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L-Carnitine

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Original Article

Biosynthesis and Metabolism of Carnitine

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ABSTRACT

This review article presents the biosynthesis, metabolism, sources, levels, and general functions of carnitine. Emphasis is placed on the expression of carnitine deficiency and insufficiency as well as the causes of these conditions. The various functions of carnitine are discussed as they may relate to disease treatment. (*J Child Neurol* 1995;10(Suppl):2S3–2S7)

Carnitine (β-hydroxy-γ-trimethylammonium butyrate) (Figure 1) is found throughout nature including most human tissues.[1] In the meal worm, *Tenebrio molitor*, carnitine is essential for life, hence it has the designation of vitamin B_T.[2] In higher animals, the major sources of carnitine are de novo synthesis and the diet. Normal levels of carnitine in human plasma have been determined for all ages.[3] Plasma carnitine increases during the 1st month of life and remains at a steady-state level for the rest of life.[3] Abnormal levels of tissue and plasma carnitine have been associated with a number of pathologic conditions. The first recognized physiologic function of carnitine was the transport of fatty acyl-coenzyme A (CoA) across the inner mitochondrial membrane for β-oxidation.[4] Recent reports have suggested that carnitine has other functions. These involve two areas: (1) carnitine may act as an acyl sink in order to maintain adequate cellular levels of free CoA,[5,6] and (2) carnitine may interact with membranes to change their physiochemical properties.[7,8]

Dietary carnitine is believed to be actively transported across the intestine in a sodium-dependent manner.[9,10] It is excreted intact by the kidney either as free carnitine or as acylcarnitine.[11] Carnitine is not degraded in humans except by some types of intestinal bacteria.[11]

CARNITINE BIOSYNTHESIS

Carnitine is synthesized from the essential amino acids lysine[12] and methionine,[13] which have been incorporated into a protein. In human tissue proteins, lysine residues are trimethylated by protein-dependent methyltransferases that use *S*-adenosyl methionine as the methyl group donor.[14] Free lysine is not methylated. When the proteins are degraded, the trimethyllysine released cannot be used for the synthesis of new proteins due to absence of a transfer RNA for trimethyllysine. Its levels are therefore sufficient for carnitine biosynthesis.

The biosynthetic pathway (Figure 2) of carnitine from ε-*N*-trimethyllysine involves several enzymes and cofactors. The first enzyme is ε-*N*-trimethyllysine hydroxylase, which hydroxylates ε-*N*-trimethyllysine at the three position.[15] This is the only mitochondrial enzyme in the pathway. It has an activity that is similar in function to proline hydroxylase and requires α-ketoglutarate, ascorbate, and Fe^{++}. The enzyme has proven difficult to isolate and has not been studied in detail.

The second enzyme, β-hydroxy-ε-*N*-trimethyllysine aldolase, catalyzes the cleavage of glycine from β-hydroxy-ε-*N*-trimethyllysine, leaving γ-trimethylaminobutyraldehyde.[16] This enzyme is reported to be similar to serine hydroxymethyltransferase.[15] This enzyme requires pyridoxal phosphate as a cofactor. Although the K_m for trimethyllysine is much higher than that for other substrates, eg, serine and threonine, no other enzyme has been implicated in this reaction.[16]

The next enzyme, γ-trimethylaminobutyraldehyde dehydrogenase, is a cytosolic enzyme that catalyzes the production of γ-butyrobetaine from γ-trimethylaminobutyraldehyde[17] with the transfer of the hydrogen ions to oxidized nicotinamide adenine dinucleotide. The synthesis of butyrobetaine can occur in most cells.[18] Trimethyllysine and butyrobetaine are found in blood and urine.[19]

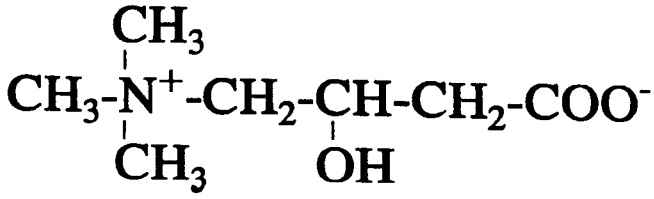

Figure 1. The structural formula of carnitine.

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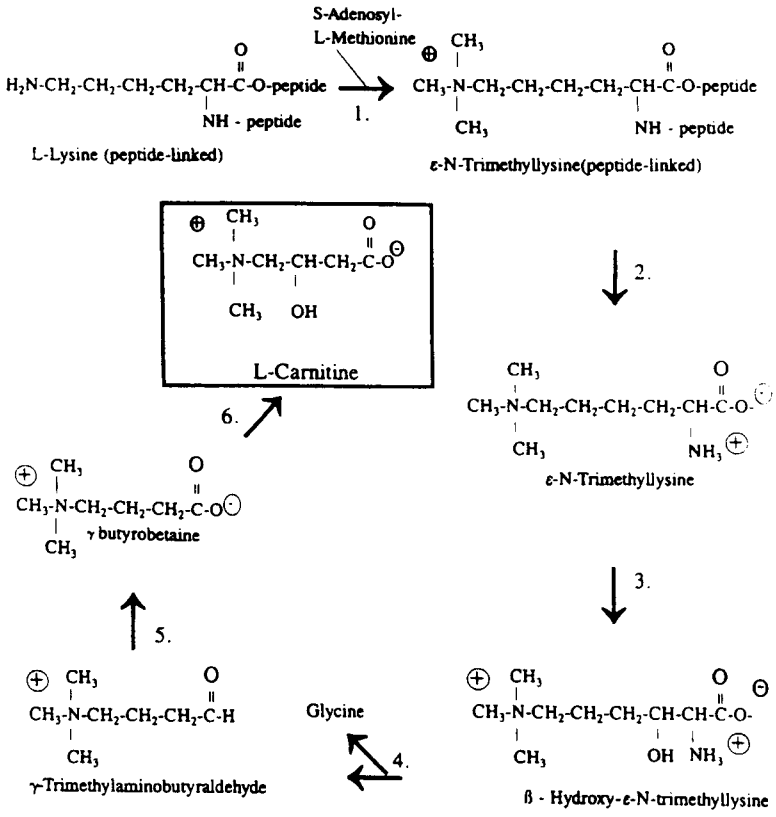

Figure 2. The biosynthesis of carnitine in mammals. Each number refers to an enzymatic activity. 1 = *S*-adenosylmethionine: L-lysine methyltransferase; 2 = protein hydrolysis; 3 = ε-*N*-trimethyllysine hydroxylase; 4 = β-hydroxy-ε-*N*-trimethyllysine aldolase; 5 = γ-trimethylaminobutyraldehyde dehydrogenase; 6 = γ-butyrobetaine hydroxylase.

The last enzyme in the carnitine pathway, γ-butyrobetaine hydroxylase, is similar to ε-*N*-trimethyllysine hydroxylase in that it requires α-ketoglutarate, ascorbate, and Fe^{++}.[20] It catalyzes the conversion of γ-butyrobetaine to carnitine. It is a cytosolic enzyme that is found in only a few tissues. In humans, this enzyme is found in the kidney, liver, perhaps the testis, and possibly the brain. The highest specific activity is found in the kidney.[21] This enzyme is missing in the rat kidney, and so the liver becomes the main site of synthesis. In the rat, it has been shown to be induced by thyroxine.[22] γ-Butyrobetaine hydroxylase is difficult to isolate, due in part to its instability in dilute solutions.

The carnitine biosynthetic pathway also requires ferrous ions and a number of vitamins: ascorbate, niacin, and pyridoxine. The net effect of this pathway is the removal of the amino acid glycine from trimethyllysine for reutilization and the production of one molecule of reduced nicotinamide adenine dinucleotide. The regulation of carnitine biosynthesis is currently not well defined. Therefore, it is essential that additional research be conducted to gain a better understanding of the treatment of patients with carnitine.

DEVELOPMENT OF THE CARNITINE BIOSYNTHETIC PATHWAY

The activity of γ-butyrobetaine hydroxylase in the 1st week of life is about 12% of that found in normal adults and increases linearly to about 30% of the normal adult level during the first 30 months of life.[23] This reduced amount of enzymatic activity is still more than adequate to produce carnitine in an efficient manner in the neonatal system.[23] Under normal conditions, trimethyllysine and butyrobetaine are quickly converted to carnitine, and only small amounts of the carnitine precursors are found in urine. Because newborn infants and premature infants are generally in an anabolic state and not degrading large amounts of protein, the levels of carnitine precursors might be limiting. For these reasons, newborn infants of all lengths of gestation may require an exogenous source of carnitine.[24] Carnitine is found in breast milk, and many soy-based commercial formulas are supplemented with carnitine.[25,26] The requirement for carnitine of premature infants is considered in another article in this supplement.

DIETARY SOURCES OF CARNITINE

Carnitine is found in high concentrations in meat and milk products, the largest amount being in red meat. Carnitine is absent or in low amounts in plants and plant products. Most soy-based commercial infant formulas now have carnitine added.[26] Approximately 15% of the carnitine ingested is absorbed in the intestine.[9] If excessive amounts of carnitine are ingested, diarrhea may result, which can be resolved by discontinuing carnitine therapy.[27]

Table 1. Carnitine Concentrations of Selected Human Tissues

Tissue	*Carnitine Level, nmol/g Wet Weight*	*Source*
Skeletal muscle	1140–3940	Angelini et al[29]
Heart	610–1300	Angelini et al[29]
Kidney	330–600	Angelini et al[29]
Liver	500–1000	Angelini et al[29]
Brain	500–1000	Angelini et al[29]
Plasma	41.4–66.6	Harper et al[30]

CARNITINE LEVELS IN NORMAL INDIVIDUALS

Normative values for total carnitine in plasma have been established for all age groups: approximately 25 μmol/L during infancy and 54 μmol/L in old age.[3] Reported urine values are highly variable.[28] This variability may be due in part to the circadian nature of excretion. The distribution of carnitine in major tissues is shown in Table 1. Muscle carnitine concentrations are greater than those in the heart or liver. This indicates that the muscle may be a site of carnitine storage.

The amount of carnitine in tissues is affected by factors other than dietary availability and synthesis. Free choline taken orally causes an increase in carnitine uptake and a decrease in carnitine excretion.[31] There are differences between the sexes in that females have lower circulating levels of carnitine than males.[3] Juvenile diabetic subjects under good control tend to have an elevated acylcarnitine to free carnitine ratio (carnitine insufficiency) (A.L. Carter and H. Wohltman, personal communication, 1991). Animal studies have indicated that both the sex hormones[32] and the glucagon to insulin ratio[33] have an effect on carnitine levels. Total plasma carnitine levels of less than 20 μmol/L in all age groups are usually considered deficient.

Carnitine in tissues and fluids is present either as free carnitine or as carnitine esters. In plasma, carnitine is present mainly in the form of free carnitine, with small amounts of acylcarnitine (approximately 10% to 15%).[34] Most plasma acylcarnitine is present as acetylcarnitine.[34] In urine, free carnitine generally accounts for 75% or less of the total carnitine. Acylcarnitines are represented by a relatively large amount of acetylcarnitine and small amounts of other acylcarnitines.[34] The relative amounts of acylcarnitine are often expressed as a ratio of acylcarnitine to free carnitine. An acylcarnitine to free carnitine ratio greater than 0.4 is considered abnormal. This state is referred to as carnitine insufficiency,[29] indicating that more carnitine is needed to handle any increased need for the production of acylcarnitines.

CARNITINE AND FATTY ACID OXIDATION

The first role ascribed to carnitine is the ability to shuttle activated long-chain fatty acids into the mitochondria for β-oxidation.[35] This process is now recognized to be under the control of at least three different proteins: carnitine palmitoyltransferase I, acylcarnitine translocase, and carnitine palmitoyltransferase II. Carnitine palmitoyltransferase I catalyzes the transfer of the fatty acid moiety from long-chain fatty acyl-CoA to carnitine.[36] This enzymatic activity is inhibited by malonyl-CoA,[37] the first unique metabolite of cytosolic fatty acid biosynthesis. Malonyl-CoA can be found in tissues that cannot synthesize fatty acids but have the capacity to oxidize fatty acids,[38] such as cardiac muscle. The carnitine palmitoyltransferase I step is the rate-limiting step in the β-oxidation of fatty acids.

The second step in this process is the transfer of the long-chain acylcarnitine from the outside to the inside of the mitochondrial membrane. This transfer is catalyzed by a mitochondrial translocase.[39] This enzyme catalyzes the transfer of one long-chain acylcarnitine molecule into the mitochondria and the export of one molecule of free carnitine or acylcarnitine out of the mitochondria.

The final step is the conversion of long-chain acylcarnitine to long-chain acyl-CoA in the mitochondrial matrix, a reaction catalyzed by carnitine palmitoyltransferase II.[40] The enzyme is located on the matrix side of the inner mitochondrial membrane. Until recently, there has been some disagreement as to whether the polypeptide chains containing the catalytic activity of the two carnitine palmitoyltransferases are the same or different.[41] The controversy centered around whether the malonyl-CoA binding site of carnitine palmitoyltransferase I was located on the same polypeptide chain as the catalytic subunit. Brown and coworkers[42] expressed a complementary DNA for rat liver carnitine palmitoyltransferase I in yeast and established that the catalytic activity and malonyl-CoA sensitivity resides in a single polypeptide. There is also little agreement as to whether the carnitine palmitoyltransferases in various organs are identical or represent different isoforms.[41]

Since the discovery that long-chain fatty acids must be transported into the mitochondria as the carnitine derivative, one question often arises: Is the amount of free carnitine available in the cell a rate-limiting factor for β-oxidation of long-chain fatty acids? For example, the amount of carnitine required for maximum activity of the carnitine palmitoyltransferase is equal to less than 2% of the total amount of free carnitine present in most tissues. Therefore, with a substantial decrease in the total amount of free carnitine in tissues, fatty acid oxidation can still proceed at normal rates.

OTHER FUNCTIONS OF CARNITINE

Besides the carnitine palmitoyltransferases discussed above, there are a number of other acyltransferases that catalyze the transfer of acyl groups of varying lengths; however, they exhibit preferences for specific chain lengths. Table 2 contains a list of acylcarnitine transferases and the K_m for each substrate. Although they all function near equilibrium in vitro, the K_ms suggest that under physiologic conditions, some of these enzymes may catalyze the reaction in only one direction.

Peroxisomes contain a fatty oxidation system that is capable of oxidizing long-chain fatty acids to a length of

Table 2. K_ms of Carnitine Acyl-CoA Transferases

	Substrates*				
Enzyme	*Carnitine*	*Acyl-CoA*	*CoA*	*Acylcarnitine*	*Source*
CAT	120	37	37	350	Bremer[43]
COT (peroxisomes, liver)	155	15	780	100	Bremer[43]
CPT II	250–450	10–20	5	40–140	Bremer[43]
CPT I	35	25	—	—	McGarry et al[38]

CoA = coenzyme A; CAT = carnitine acetyltransferase; COT = carnitine octanoyltransferase; CPT = carnitine palmitoyltransferase.
*μmol/L.

approximately six to eight carbons.[44] The peroxisome contains a carnitine acetyltransferase and a carnitine octanoyltransferase[5] that use long-chain fatty acids. These two transferases seem to be involved in the oxidation of fatty acids by this organelle. There is a long-chain carnitine transferase located in the endoplasmic reticulum whose function is still unknown.[45]

Carnitine transferases are thought to function in the regulation of the free CoA/acyl-CoA ratio in tissues and organelles. It has been suggested that in sperm[46] and macrophages[47] acetylcarnitine may be a storage form of energy for the cell. Carnitine has been postulated to function in the removal of poorly metabolized acyl-CoAs to prevent CoA sequestration. It is becoming increasingly clear that a main function of carnitine is the regulation of free CoA in cells and perhaps in different cellular organelles.

Some observations concerning the physiologic effects of carnitine cannot be explained at the present time by the acylation of fatty acyl-CoA derivatives. Examples include a role in limiting the effects of doxorubicin cardiotoxicity,[48] the stabilization of red blood cell membranes,[9] and the enhancement of Ca^{++} transport.[49] These effects seem to occur to the same extent whether D- or L-carnitine is used. This indicates that these effects are caused by the interaction of carnitine with membranes in a physical reaction. The most likely site for these reactions to occur is in association with cardiolipin.[50]

PHARMACEUTICAL USE OF CARNITINE

The most frequently encountered clinical manifestation of abnormal carnitine metabolism involves a total carnitine level below normal. In evaluating the causes of low carnitine levels as discussed in the subsequent articles of this supplement, several different conditions should be considered: (1) Is there an effect of exogenous carnitines on carnitine biosynthesis or does the patient have an adequate capacity to synthesize carnitine? (2) Is there adequate carnitine in the diet and is there sufficient absorption? (3) Is the excretion of carnitine normal? All of these questions should be addressed to determine whether there is a primary defect in the handling of carnitine.

A second type of aberration in carnitine metabolism occurs when there is an abnormally high amount of acylcarnitine relative to free carnitine. This condition, called carnitine insufficiency, can occur in any tissue and may be independent of the plasma carnitine levels. Treatment of individuals with carnitine insufficiency may require administering carnitine irrespective of the total amount of carnitine present to correct the acylcarnitine to free carnitine ratio. This is discussed in detail elsewhere in this supplement.

Finally, a third type of question often asked is: Are there any underlying conditions manifested in the patient that require treatment with carnitine even though carnitine levels in plasma are normal? For example, patients with cardiomyopathy caused by a transport defect in the heart usually present with normal to high carnitine levels.[51] In treating a patient with carnitine, it is important to focus on the clinical state of the patient. Improvement in the expected characteristic of the patient is generally more important than simply achieving a certain level of carnitine or a specific ratio of acylcarnitine to free carnitine in the plasma or tissues. If symptoms improve, carnitine therapy is probably needed as long as the underlying problem that led to the symptoms is still present.

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