicity

Carnitine is well tolerated because excesses are readily excreted into the urine. Doses exceeding 3 g/d may produce a fishy body odor resulting from degradation to trimethylamine by intestinal bacteria.

Recent Research

Recently, it has become clear that acylcarnitines are important markers of type 2 diabetes mellitus (T2D) and insulin resistance. Historically, the patterns of specific acylcarnitine molecules in biofluids, such as blood and urine, have been used diagnostically to identify enzyme deficiencies associated with inherited disorders of metabolism, because enzyme precursor–product relations are shifted to favor precursor accumulation in these cases. In humans with T2D and in animal models of insulin resistance, abnormal acylcarnitine blood and tissue concentrations are observed. For instance, a higher prevalence of medium-chain acylcarnitines has been proposed to reflect inefficient or incomplete LCFA β-oxidation under these conditions. Increased LCFA carnitines are also not uncommon in T2D and insulin resistance. These outcomes are thought to result from an excess availability of cellular LCFAs (contributed in part from typically higher circulating LCFAs under these conditions) relative to mitochondrial capacity to fully combust these fuels. Metabolism of carnitine by gut microbiota to trimethylamine and trimethylamine-*N*-oxide has drawn attention recently because the latter two compounds have been associated with increased risk of atherosclerosis. Nevertheless, it remains to be established whether this gut conversion is relevant to human health outcomes.

Mitochondrial enzymes, such as carnitine acetyltransferase (CrAT) and carnitine palmitoyl transferase 2, generate short-to-medium-chain and long-chain acylcarnitines, respectively, thereby acting as critical modulators of matrix acyl-CoA concentrations. Newly emerging results indicate that CrAT in particular is critical for proper control of the fate of both FA and pyruvate oxidation, thereby potentially contributing to tissue metabolic fuel "choice." Analogous to ketogenesis, active acetylcarnitine generation maintains the mitochondrial acetyl-CoA pools within boundaries that limit inhibition of acetyl-CoA-sensitive enzymes, such as pyruvate dehydrogenase, and diminution of CrAT activity seems to dampen normal pyruvate (and thus glucose) oxidation in tissues, such as muscle, that display low amounts of ketogenesis. It remains to be established just how important changes in CrAT and other acylcarnitine-generating systems are to the insulin-resistance/T2D phenotype and to determine how this system influences other dehydrogenase enzymes, including those involved with mitochondrial amino acid oxidation. Nonetheless, it is clear that the dynamic balance between acyl-CoA and acylcarnitine interconversion is a critical process for metabolic homeostasis and maintenance of normal mitochondrial function.

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[2]Abbreviations used: CrAT, carnitine acetyltransferase; LCFA, long-chain FA; SLC, solute carrier; T2D, type 2 diabetes.

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