CARNITINE and Vegetarianism

by Dr. Van Beveren

It is well known that carnitine has important roles in the transport of long-chain fatty acids into mitochondria and that a deficiency of carnitine results in muscle weakness, myalgia and hypotonia. Acylcarnitine is the bound form of fatty acids to carnitine. At present, most people regard acylcarnitine as a transient substance of fatty acid metabolism in mitochondria. Recently, we found that serum acylcarnitine has a very important physiological role for the brain, that is, conveying an acetyl moiety into the brain. Our recent study revealed that high amounts of acetyl moiety of acetylcarnitine are taken into the brain. The uptake of L-carnitine labeled with 11C was extremely low. This means that not free carnitine but acylcarnitine has an important physiological role to convey an acetyl moiety into the brain.

The etiology of Chronic Fatigue Syndrome (CFS) might be related to the abnormality of energy metabolism. To clarify this question, we studied the serum concentration of carnitine and acylcarnitine in 1991 and 1992. The results indicated that the vast majority of patients with CFS has serum acylcarnitine deficiency, but free carnitine levels were normal (Clin. Infect Dis, 1994;18(supple 1):S62-67). However, the physiological and biological roles of serum acylcarnitine were unclear at that time, which led us to study the dynamics and physiological meanings of serum acylcarnitine using positron CT from 1993.

Mammals have a certain regulatory system of serum acylcarnitine in the liver (Biochem Biophys Res Commun, 1996;225:740-746.). Previous to our studies, the levels of acetylcarnitine uptake into the brain were reported to be extremely low when studied using acetyl-L-[3H]carnitine. We showed that serum acylcarnitine has in fact a very important role for the brain, that is, conveying an acetyl moiety into the brain (Biochem Biophys Res Commun, 1997;231:488-493.). More recently, when we studied the uptake of acetyl-L-carnitine labeled with 11C into the brain in eight patients with CFS and eight age and sex-matched controls in Sweden, we observed that the CFS patient group has extremely low levels of uptake of serum acylcarnitine into the brain, especially anterior cingulate and dorsal prefrontal cortices which are thought to be somehow related to mood. Since most of patients with CFS have neuropsychologic complaints (difficulty in thinking, inability to concentrate, etc.), we deducted that these abnormalities might be related to the symptoms of patients with CFS.

Dr. BAB Bowman reported that the progression of Alzheimer's disease has been significantly reduced in patients who had received acetyl-carnitine for one year in a double-blind, randomized and controlled clinical trial (Bowman, BAB, Nutr Rev, 1992;50:142-144). He administered 4 gms of acylcarnitine per day for his patients, and there were few side effects. When I administered 4 gms of acylcarnitine per day to three normal healthy volunteers for seven days, the concentration of acylcarnitine in serum increased 20 percent to 30 percent after two hours of administration. There were no side effects. Therefore, we chose 4 gms of acylcarnitine per day.

L-carnitine is a quarternary amine found in meat and dairy products and is synthesized in the human liver and kidneys from 2 essential amino acids, lysine and methionine. Carnitine may increase transport of free fatty acids across mitochondrial membranes and enhance fatty acid oxidation and utilization of energy, therefore sparing muscle glycogen. Secondly, carnitine may buffer pyruvate, thus reducing muscle lactate accumulation with fatigue. Carnitine may prolong exercise.

Recently a multicenter trial giving acetyl-carnitine at 2 gms per day for 1 year affected the progression of cognitive and functional impairment in Alzheimer's disease. This was a placebo, double-blind trial. The 2 gm dose was well tolerated, except for some agitation such as restlessness and motor overactivity. Sixty-three patients in this study received acetyl-carnitine and 67 received placebo. Although intraindividual variability was high, the acetyl-carnitine group showed a consistently reduced rate of progression, which was statistically significant for the Blessed Dementia Scale and for the 3 neuropsychological tests. Acetyl-L-carnitine induces

acetyl-carnitine release in the striatum and hippocampus. A 2 gm dose of acetyl-carnitine used in this study contains 1.6 gm of carnitine, about 5 to 10 times the average daily intake in the United States.

Carnitine is a cofactor in carbohydrate metabolism and has been shown to reduce the buildup of toxic metabolites in ischemic conditions. Carnitine may have benefit in the treatment of myocardial infarction by enhancing glucose oxidation, preserving myocardial carnitine, reducing the loss of high-energy phosphates and reducing the accumulation of toxic esters. Carnitine has shown benefit in the treatment of ischemic heart disease and peripheral arterial occlusive disease.

CARDIOVASCULAR DISEASE - Carnitine - L-Carnitine is a physiologically required form of carnitine and is a nitrogenous component of muscle that plays an important role in the oxidation of fatty acids in mammals. Both L-carnitine and its derivative, propionyl-L- carnitine, which appears to have better bioavailability, have been utilized in cardiovascular diseases, which include ischemic heart disease, congestive heart failure, arrhythmias and peripheral cardiovascular disease. L-Carnitine functions, which may have cardiovascular benefits, include correction of carnitine deficiency state; facilitation of fatty acid and glucose oxidation in conditions of limited oxygen availability; removal from mitochondria of harmful fatty acyl groups that accumulate as a result of normal and pathologic metabolism; and free-radical scavenging after reperfusion of ischemic myocardium. Taking 1-2 g of oral carnitine in divided doses daily is adequate for most therapeutic purposes. Intravenous doses range from 40-100 mg/kg. For children, L-carnitine is administered orally at 100 mg/kg/day. One of carnitine's most important functions is the oxidation of long-chain fatty acids, as well as allowing for the removal of short- and medium-chain fatty acids from the cell. Carnitine is known to enhance aerobic metabolism of carbohydrates and enhance the rate of oxidative phosphorylation. An activated long-chain fatty acid is able to cross the inner mitochondrial membrane by conjugating itself to a carnitine molecule, producing acylcarnitine. The enzyme needed for this is found on the outer mitochondrial membrane. Acylcarnitine is shuttled across the inner mitochondrial membrane by another enzyme. Then the long-chain fatty acid reconjugates with a CoA molecule found in the matrix, and is now ready to undergo oxidation. This reconjugation is then done by the enzyme carnitine acyltransferase II. Carnitine is synthesized from the amino acids lysine and methionine in the liver and kidney. Micronutrients that are needed for this are iron, niacin, vitamin C and pyridoxine. Adult carnitine requirements are satisfied by dietary sources and biosynthesis. Primary dietary sources of carnitine include meat and dairy products. Primary carnitine deficiency is usually seen in uncommon genetic disorders. Secondary forms of carnitine deficiency are seen in renal tubular acidosis and chronic renal failure. Carnitine deficiency can occur in metabolic disorders in which circulating concentrations of organic acids are high. Diseases in which there is leakage of carnitine into plasma include ischemic heart disease. Almost all dietary L-carnitine is absorbed from the intestine. Results of some studies have shown that administration of propionyl–L-carnitine, which is a naturally occurring analogue of L-carnitine, is more effective in the treatment of carnitine deficiency and cardiomyopathy than that of exogenous L-carnitine. A possible reason is for the anaplerotic utilization of its propionate group as a source of tricarboxylic acid (TCA) cycle intermediates, in the presence of an optimal amount of adenosine triphosphate (ATP) and free L-carnitine, which leads to a suppression of toxic hydroxyl radicals and increased energy production. Myocardial ischemia results in the accumulation of fatty acid esters, primarily because of the inhibition of beta-oxidation, but also because of increased formation of endogenous fatty acids from phospholipid hydrolysis. These compounds have detergent properties, which are damaging to cellular and intracellular membranes. High levels of fatty acids inhibit glucose metabolism, which further depletes energy stores. Carnitine protects against these negative effects by decreasing these fatty acyl CoA esters through formation of corresponding acylcarnitine compounds, which are less harmful to the cell. Also, short- and medium-chain acylcarnitines are able to diffuse across the cell membrane and can be eliminated into the blood and urine. In ischemic heart disease, carnitine levels are very low, either because of leakage from damaged tissue or the high rate of esterification. Carnitine has been used with some success in ischemic heart disease, congestive heart failure and arrhythmias. "Carnitine and Its Role in Cardiovascular Disease," Retter AS, Heart Disease, 1999;1:108-113. (Address: Avi S. Retter, MD, Temple Univ Med Center, Dept Intern Med, 3401 North Broad St (8PP), Philadelphia, PA 19140, U.S.A.)

VEGETARIAN - L-Carnitine - A vegetarian diet might result in a low intake of carnitine and biosynthesis of L-carnitine. Carnitine is found abundantly in mammalian tissues and is an important factor in cellular energy metabolism. Under normal conditions, approximately 300 umol of carnitine per day are ingested in the diet (approximately 50 mg) and 100 umol of carnitine (approximately 20 mg) are biosynthesized. Some strict vegetarians ingest less than 5 mg of carnitine per day and rely almost totally on carnitine biosynthesis for their carnitine needs. Carnitine is synthesized from methionine and lysine, which are not found abundantly in plants. Strict vegetarians can develop carnitine deficiency. Humans ingesting a lacto-ovo or a strict vegetarian diet over years have shown a reduction in plasma carnitine concentrations. Carnitine tissue stores have to drop below 50% of normal to lead to a significant decrease in physical performance or organ function. This probably does not happen in strict vegetarians, even if this diet is ingested for years. "L-Carnitine and Vegetarianism,"

Carnitine helps in the transfer of free fatty acids across the mitochondrial membrane, and improves cardiac function.

Carnitine production is enhanced in the body by the consumption of vitamin C and lysine.

There are 4 metabolic actions of carnitine that have been utilized as therapeutic rationales: to correct an absolute relative carnitine deficiency, to enhance fatty acid oxidation, to accept and shuttle unmetabolized acyl groups from the mitochondria and to increase levels of free unesterified coenzyme A and thereby increase the intracellular free-CoA/acyl-CoA ratio, an important regulator of enzyme activation/deactivation. It also may be involved in the treatment of inborn errors of metabolism. Despite extensive clinical use of carnitine in the last 15 years and the publication of thousands of articles, there is relatively few well-controlled studies assessing clinical effects of carnitine therapy.

Dr. Van Beveren
Nutritional Biochemist and Clinical Physiologist
www.princetonhic.com