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L-Carnitine Supplementation: A New Paradigm for its Role in Exercise

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Summary. Early research investigating the effects of *L*-carnitine supplementation has examined its role in substrate metabolism and in acute exercise performance. These studies have yielded equivocal findings, partially due to difficulties in increasing muscle carnitine concentrations. However, recent studies have proposed that *L*-carnitine may play a different role in exercise physiology, and preliminary results have been encouraging. Current investigations have theorized that *L*-carnitine supplementation facilitates exercise recovery. Proposed mechanism is as follows: 1) increased serum carnitine concentration enhances capillary endothelial function; 2) increased blood flow and reduced hypoxia mitigate the cascade of ensuing, destructive chemical events following exercise; 3) thus allowing reduced structural damage of skeletal muscle mediated by more intact receptors in muscle needed for improved protein signaling. This paradigm explains decreased markers of purine catabolism, free radical formation, and muscle tissue disruption after resistance exercise and the increased repair of muscle proteins following long-term *L*-carnitine supplementation.

Keywords. Amino acids; Exercise recovery; Hormones; Metabolism; Skeletal muscle.

Introduction

Carnitine (*L*-3-hydroxytrimethylaminobutanoate) is a naturally occurring compound that can be synthesized in mammals from the essential amino acids lysine and methionine [1] or ingested through diet. Primary sources of dietary carnitine are red meat and dairy products; however, commercially-produced supplements are also available and have been shown to be safe in humans [2]. Carnitine is stored primarily in skeletal muscle, but is also found in plasma (although in much smaller concentrations) [3]. Biologically, carnitine is essential for the transport of long-chain (carbon chain length $\geq$10) fatty acids across the outer- and inner-mitochondrial membranes (carnitine palmitoyltransferase I and II, respectively). Based on

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this function, early work investigating the effects of carnitine focused on the paradigm that carnitine supplementation would enhance skeletal muscle carnitine concentrations and increase transport (and thus oxidation) of fatty acids. Studies investigating this mechanism of action have yielded conflicting results. More recent studies, however, have focused on a different paradigm: carnitine's ability to reduce hypoxic stress and enhance recovery from exercise, which will be the focus of this review.

Early Research: Carnitine Supplementation and Fat Metabolism

A justification for carnitine supplementation in athletes was provided by *Arenas et al.* [4]. Researchers investigated the effects of physical training (6 months) on carnitine metabolism in sprinters and endurance runners. Participants were supplemented with either *L*-carnitine ($2\,g \cdot day^{-1}$ orally) or placebo (P) for the duration of the study. Athletes receiving P had significantly less muscle carnitine following 6 months of training; alternately, those athletes receiving *L*-carnitine had a significant increase in muscle carnitine following training plus supplementation. Although performance was not measured in this study, the authors hypothesized that 1) reduced muscle carnitine following training could reduce fatty acid metabolism; and 2) carnitine supplementation during training could negate the decline in (or even enhance) fatty acid metabolism.

Investigations of carnitine's effects on acute exercise performance have examined various endpoints, including fat oxidation, aerobic capacity (VO_{2max}), lactate, and physical performance. These studies have shown equivocal findings in response to various doses and durations of carnitine supplementation (see Table 1). Some of these studies have shown no increase in muscle carnitine concentrations [5, 6], which would explain the lack of significant findings on exercise metabolism.

A New Paradigm for Carnitine

A new line of research in the area of *L*-carnitine and exercise has recently evolved. Studies have indicated that a novel role for *L*-carnitine may reside in its ability to optimize recovery from the hypoxic effects of exercise [7]. Exercise places physiological stress on the body derived from two different stimuli: 1) immediately,

Table 1. Acute effects of *L*-carnitine supplementation on exercise

Endpoint	Finding	References
Fat metabolism	Increase	[30]
	No change	[6, 31–34]
VO_{2max}	Increase	[31, 35, 36]
	No change	[37]
Lactate	Decrease	[36, 38]
	No change	[5, 32, 34, 37, 39, 40]
Exercise performance	Increase	[35]
	No change	[39, 40]

the mechanical forces associated with exercise cause cellular structural damage; and 2) subsequently, chemical responses related to muscle damage and the tissue repair process cause tissue alterations that can be observed for up to ten days post-exercise.

Mechanical stress to muscle tissue is primarily mediated by the intensity of the eccentric muscle actions (muscle lengthening under force). Loading that is greater than concentric (muscle shortening) maximal strength (*e.g.*, lowering weights with 105–120% of the weight that can be raised) can lead to significant damage to contractile units. The mechanical stress of such overload can create muscle tissue damage and produce dramatic deformation in the geometrical organization of muscle fibers sarcomeres [8]. Such damage can be significant, if not injurious, due to the loss of the structural integrity and contractile function [9]. Under such conditions, the structure of the circulatory vessels is altered by changes in capillary luminal shapes and areas [10].

Whereas most exercise results in some disruption of muscle fibers due to mechanical stress, chemical factors associated with exercise stress can result in more long term dysfunction due to free radical scavenging, which can continue to degrade tissue structures over the recovery period of 5 to 10 days [11, 12]. This problem is exacerbated by the increased release of cortisol, which has negative effects on immune cell activation. These chemical responses to the mechanical stress of exercises cause physical performance decrements and delayed-onset muscle soreness (DOMS) [13].

A new role of *L*-carnitine may rest in its ability to reduce chemical damage to tissues and help the process of muscle tissue repair and remodeling. Potentially, *L*-carnitine may improve blood flow during and following exercise, and optimize the signals supporting tissue repair processes. Over the past several years, we have investigated this theoretical potential and developed a new paradigm for the use of *L*-carnitine in exercise.

Reduction of Tissue Hypoxia and Free Radical Damage

Figure 1 shows the underlying components of our paradigm. Independent of mechanical damage, exercise results in breakdown of adenosine triphosphate (*ATP*), accumulation of adenosine diphosphate (*ADP*) within the smooth muscle of the pre-capillary sphincter (Fig. 1, #1a), and activation of the enzyme adenylate kinase (Fig. 1, #1b). Adenylate kinase then catalyzes the formation of *ATP* and adenosine monophosphate (*AMP*) from two molecules of *ADP* (Fig. 1, #1c). Accumulation of *AMP* leads to the formation of hypoxanthine that diffuses out of the capillary endothelial cell. Hypoxia induced by exercise (Fig. 1, #2a) also causes a mismatch between *ATP* supply and demand resulting in the malfunction of *ATP*-dependent calcium pumps (Fig. 1, #2b) and intracellular accumulation of calcium.

The increase in intracellular calcium activates calcium-dependent proteases (Fig. 1, #2c) that lead to the proteolytic cleavage of a portion of xanthine dehydrogenase converting it to xanthine oxidase (Fig. 1, #2d) [14]. Recent work by *Hellsten et al.* [15] provides evidence for an increase in xanthine oxidase in human vascular cells of skeletal muscle following exercise. Xanthine oxidase then catalyzes the formation of xanthine from hypoxanthine (Fig. 1, #3a) and converts it to

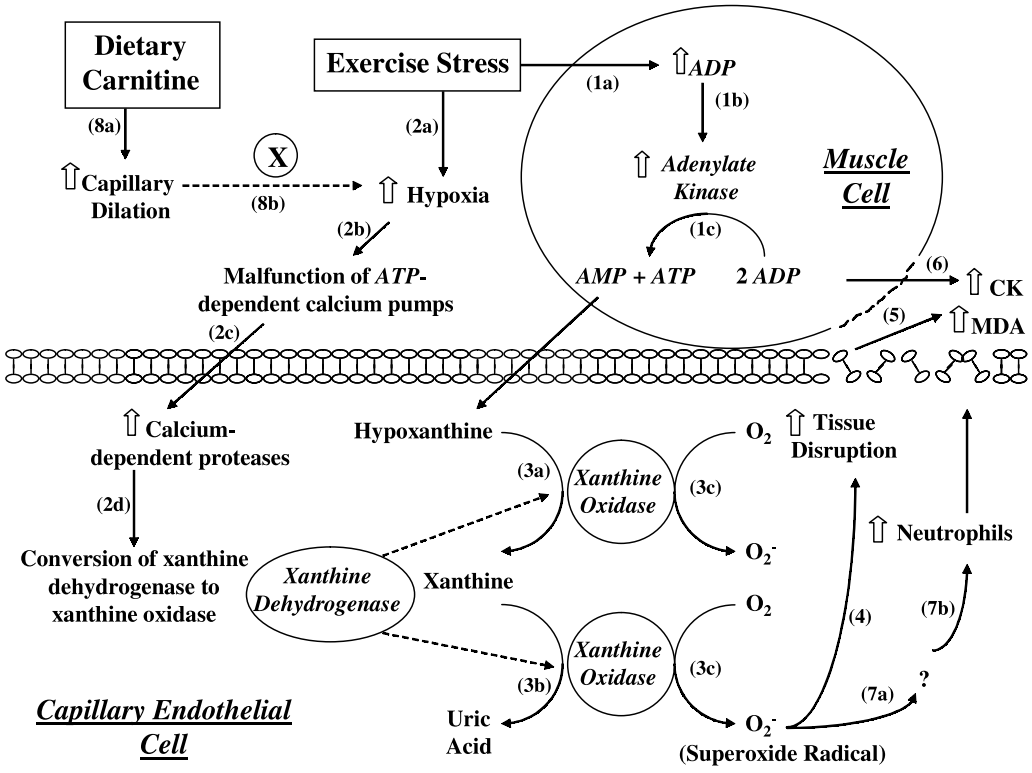

Fig. 1. Theoretical paradigm for the role of *L*-carnitine in exercise recovery; numbers indicate areas of recent or current research; see text for details

uric acid (Fig. 1, #3b). These reactions utilize molecular oxygen as an electron acceptor and form a superoxide radical (Fig. 1, #3c). The superoxide radical can combine with iron and form reactive hydroxy radicals that attack polyunsaturated fatty acids in cell membranes (Fig. 1, #4). This attack initiates a chain of lipid peroxidation reactions.

Lipid peroxidation results in the formation of numerous aldehydes of different chain lengths, such as the 3-carbon product malondialdehyde (*MDA*) (Fig. 1, #5). *MDA* is thus used as a plasma marker of free radical damage. The disruption to the cell membrane results in leakage of cytosolic proteins such as creatine kinase (CK) (Fig. 1, #6). Finally, superoxide radicals also form intermediates (Fig. 1, #7a) that attract neutrophils (Fig. 1, #7b), furthering membrane disruption.

L-Carnitine may have a role in reducing the hypoxic stress of tissues. Studies have attempted to show that *L*-carnitine has vasodilation properties. Ischemia in endothelial cells can result in carnitine release, increased oxidative stress, and compromised blood flow [16]. These responses can be ameliorated by carnitine administration [17].

Incorporating this theory into an exercise model, *Giamberadino et al.* [18], demonstrated that 3 grams of *L*-carnitine $\cdot$ day^{-1} for 3 weeks attenuated eccentric exercise-induced. This was evidenced by reduced creatine kinase concentrations (a marker of sarcolemmal damage) and subjective indicators of muscle pain and tenderness. The authors suggested that *L*-carnitine enhanced oxygen availability,

which subsequently attenuated the accumulation of free radicals that is common after exercise stress. From these suggestions, we have developed our model for the role of *L*-carnitine in recovery following exercise.

Our research group recently tested this paradigm by examining the influence of *L*-CARNIPURE®, *L*-carnitine *L*-tartrate (*LCLT*), on markers of purine catabolism, free radical formation, and muscle tissue disruption after resistance exercise [7]. Using a balanced, crossover design (1 wk washout), ten resistance-trained men consumed a placebo or *LCLT* supplement (2 g *L*-carnitine $\cdot$ day^{-1}) for three weeks. Blood samples were obtained on six consecutive days (D1 to D6). On D2, subjects reported to the laboratory for pre-exercise blood draws, a hypoxic back squat protocol (5 sets of 15–20 repetitions at 50% one-repetition maximum), and serial post-exercise blood draws. Muscle tissue damage at the mid-thigh was assessed using magnetic resonance imaging (MRI) prior to exercise (D1) and following exercise (D3 and D6). Exercise-induced increases in plasma markers of purine catabolism (hypoxanthine, xanthine oxidase, and serum uric acid) and circulating cytosolic proteins (myoglobin, fatty acid binding protein, and CK) were significantly ($p < 0.05$) attenuated by *LCLT*. Similarly, exercise-induced increases in plasma malondialdehyde returned to resting values sooner during *LCLT* supplementation compared to placebo. The amount of muscle disruption assessed *via* MRI was 41–45% lower following *LCLT* than placebo supplementation.

These data indicated that *LCLT* supplementation was effective in enhancing exercise recovery and mediating muscle damage, and therefore supported our experimental paradigm for the role of *L*-carnitine in exercise recovery. The supplementation regimen used in this study (2 g *L*-carnitine $\cdot$ day^{-1} for three weeks) resulted in increased serum carnitine concentrations [7]. We propose that enhanced serum carnitine leads to accumulation within endothelial cells and enhanced (directly or indirectly) vasodilation of the capillary vessel. The subsequent increase in blood flow and delivery of oxygen to muscle tissue may reduce the magnitude of exercise-induced hypoxia and thus attenuate the cascade of events that lead to free radical formation and membrane disruption.

Hormones in the Recovery Process Paradigm

A host of hormones are involved with the signaling of protein synthesis and immune cell function following tissue damage. The mechanisms by which such signals are involved remain a topic of current research. Primary anabolic hormones are growth hormone(s), growth factors, and androgens, which have all been viewed as potential players in the normal exercise recovery process. In addition, cortisol has been cast as an important hormone in the repair process due to 1) its role in contractile protein breakdown in attempt to spare muscle glycogen and 2) its negative effects on immune cell activation during the inflammatory process.

Previous research has investigated *L*-carnitine's influence on hormonal responses to physical stress. Uptake of carnitine occurs in the central nervous system [19] and the testes [20]. Studies have indicated that carnitine is involved in the central (hypothalamic/pituitary) regulation and peripheral (testes) production of testosterone. At the level of the hypothalamus, carnitine has been shown to restore lutenizing hormone pulsatility and gonadal function in those with hypothalamic

disorder [21]. Furthermore, supplementation stimulated *in vitro* K^+-induced gonadotropin releasing hormone (GnRH) from the hypothalamus [22, 23]. In the testes, carnitine may be involved in the transport of fatty acids into mitochondria and/or serve as an energy substrate [24]. Thus, *L*-carnitine could be influencing recovery, from brain-level signaling processes to substrate availability and transport in the testes [25].

Direct influence of *L*-carnitine on stress/recovery responses has been investigated. In rats exposed to chronic intermittent cold-water swimming, supplementation with acetyl-*L*-carnitine mediated the decline in testosterone observed following P supplementation [26]. *L*-Carnitine could help mediate enhanced tissue repair following exercise due to improvement of blood flow.

We [27] examined the influence of *LCL*T supplementation on the normal tissue repair recovery response signals (*i.e.*, testosterone [T], immunofunctional and immunoreactive growth hormone, insulin-like growth factor-1 [IGF-1], and insulin-like growth factor-binding protein-3 [IGFBP-3]) to acute resistance exercise using a balanced, cross-over, placebo-controlled research design. Ten healthy, recreationally weight-trained men volunteered and were matched for body size and strength. After 3 weeks of supplementation ($2\,g \cdot d^{-1}$ *LCL*T or P), fasting morning blood samples were obtained on six consecutive days (D1–D6). On D2, participants performed the same squat protocol as used previously in our laboratory (5 sets of 15–20 repetitions). Blood samples were obtained before exercise and 0, 15, 30, 120, and 180 minutes post-exercise. After a 1-week washout period, participants then consumed the other supplement for a 3-week period, and the same experimental protocol was repeated. Similar to our previous research [7], *LCL*T reduced the amount of exercise-induced muscle tissue damage assessed *via* MRI of the thigh. Exercise induced increases in GH, IGFBP-3, and T. *LCL*T supplementation significantly ($p < 0.05$) increased IGFBP-3 concentrations prior to and at 30, 120, and 180 minutes after acute exercise. No other direct effects of *LCL*T supplementation were observed in absolute concentrations of the hormones examined. Blood flow enhancement to tissues may help mediate quicker recovery following exercise stress.

In a recent meeting [28] we presented the first evidence that *LCL*T supplementation by improving blood flow under hypoxic conditions may enhance recovery at the level of the tissue receptor (*e.g.*, androgen receptor (AR). The combination of food ingestion as well as *LCL*T enhanced recovery of muscle *per* our improved blood flow mechanisms allowing greater interactions with protein repair mechanisms [29]. These results did provide some initial indications that repair of muscle tissue *via* improved blood flow, reduced free radicals, and more intact tissue aids recovery and was enhanced by *LCL*T supplementation.

The timing of increased protein synthesis *via* intake of nutrients may well be linked to the interface of optimal use of *LCL*T supplementation. With the use of such supplementation each day concomitant with meals and physical training, *LCL*T appeared to augment recovery response of muscle at rest and may be important during physical training or periods of high activity in an active lifestyle. Nevertheless, such data has started to shed light on the interaction of *LCL*T with the recovery process of which nutrient intake and protein synthesis are intimately involved.

Summary

The role of *L*-carnitine in the recovery process from exercise is a new paradigm for the study of this chemical compound. *L*-Carnitine's impact on hypoxia related tissue damage has opened an innovative area of study. Future research may have an impact not only on our understanding of exercise-induced damage and repair processes, but also other physiological challenges, from surgery to spaceflight, in which recovery plays an important role. The physiological roles of *L*-carnitine related to exercise recovery remains an exciting new vista for further investigation.

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