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Carnitine Supplementation and Exercise

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Introduction

The name carnitine originates from the Latin word for flesh or meat, caro, carnis. Because it was originally isolated from muscle extracts at the beginning of the century, scientists assumed that carnitine has something to do with muscle function. In the late 1940s, Gottfried Fraenkel, studying the B-vitamins in the yellow mealworm *Tenebrio molitor*, showed that carnitine is essential for the normal growth of the mealworm. In 1955, Fritz discovered that carnitine isolated from muscle extract stimulated fatty acid (FA) oxidation in liver slices and homogenates. At the same time, Friedmann and Fraenkel reported the reversible formation of acetylcarnitine from acetyl-CoA and carnitine (1). These experiments led to the hypothesis that carnitine acts as a carrier of FA across the mitochondrial membrane.

Synthesis of Carnitine

In the body, carnitine is present in esterified forms (eg. carnitine + FA) as both short-chain and long-chain acylcarnitines, and also as free carnitine. Carnitine is synthesized endogenously from two essential amino acids, lysine and methionine, with lysine providing the carbon backbone of the molecule. While the initial steps of carnitine synthesis take place in a number of different regions of the body, the final steps that result in the production of carnitine occur only in the brain, liver and kidneys. Tissues such as myocardium and skeletal muscle, which depend on fatty acid oxidation and thus require carnitine, are highly dependent on transport, via the bloodstream, of carnitine from the sites of final synthesis (1). Besides being synthesized, carnitine is absorbed by a stereospecific, sodium dependent active transport process in the duodenum and ileum, but not in the colon (2). In addition, carnitine is also absorbed in the intestine by passive transport. Because the muscle/blood carnitine level ratio is about 50 to 100, carnitine entering skeletal muscle or myocardium has to cross the cell membrane by an active transport gradient (1). Note that L-carnitine is the physiologically active isomer, and D-carnitine can actually decrease the efficiency of cellular metabolism.

Functions of Carnitine

Carnitine transports FA into the mitochondria for utilization in energy-generating processes; long-chain FA oxidation is carnitine-dependent in all tissues. FA are activated to their CoA esters within the cytoplasm. Activated FA are esterified to acylcarnitines with carnitine at the outer side of the inner mitochondrial membrane by carnitine-acyl-transferase I (CAT I). Acylcarnitines are easily transported across the mitochondrial membrane by carnitine translocase. In the mitochondrial matrix, the acylcarnitines are reconverted to acyl-CoA molecules and carnitine by CAT II. Acyl-CoAs undergo β -oxidation to form acetyl-CoA, which in the muscle is oxidized in the citric acid cycle, but in the liver is used for the formation of ketone bodies. Carnitine is then recycled to the cytoplasm (1).

Different acyl-CoA compounds may accumulate within the mitochondria in exercise, fasting, ischemia, and diabetes, because the inner mitochondrial membrane is impermeable to intramitochondrial CoAs also. Another enzyme, the carnitine-CoA acetyltransferase is located at the inner surface of the inner mitochondrial membrane (2). This enzyme might be involved in buffering the mitochondrial pool of acetyls by releasing CoA from its thioesters and transferring it to carnitine. This produces acylcarnitines which can be transported out of the mitochondria to be catabolized in the liver or excreted in the liver (1). By liberating CoA from acetyl-CoA, carnitine modulates the intramitochondrial acyl-CoA/free-CoA ration, which in vitro stimulates the pyruvate dehydrogenase complex (PDC) (K). Increasing the concentration of free CoA also restores the metabolic flux in the TCA cycle. Thus, carnitine has the following functions (4):

1. Facilitation of β -oxidation by transporting activated long-chain fatty acids into the mitochondria.
2. Stimulation of the activity of the PDC by decreasing the acetyl-CoA/CoA ration.
3. Enhancement of the metabolic flux in the TCA cycle by increasing the concentration of free CoA

Levels of Carnitine at Rest and During Exercise

The total carnitine pool of a healthy 70kg adult is about 100mmol. In humans, 98% of the carnitine is in the skeletal and cardiac muscle, 1.6% in the liver and kidney, and only about 0.4% in the extracellular fluid (5). At rest, approximately 80% of the muscle total carnitine pool is present as free carnitine, 15% as short-chain acylcarnitines and 5% as long-chain acylcarnitines. During upto 60 minutes of low intensity exercise,

no significant changes are observed in the muscle carnitine pool, as expected. In contrast, within 10 minutes of high-intensity (above the lactate threshold) exercise, the percentage of free carnitine falls to 20-50% of the total pool, and the percentage of the pool in the form of short-chain acylcarnitines rises to 45-75% (6). Total muscle carnitine during exercise remains unchanged. Skeletal muscle acylcarnitine level is positively correlated with both the muscle lactate content and the muscle acetyl-CoA content, suggesting that any acute change in the carnitine pool will probably have limited impact on overall cellular metabolism due to high fluxes through the acyl-CoA pool. Thus, the skeletal muscle carnitine pool undergoes characteristic changes during exercise which reflect the metabolic state of the muscle. While the plasma carnitine pool also experiences changes in its makeup, these changes are not as significant or tightly correlated with metabolic activity as the changes experienced by the muscle carnitine pool.

Theoretical Reasons why Carnitine may Improve Exercise Capacity

In the course of maximum and supramaximum (exceeding the capacity of the TCA cycle) metabolism, also called the lactate threshold, glycolysis is stimulated to generate pyruvate, which is then converted to acetyl-CoA and/or lactate. Lipolysis is also quite active, resulting in an increased concentration of acyl-CoA, and especially acetyl-CoA. The result is an increase in the acetyl-CoA/CoA ratio, theoretically inhibiting the PDC-mediated oxidative utilization of glucose. Note, however, that some in-vivo experiments indicate that the full catalytic activity of the PDC is reached very rapidly, and is maintained throughout prolonged exercise until exhaustion (1). Carnitine, by acting as a acetyl group buffer, can theoretically provide a number of potential advantages to cells functioning at or above their anaerobic threshold (7):

1. It will maintain a pool of free CoA even when the rate of acetyl-CoA formation exceeds the rate of condensation of acetyl-CoA with oxaloacetate, thus ensuring that the oxidation of α -ketoglutarate to succinate at a later step in the TCA cycle continues unimpeded.
2. It will help the transport of long chain fatty acids into the mitochondria, and prevent the flooding of the mitochondrial matrix by acetyl-CoA esters.
3. By forming an additional sink for pyruvate, acetylcarnitine, as an alternative to lactate as an accumulation product of anaerobic metabolism, serves as a path for increasing the oxygen debt of the muscles.
4. Carnitine may improve the transport of adenine nucleotides across the inner mitochondrial membrane in conditions of "flooding" of long-chain acyl-CoA at the inner mitochondrial membrane level.

For all of these reasons, carnitine is believed to play a theoretically important role in efficiently regulating the energy flow from different oxidative sources. Since carnitine supplementation has no negative side effects, these theoretical benefits encouraged the use of carnitine as an ergogenic aid.

Experimental Results of Carnitine Supplementation

Dubelar et al. examined the effects of carnitine infusion on an in situ fatigue test on muscle latissimus dorsi (8). The carnitine infusion increase serum carnitine from 23 to 322 mmol/L while muscle carnitine remained unchanged. L-carnitine increased the contractile force of this muscle by 34%, and also increased the total amount of work performed. Another study measured the direct in vitro effects of carnitine on isolated rat skeletal muscle strips (9). Carnitine incubation increased muscle carnitine level 5 to 6 times and delayed fatigue development in type I muscle but not in type II glycolytic muscle. However, carnitine did not modify lactate accumulation or glycogen depletion during the fatigue protocol.

The results of human trials of carnitine supplementation are markedly ambiguous. While some studies show that carnitine supplementation has a positive effect on maximal oxygen consumption (VO_{2max}), respiratory quotient, plasma lactate or other exercise-related variables, there are also a number of studies that indicate that carnitine supplementation has absolutely no effect. While these studies differ in their experimental design and variables studied, the contradictory results suggest that if carnitine does have any effect, it is likely to be complex and relatively small.

One of the first studies of carnitine supplementation was conducted in 1985 by Marconi et al, who studied the effects of carnitine supplementation (4g./day for 2 weeks) on the aerobic and anaerobic performance of 6 competitive walkers (10). VO₂max increased by 6%, from 54.5 ± 3.7 to 57.8 ± 4.7 ml/kg/min. Another study conducted by Gorostiaga et al. investigated the effects of L-carnitine addition (2g/day for 4 weeks) to the diet of endurance-trained humans during submaximal exercise (11). Ten subjects performed a control test (C) consisting of 45 minutes of cycling at 66% of VO₂max, followed by 60 minutes of recovery in a sitting position. Each subject repeated this trial after four weeks of placebo (P) or L-carnitine (LC) treatment (double-blind, cross-over design). The respiratory quotient was lower ($p < 0.05$) for the LC treated group than the P or C groups during exercise. Furthermore, oxygen uptake, heart rate, blood glycerol and resting plasma free fatty acid concentrations were all higher in the LC than the P or C groups, although these differences weren't significant. Together, these observations all suggest increased lipid utilization by muscle during exercise in the LC group.

Two additional studies examining the effects of carnitine supplementation on respiratory chain enzymes also supported the hypothesis that carnitine affects exercise performance. In one study by Huertas et al., the effects of L-carnitine on respiratory chain enzymes in the muscle of long distance runners were studied in 14 athletes (12). These subjects received either a placebo or L-carnitine (2g/day) during a 4-week training period. Athletes receiving L-carnitine showed a significant increase ($p < 0.01$) in the activities of rotenone-sensitive NADH cytochrome c reductase, succinate cytochrome c reductase and cytochrome oxidase. Another similarly designed study demonstrated that athletes receiving L-carnitine showed a dramatic increase ($P < 0.001$) in the pyruvate dehydrogenase complex activities, but no change in the levels of carnitine palmitoyl transferase (13). Taken together, these two studies suggest that the improvement in maximal oxygen consumption (VO₂max) observed in long distance runners after L-carnitine administration is based at a biochemical level on increased levels of some respiratory chain enzymes.

Contradicting these studies are a number of others that show carnitine supplementation as having no effect on exercise capacity. For example, in one study by Vukovich et al, three hours after a meal subjects cycled for 60 minutes at 70% VO₂max (Con) (14). Subjects then randomly completed two additional trials following 7 and 14 days of carnitine supplementation (6g/day.) There were no differences in VO₂, respiratory exchange ratio, heart rate, or g/min of carbohydrate or fat oxidized among the different groups. Although carnitine supplementation increased the amount of total serum carnitine, muscle carnitine levels were surprisingly unchanged. The increased level of serum carnitine did not appear to alter lipid oxidation. Similar, another study investigating the effect of supplementation upon maximum and submaximum exercise capacity, using two groups of healthy, untrained subjects in a double-blind cross-over trial, found that treatment with L-carnitine demonstrated no significant changes in VO₂max or in maximum heart rate (15). Another study demonstrated that L-carnitine supplementation does not provide an ergogenic benefit during repeated bouts of high-intensity anaerobic exercise in highly trained swimmers (1).

Adding to the confusion is a study by Vecchiet et al., in which the effects of a single dose of L-carnitine administered ninety minutes before exercise were studied in a double-blind, cross-over trial (16). Two grams of carnitine or a placebo were administered orally to ten moderately trained young men ninety minutes before they began exercise on a cycle ergometer. Exercise intensity was increased every 3 minutes until they became exhausted. After 72 hours recovery, the exercise regime was repeated, but this time the subjects who had previously received carnitine were now given a placebo (and vice versa.) At the maximum exercise intensity, treatment with L-carnitine significantly increased both maximal oxygen uptake, and power output. Moreover, at similar exercise intensities in the L-carnitine trial, oxygen uptake, carbon dioxide production, pulmonary ventilation and plasma lactate were all reduced. The interval between carnitine intake and the time of exercise is significant because plasma carnitine reaches its maximum level in approximately 2 hours. Also significant is the fact that such a small dose would have a very small effect on the total muscle carnitine pool, especially in such a short period of time.

Discussion

While several studies do show that carnitine has some positive physiological effect, the variability in the outcomes of different indicates that any ergogenic benefits are likely to be subtle, and perhaps restricted to specific populations or specific types of exercise. The fact that effects can be seen even when

the total muscle carnitine pool does not experience any major changes suggests that the effects of carnitine may be more complex in vivo than biochemical studies of carnitine function indicate. One possibility, for example, is that carnitine supplementation affects the smooth muscle cells in blood vessels, thus causing changes in blood flow to working muscles. For this reason, it appears that carnitine supplementation may have different effects depending on the size and time course of the dose, the nature of the subjects, the type and duration of exercise, and the interval between carnitine administration and subsequent exercise. Regardless, further experimentation with a variety of different experimental protocols testing specific hypotheses needs to be done before the benefits of carnitine supplementation can be adequately evaluated.

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