REVIEW ARTICLE

Supplementation of L-Carnitine in Athletes: Does It Make Sense?

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Studies in athletes have shown that carnitine supplementation may foster exercise performance. As reported in the majority of studies, an increase in maximal oxygen consumption and a lowering of the respiratory quotient indicate that dietary carnitine has the potential to stimulate lipid metabolism. Treatment with L-carnitine also has been shown to induce a significant postexercise decrease in plasma lactate, which is formed and used continuously under fully aerobic conditions. Data from preliminary studies have indicated that L-carnitine supplementation can attenuate the deleterious effects of hypoxic training and speed up recovery from exercise stress. Recent data have indicated that L-carnitine plays a decisive role in the prevention of cellular damage and favorably affects recovery from exercise stress. Uptake of L-carnitine by blood cells may induce at least three mechanisms: 1) stimulation of hematopoiesis, 2) a dose-dependent inhibition of collagen-induced platelet aggregation, and 3) the prevention of programmed cell death in immune cells. As recently shown, carnitine has direct effects in regulation of gene expression (i.e., carnitine-acyltransferases) and may also exert effects via modulating intracellular fatty acid concentration. Thus there is evidence for a beneficial effect of L-carnitine supplementation in training, competition, and recovery from strenuous exercise and in regenerative athletics. *Nutrition* 2004;20:709–715. ©Elsevier Inc. 2004

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INTRODUCTION

Dietary supplements to improve performance are familiar to many athletes. Manufacturers more or less aggressively claim that the substances improve the performance of athletes (i.e., act as ergogenic aids) and/or speed up their recovery from exercise. Most of these claims are purely speculative and based on assumptions about how the dietary supplement influences metabolism. The substance L-carnitine has been particularly popular as a potential ergogenic aid because of its role in the conversion of fat into energy.[1,2] For a scheme, the reader is referred to Figure 1.

L-carnitine was first discovered in muscle extracts by two Russian scientists[3] who named the substance for the Latin word *carnis* (flesh or meat). Its chemical structure was established in 1927, and in 1935 a pioneer article about L-carnitine was published,[4] which triggered numerous studies on the physiological functions of the chemical. In 1959 Fritz showed that carnitine increases long-chain fatty oxidation in liver and heart.[5] Another name for L-carnitine was *vitamin B T* (T = *tenebrio*) because the larva of black beetle *Tenebrio molitor* (Tenebrionidae, Coleoptera) requires L-carnitine as a growth factor in addition to folic acid and other known B vitamins. Considering the chemical structure, the choline-like metabolite L-carnitine (3-hydroxy-4-N,N,N-trimethylaminobutyrate, L-3-hydroxy-4-N-trimethylaminobutyric acid or γ-trimethylamino-β-hydroxybutyric acid) is a quaternary amine. In phrenic nerve diaphragm preparations, its effect, namely induction of tetanic fade, can be reduced by addition of choline.[6]

The function that has been investigated most thoroughly scientifically is the carnitine-dependent transport of fatty acids through the inner mitochondrial membrane. Other established functions of L-carnitine are the preservation of membrane integrity, the stabilization of a physiologic coenzyme A (CoA) acetyl-CoA (coASH) ratio in mitochondria, and the reduction of lactate production.[7,8] In vitro investigations have strongly supported the notion that L-carnitine is able to inhibit apoptosis (programmed cell death)[9–11] (Figure 2).

The intracellular homeostasis of carnitine is controlled by different membrane transporters. The organic cation transporters (OCTNs), in particular OCTN2, physiologically the most important, operate on intestinal absorption and renal reabsorption of L-carnitine and play a major role in tissue distribution and variations in transport rates. Inborn or acquired defects on this carnitine transport mechanism lead to primary or secondary carnitine deficiency. The OCTN2 mRNA content of cells is reduced with aging[12] and by oxygen radicals.[13] OCTN2 is directly inhibited by several agents and substances known to induce systemic carnitine deficiency.

Secondary carnitine deficiency is often seen in patients on regular hemodialysis,[14] with metabolic disorders, and in pregnancy.[15]

L-carnitine, widely available over the counter, is also favored among athletes. Rumors that L-carnitine supplementation helped the Italian national soccer team to win the world championship in 1982 contributed immensely to its popularity. The most important claim relates to the role of carnitine in fat metabolism. L-carnitine is often advertized to improve fat metabolism, reduce fat mass, and increase muscle mass. In other words, the substance is portrayed as a "fat burner." Therefore, carnitine is often recommended for conditions in which weight loss is indicated. Endurance athletes use carnitine to increase the oxidation of fat during exercise and spare muscle glycogen. This review critically examines whether the claims associated with L-carnitine are justified.

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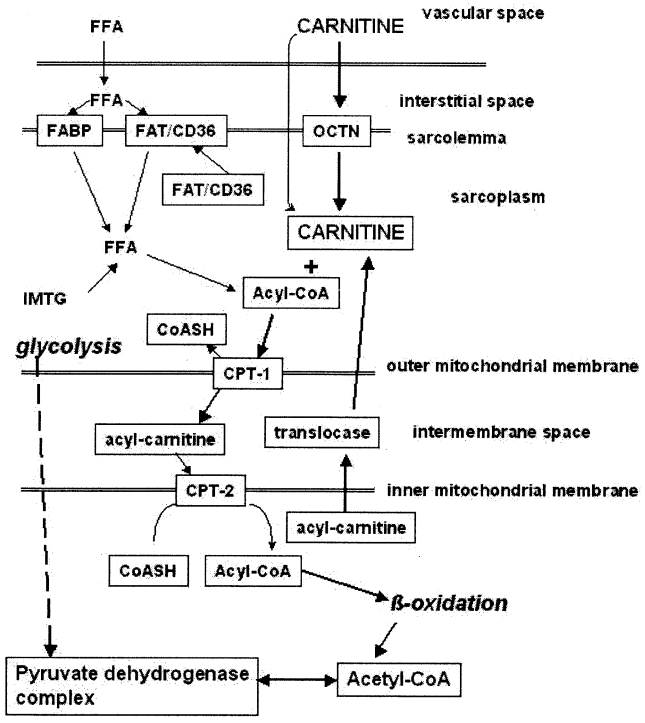

FIG. 1. Role of L-carnitine in oxidative metabolism. L-carnitine's primary function (blue arrows) is to "shuttle" fatty acids into the mitochondria by CPT-I. CPT-II mediates the further progression toward β-oxidation. Carnitine's secondary function affects the CoASH/CoA ratio. CoASH is a two-carbon compound; CoA is a vitamin B derivative. Supplemental L-carnitine can react with some of the excess CoASH groups that accumulate during strenous exercise, thereby producing acetylcarnitine. This lowers the CoASH/CoA ratio, which in turn activates the enzyme PDH. PDH causes some pyruvate to be converted to CoASH as opposed to lactic acid. Less lactic acid can mean delayed fatigue. Further, L-carnitine reacts with the excess CoASH/CoA groups to form acetylcarnitine (green arrow), free CoA is released. Free CoA is necessary for continuous operation of the Krebs cycle. Moreover, stimulating PDH enhances flow through the Krebs cycle; as a consequence, maximum oxygen capacity (the capacity for aerobic regeneration of adenosine triphosphate) is increased. Together with a decreased respiratory quotient (the quotient of exhaled CO_2 equivalents per inhaled O_2), this can mean increased exercise performance. CoA, coenzyme; CoASH, CoASH, acetyl coenzyme A; CPT, carnitine palmitoyltransferase; PDH, pyruvate dehydrogenase.

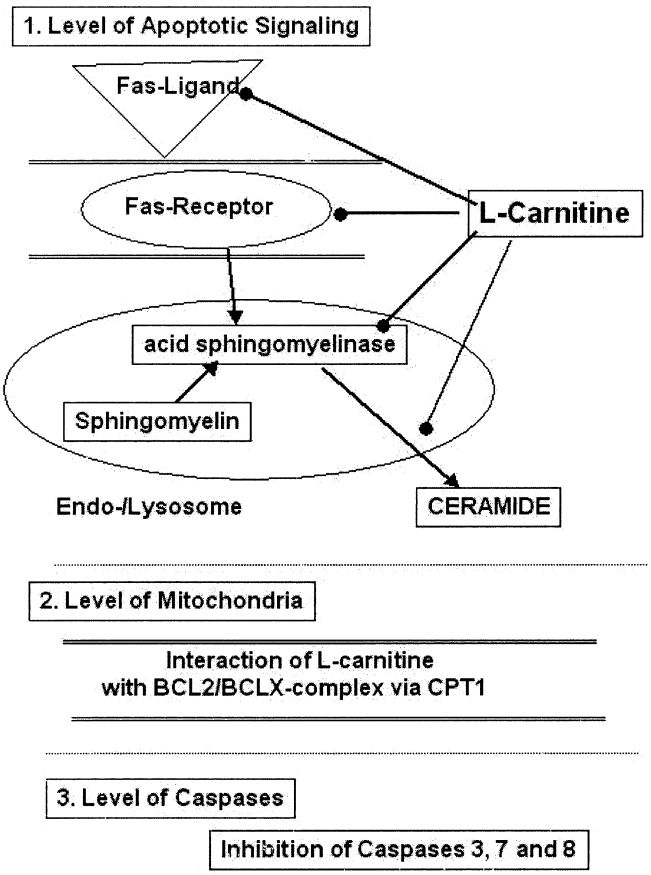

FIG. 2. Biochemical and physiologic changes during apoptosis. Scheme showing the role of carnitine in the regulation of apoptosis. At the level of signal transduction, carnitine counteracts synthesis of ceramide by inhibiting the key enzyme of ceramide synthesis, acid sphingomyelinase. Thus, activation of proapoptotic Bax/Bad by ceramide is inhibited. Association of CPT1 with antiapoptotic Bcl-2 counteracts proapoptotic Bax/Bad, which induces mitochondrial permeability transition pore opening and, as a consequence, release of cytochrome c into the cytoplasm, where it participates in caspase activation, which is inhibited by carnitine. CPT1, carnitine palmitoyltransferase.

ENDOGENOUS SYNTHESIS AND REGULATION OF CARNITINE BODY POOLS

Carnitine is synthesized in mammals from the essential amino acids lysine and methionine.[16,17] Availability of the intermediate trimethyl lysine limits carnitine biosynthesis, and most of the trimethyl lysine body stores are located in skeletal muscle protein. As a consequence, skeletal muscle protein turnover is considered to be the rate-limiting step in carnitine biosynthesis.[18] The last step, the hydroxylation of butyrobetaine to carnitine, is limited to liver, kidney, and brain; other tissues depend on active uptake of carnitine from the circulation. The enzymes involved in carnitine biosynthesis, their cofactors, and subcellular localization has been extensively reviewed by Vaz et al.[19]

CARNITINE IN THE HUMAN BODY

Skeletal muscles are the main reservoir of L-carnitine in the body and possess an L-carnitine concentration at least 50 to 200 times higher than in blood plasma, where average concentrations are between 41 (females) and 50 (males) μM/L.[20] Considering diet, red meat and dairy products represent the major sources. Even with a diet largely lacking carnitine, healthy humans are able to synthesize enough of it. Therefore, L-carnitine is not regarded as a vitamin, but as a vitamin-like substance.

Carnitine is excreted from the body only by urine and bile, where it was demonstrated that long-chain acyl derivatives accumulate.[20] Daily losses are minimal (<60 mg/d) and are reduced to less than 20 mg/d on a meat- and carnitine-free diet.

ROLE OF CARNITINE IN FAT METABOLISM

L-carnitine plays an important role in fat metabolism. In the overnight-fasted state, during the resting state, and during exercise of low to moderate intensity, long-chain fatty acids represent up to 80% of the energy sources. The best described function of L-carnitine is in its role as a cofactor of carnitine, acyltransferases transporting long-chain fatty acids across the mitochondrial inner membrane.[21] In the absence of L-carnitine, the inner mitochondrial membrane would be impermeable to long-chain fatty acids and fatty acyl-CoA esters. Once inside the mitochondria, these com-

TABLE I.

SUMMARY OF SELECTED TRIALS ANALYZING THE EFFECT OF DIETARY L-CARNITINE IN ATHLETES

Dose	Results	Subjects (*n*)	References
Improved muscle function, exercise performance, and/or recovery with dietary L-carnitine			
1 g of endovenous before exercise	Significant changes in FFA, triacylglycerols, lactic acid after exercise, improved athletic performance	17	Dragan et al.[56]
2 g before high-intensity exercise	Stimulation of PDH activity, decrease of plasma lactate and pyruvate	10	Siliprandi et al.[7]
2 g before high-intensity exercise	Increased VO_{2max}	10	Vecchiet et al.[58]
2 g/d for 4 wk	Enhanced activity of respiratory-chain enzyme activities in muscle	14	Huertas et al.[43]
2 g/d for 4 wk	Enhanced activity of PDH-complex enzymes and VO_{2max} in long-distance runners	16	Arenas et al.[42]
4 g/d for 2 wk	Increase in VO_{2max}	6	Marconi et al.[60]
6 g plus glucose infusion	Reduction of the inducible increase in plasma glucose	47	Angelini et al.[61]
2 g/d for 28 d	Increased lipid use in muscle, lower RQ	10	Gorostiaga et al.[45]
3 g/d for 7 d	Lower RQ	7	Wyss et al.[44]
3 g/d for 10 d	Increase in long-chain fatty acid oxidation, lower RQ	10	Muller et al.[46]
1 g/d for 3 wk (young athletes)	Improved athletic performance, lower lactic acid	110	Dragan et al.[55]
1 g/d for 6 wk + 2 g/d for 10 d before competition	Treated group showed better the stress-induced efforts and obtained higher performances	7	Dragan et al.[57]
1 g/d for 6 wk	Prevention of training decreased total and free carnitine positive effect on recovery	24	Arenas et al.[59]
3 g/d for 3 wk	Protective effect against muscle damage	6	Giamberardino et al.[54] 1996
2 g/d for 3 wk	Protective effect against muscle damage	10	Kraemer et al.[47]
	Total cases	305	
No effect of dietary L-carnitine on muscle function or exercise performance			
2 g before start and after 20 km of a marathon	No effect on performance	7	Colombani et al.[62]
1 g before and after treadmill ergometry	No effect on maximal exercise	9	Nuesch et al.[63]
4 g/d for 14 d	No effect on muscle carnitine content and lactate accumulation	8	Barnett et al.[33] Vukovitch et al.[41] (same probands in both studies)
3 g/d for 7 d	No changes in RO, heart rate, perceived fatigue, and blood parameters	9	Decombaz et al.[65]
5 g/d for 5 d	No influence on muscle substrate use	7	Soop et al.[66]
2 g/d for 4 wk	No effect on VO_{2max}	10	Oyono-Enguelle et al.[67]
2 g/d for 7 d	No benefit on high-intensity anaerobic exercise	20	Trappe et al.[64]
	Total cases	70	

pounds can be degraded to acetyl-CoA through a process known as β-oxidation. Carnitine also plays a decisive role in maintaining the acetyl CoA/CoA ratio in the cell. During high-intensity exercise, there is a large production of acetyl-CoA. This increase in turn inhibits the pyruvate dehydrogenase (PDH) complex and reduces flux through the PDH complex.[22] As a consequence, acetyl-CoA gives rise to lactate. Acetyl-CoA reacts with free carnitine to form acetyl-carnitine and CoA.

$$\text{acetyl-CoA} + \text{carnitine} \rightarrow \text{acetyl-carnitine} + \text{CoA}$$

Carnitine therefore may supress the accumulation of lactic acid, thereby enhancing high-intensity exercise performance. This has been confirmed in several studies, which are summarized in Table I. Results from a pilot study in patients with the human immunodeficiency virus receiving nucleoside analog therapy have suggested that L-carnitine may be helpful for patients who have nucleoside analog–related lactic acidosis with blood lactate levels higher than 10 mM/L.[23] Sweeney et al.[24] showed that addition of L-carnitine may improve the quality of platelet concentrates that are stored beyond 5 d by providing better pH preservation, less glucose consumption, and less lactate generation.

Historically, skeletal muscle was seen mainly as the site of lactate production during contraction, and lactate production was associated with insufficient muscle oxygenation and consequently fatigue. Later, it was recognized that skeletal muscles not only play an important role in lactate production but also in lactate clearance, and this improved understanding has led to a renewed interest in the metabolic fate of lactate in skeletal muscle and other tissues. Tracing studies using radioactive labeled lactate have shown that skeletal muscle extracts lactate from the circulation despite a substantial net lactate release, and that skeletal muscle has a large capacity for lactate oxidation; these processes are enhanced with exercise.[25,26]

BUFFERING THE MITOCHONDRIAL COENZYME A POOL

In some metabolic conditions, e.g., exercise, ischemia, fasting or acute stress, increased PDH activity and fatty acid supply from activated lipolysis may exceed the rate of acetyl-CoA oxidation, which leads to an accumulation of acetyl-CoA and of short-chain

acyl-CoA esters, which are mainly degradation products of branched-chain amino acids. The acetyl-CoA/CoASH ratio is an important regulating factor of the oxidation of pyruvate, α-ketoglutarate, and fatty acids. All of them depend on the availability of a common mitochondrial CoASH pool.[27] During this critical period, it is possible that excess acetyl groups are converted into acetylcarnitine by carnitine acetyltransferease. Carnitine forms esters with a wide range of acyl groups.[20] The acylation state of the mobile carnitine pool is linked to that of the limited and compartmentalized CoA pools, and the carnitine translocase allows the transfer of these excess acyl groups as carnitine esters to the cytoplasm. Hence, more CoASH is available in the mitochondrial matrix. The cytosolic concentration of carnitine is about 100 times higher than that of free CoA (approximately 2.5 and 0.014 mM, respectively).[28] It is important that an equilibrium is rapidly established between the carnitine esters in the tissues and the carnitine pool in the plasma.[29,30] Compared with free carnitine, carnitine esters are released into the plasma much more quickly (possibly via OCTN1) and excreted faster by the kidneys. It should be noted that an equilibrium of the acylcarnitines between tissue and plasma, described above, develops at a lower pace in muscle than in liver and kidney.

The debate as to whether cells are able to interconvert acetyl-CoA and acetylcarnitine within the cytosolic compartment is very important because its outcome has implications on the fate of acetylcarnitine released from mitochondria and peroxisomes and for the ability of the intramitochondrial and cytosolic pools of acetyl-CoA to communicate at all through acetylcarnitine.

Thus a buffer is formed when acetyl-CoA production is high, and circulatory acetylcarnitine may facilitate replenishment of acetyl-CoA elsewhere.[27,31]

CARNITINE AS A WEIGHT LOSS AGENT

The rationale for carnitine supplementation as a weight-loss agent is based on the assumption that regular oral ingestion of the substance increases its intracellular concentration. This would trigger increased fat oxidation and gradual reduction of the body's fat reserves. Several studies have shown that oral carnitine ingestion (up to 6 g/d for 14 d) does not change muscle carnitine concentration in healthy non-obese humans and does not promote weight loss.[32,33] This is not in keeping with clinical studies finding that supplementary carnitine is effective in the management of obese individuals.[34] A recent report[35] has indicated that inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake. Dietary carnitine stimulates activity and transcriptional rate of carnitine palmitoyltransferase,[36] which would explain a stimulation of appetite by L-carnitine supplementation. Thus, claims that carnitine supplementation promotes weight loss in healthy non-obese subjects are not sufficiently substantiated and need to be investigated in more detail.

Recent data have indicated that high doses of L-carnitine modulate glucocorticoid receptor function and, hence, might mimic some of the biological activities of glucocorticoids, which are known to stimulate lipolysis in adipose tissue.[37] In cases of hyperlipidemia, stimulation of carnitine acyltransferases after dietary supplementation with L-carnitine has been observed in blood cells.[38] For the sake of completeness, it should be mentioned that the drug etomoxir, an inhibitor of carnitine palmitoyltransferase, decreases whole-body fat oxidation,[39] and anticonvulsants, which induce a deficiency in carnitine, stimulate body weight gain.[40]

EXERCISE

Carnitine is critical for normal skeletal muscle bioenergetics for at least three reactions. First, L-carnitine is required for long-chain fatty acid oxidation; second, it assists in removing accumulated acyl groups from the mitochondria; and third, it plays an important role in detoxification. Muscles require optimum performance of these metabolic processes during peak exercise. Theoretically, carnitine availability may be the limiting factor for fatty acid oxidation or the removal of acyl-CoAs during exercise. If this is true, carnitine supplementation in otherwise healthy persons would improve exercise performance.

Results listed in Table I show that an improvement in muscle function exercise performance and/or recovery with dietary L-carnitine has been observed in the majority of cases (305 subjects in 14 studies), whereas beneficial effects failed to be observed in at least 70 cases (from 7 studies). Results of those studies, which deny an effect of carnitine supplementation on maximum oxygen consumption or respiratory quotient in healthy athletes, may be accounted for by interindividual differences. Different methodologic approaches also may be responsible for the contradictory results. Thus, the observation that L-carnitine supplementation does not affect steady-state muscular carnitine content[32,41] appears to be in contrast to a stimulation of enzyme activities in muscle cells induced by dietary L-carnitine as reported by Arenas and Huertas.[42,43] These data and reports showing an increased lipid use, which is associated with a lower respiratory quotient,[44–46] indicate that L-carnitine stimulates muscular metabolism by increasing turnover rates without affecting steady-state carnitine concentrations. A decrease of plasma lactate as induced by L-carnitine may also be due to its effects on metabolic enzymes of blood cells, which have an active carnitine metabolism (see below). The protective effect of L-carnitine on blood cells, especially platelets, that are known for their role in wound healing, could account for the protective effect of L-carnitine against exercise-induced muscle damage.[47,48] In addition, clinical studies have shown consistent benefits of carnitine administration in individuals with heart diseases.

Drug application, malfunction of OCTN2 (a high affinity carrier for L-carnitine) and dialysis therapy may lower skeletal muscle carnitine content in patients with renal diseases, because the low-affinity carrier OCTN1 needs higher carnitine concentrations. Preliminary data have shown beneficial effects of carnitine supplementation by improving muscle function and exercise capacity in patients with renal diseases.[49,50]

At rest, approximately 80% of the muscle total carnitine pool is present as L-carnitine, 15% as short-chain acylcarnitines, and 5% as long-chain acylcarnitines. During low-intensity (i.e., below the lactate threshold) exercise, no significant changes are observed in the muscle carnitine pool. In contrast, within 10 min of exercise at high-intensity workloads, the muscle carnitine pool is redistributed to short-chain acylcarnitine (primarily acetylcarnitine), with only 20% to 50% of the total pool as carnitine and 45% to 75% of the total carnitine as short-chain acylcarnitines.[51]

This redistribution of the carnitine pool slowly normalizes after the cessation of high-intensity exercise but does not return to the resting distribution of 60 min after 30 min of high-intensity exercise. Despite these dramatic fluctuations in muscle, exercise alters the plasma carnitine pool to a much smaller degree.[52] Previous observations have suggested that any changes in carnitine metabolism during exercise might depend on the exercise workload, indicating that the effect of L-carnitine is more pronounced at higher workloads.

Endurance Exercise

The notion that carnitine could be an ergogenic aid for endurance exercise is based on three assumptions. The first assumption is that the carnitine concentration present in muscle would be too low to allow carnitine acyltransferases to operate at a high rate and to support the increased rate of fat oxidation during exercise. Second, oral ingestion of carnitine would result in an increase of the total carnitine concentration in muscle. Third, this increase in muscle

carnitine would result in an increased rate of oxidation of intramuscular fatty acids and triacylglycerols during exercise, thereby reducing muscle glycogen breakdown and postponing fatigue. The scientific literature contains some hints for benefits of carnitine supplementation for skeletal muscle during exercise (Table I).

High-Intensity Exercise

During high-intensity exercise, the free carnitine concentration in muscle will decrease because the compound reacts with acetyl-CoA. During training at very high intensities, the free carnitine concentration may decrease to very low levels. Values as low as 0.5 to 1.0 mM/kg of muscle (wet weight) have been reported after 3 to 4 min at 90% maximum oxygen consumption. These values approach the concentration needed for half-maximal activity of carnitine acyltransferases for carnitine (0.25 to 0.45 mM/L) measured in vitro. This decrease in free carnitine has been suggested as one of the mechanisms for the reduction of plasma fatty acid and intramuscular triacylglycerol oxidation during high-intensity exercise.[53]

Most studies have demonstrated a more or less improved exercise performance and maximum oxygen consumption in elite and nonprofessional athletes, especially when higher doses of L-carnitine were supplemented for longer periods (Table I).[7,42–46,54–61] However, some original investigations have failed to show effects of carnitine supplementation on maximum oxygen consumption, high-intensity exercise performance, and lactate accumulation in healthy athletes (Table I).[32,41,62–67]

A consequence of high-intensity training is hypoxia, which increases the concentration of ammonia in blood.[68] However, whether blood lactate and blood ammonia levels increase concomitantly depends on exercise intensity.[69] Exercise under hypoxic conditions stimulates muscle glucose transport and lowers the concentration of free carnitine.[70] In rodents used as model organisms, carnitine supplementation appeared to prevent ammonia toxicity during exercise under hypoxic conditions on three levels: 1) activation of urea cycle enzymes, 2) interaction with glutamate receptors, and 3) reduction of free radicals. Muscle soreness and accumulation of creatine kinase during recovery were attenuated in individuals who were supplemented with L-carnitine (3 g/d for 3 wk). These findings indicated that carnitine supplementation may have a beneficial effect on recovery from exercise.[54] The studies of Volek et al.[48] and Kraemer et al.[47] examined the role of carnitine supplementation in acute exercise stress and its influence on biochemical events during recovery. Several biochemical markers indicated that carnitine can reduce catabolism of purines, free radical formation, sarcolemma disruption, and perceived soreness.[48]

IMMUNE SYSTEM

Acute bouts of prolonged, strenuous exercise are often associated with immune suppression and an increased risk of infection.[71] Although high-performance athletes cannot be described as clinically immune deficient, there is evidence that several parameters of the immune system are suppressed after prolonged periods of intense physical exercise. These are decreases in neutrophil function, serum and salivary immunoglobulin concentrations, natural killer cell activity, secretory immunoglobulin A secretion rate, and neutrophil and macrophage phagocytic activities. Moreover, the incidence of symptoms of upper respiratory tract infection increases during periods of endurance training.[72–76] This suggests the possibility of clinically relevant immune suppression in well-trained athletes. The problem is further complicated by the effect of nutrition, because the nutritional regimen itself interferes with the immune response. An increase of fat intake significantly increased endurance and did not adversely affect the levels of pro-inflammatory cytokines (interleukin-1β, interleukin-6, and tumor necrosis factor-α) in runners.[77,78]

Uptake of L-Carnitine Into Blood Cells

Increases in lymphocyte and granulocyte carnitine concentrations may reflect their enhanced metabolic state during immunoglobulin formation or phagocytosis. Uptake of L-carnitine into granulocytes has been documented in inflammatory disorders subsequent to multiple trauma and bacterial infections; in patients with Crohn's disease (chronic inflammatory bowel disease), the carnitine concentrations were increased in T lymphocytes.[79,80] De Simone et al.[81] showed that peripheral blood mononuclear cells from patients with the acquired immunodeficiency syndrome and normal serum carnitine levels are depleted in intracellular carnitine, which indicates that serum carnitines do not strictly reflect cellular concentrations.

In patients with the acquired immunodeficiency syndrome who were treated for 2 wk with high-dose L-carnitine (6 g/d), a significant trend toward the restoration of appropriate intracellular carnitine levels was found.[82] Concerning some similarities of immune suppression in patients with the acquired immunodeficiency syndrome and in elite athletes as shown for Epstein Barr virus reactivation,[72] such pharmacologic doses of L-carnitine appear to be recommendable for elite athletes. Preliminary observations have suggested that L-carnitine preloading also protects peripheral blood lymphocytes from old donors when such cells are exposed to oxidative stress.[83] Concerning age-associated downregulation of carnitine acyltransferases,[12] nutritional supplemention of L-carnitine may be especially helpful for all individuals.

Stimulating Activity of L-Carnitine on Hematopoiesis

The work of Matsumura et al.[84] was aimed at clarifying the relation among L-carnitine, stem cells, and progenitor cells of the hematopoietic system. The substance was found to stimulate erythropoiesis. The study corroborated investigations on patients with renal anemia by showing that the effect of erythropoetin could be further enhanced by L-carnitine.[85] Thus, L-carnitine supplementation may support erythropoiesis in training at higher altitudes and/or in hypoxia chambers, where such conditions are simulated.

Inhibition of Apoptosis in Immune Cells by L-Carnitine

Signal transduction via the surface glycoprotein Fas, also known as CD95, is considered the most important pathway for the regulation of programmed cell death (i.e., apoptosis). L-carnitine inhibits apoptosis by interaction with the Fas ligand and the Fas-receptor systems.[86] Signal transduction via the Fas receptor activates acid sphingomyelinase (in lysosomes), as a consequence, a breakdown of sphingomyelin and a release of ceramide occur. Immediate inhibition of acid sphingomyelinase has been shown under such conditions in vivo and in vitro.[11] In addition, an inhibition of caspases 3, 7, and 8 and an inhibition of the so-called mitochondrial permeability transition could be induced by L-carnitine addition.[10,87] Another antiapoptotic mechanism of carnitine was detected in T lymphocytes, where addition of L-carnitine and, hence, a reduction of ceramide stimulated the level of insulin-like growth factor-1 in serum.[88] Insulin-like growth factor inhibits dimerization of apoptosis regulating proteins BCL-2–BAX in the mitochondrial membrane.[89] It also inhibits activation of transcription involving the BCL-2 promoters.[90] An overview on the role of L-carnitine in regulation of apoptosis is shown in Figure 2.

SAFETY ASPECTS OF L-CARNITINE

It is not easy to make a clear distinction or classification for a substance, which, on one hand, is synthesized endogenously and,

on the other, has to be taken with food. L-carnitine belongs to a group of substances that is sold over the counter as a nutritional supplement but is also a prescribed drug. Because the investigations refer to a heterogeneous population of humans, large individual variations have to be taken into account. An LD for carnitine in rats was determined as 8.9 to 9.1 g/kg, which corresponds to 630 g/d in humans.[91]

With the exception of dialysis patients, the clinical (pharmacologic) dosage is 48 mg[92] or 50 to 350 mg of carnitine per kilogram of body weight.[93] Extrapolation of these values to 70 kg yields a dose of 3 to 3.5 g/d as the lowest amount with which a pharmacologic effect can be expected. L-carnitine supplementation in amounts larger than 4 g/d may induce slight gastrointestinal distress.[33] The dose of 2 g/d is sufficient for recovery.[47,48]

CONCLUSIONS AND DIRECTIONS FOR FURTHER WORK

On a theoretical basis, the benefits of carnitine supplementation for skeletal muscle during exercise in athletes have been documented in more than 300 subjects participating in placebo-controlled studies. However, interindividual differences in response to supplementation should be taken into account when carnitine is applied as an ergogenic aid and for weight control. In addition, L-carnitine may attenuate side effects of high-intensity training by reducing the magnitude of exercise-induced hypoxia. L-carnitine supplementation favorably affects markers of recovery from exercise stress, and it is well documented that the chemical supports the immune system.

Novel data regarding the cooperative effect of L-carnitine on thyroid and steroid hormones provide the basis for future research concerning a systemic effect of L-carnitine supplementation in athletes. Further clinical research is needed to define the optimal use of carnitine as a therapeutic instrument to improve exercise performance, in diseased individuals, and to potentially assist healthy individuals of different age groups.

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