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Review Article

L-Carnitine Essential Amino Acid: Beneficial Health Perspective

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ABSTRACT

Background: L-carnitine is a quaternary ammonium compound. It and its two derivatives, (acetyl-L-carnitine and propionyl-L-carnitine), are considered essential amino acids. L-carnitine has been shown to improve physical performance in patients with certain diseases, including advanced cancer, fatigue, metabolic syndrome, and cardiovascular disease. L-carnitine is an important factor in the metabolism of long-chain fatty acids to produce energy. It exhibits a wide range of biological activities including anti-inflammatory, antiapoptotic, neuroprotective, and gastroprotective properties. L-carnitine prevents oxidative stress and regulates nitric oxide, cellular respiration, and the activity of enzymes included in defense against oxidative damage. Furthermore, these effects are attributed to its antioxidative and free radical scavenging activity. It also acts on cellular DNA and membranes, protecting them against destruction induced by free oxygen radicals. This study aimed to provides the evaluation of L-carnitine, outlining its clinical applications as well as its mechanism of action.

Conclusions: Researchers have frequently emphasized the significance of L-carnitine administration as the cornerstone for protection against various diseases.

Keywords: Essential amino acid; L-Carnitine; Neuroprotective; Antioxidative; Antiapoptotic.

INTRODUCTION

L-Carnitine (LC) is a necessary amino acid. It is necessary for long-chain fatty acids, particularly those that demand a lot of energy, to be transported across the mitochondrial membrane in cells. It is the most active component required for lipid metabolism during the β-oxidation of long-chain fatty acids to generate ATP. Furthermore, LC's anti-inflammatory, anti-apoptotic, and antioxidant properties may be connected to its moderating action [1].

L-carnitine is further engaged in the elimination of unwanted intermediate metabolic products and the regulation of the mitochondrial Coenzyme A (CoA) pool. Because of its special qualities, it can also be used to remove xenobiotics from cells and buffer excess acyl residues in cell metabolism. L-carnitine functions to protect cellular membranes, prevent the buildup of fatty acids, regulate glucogenesis and ketogenesis, and eliminate harmful metabolites [2].

Chemical structure:

L-carnitine is β-hydroxy-γ-trimethyl-aminobuty rate **(Figure 1)** [3].

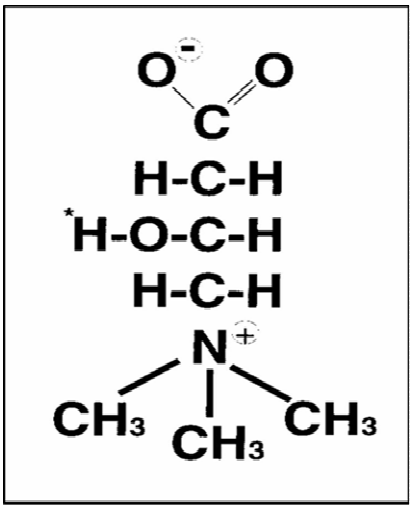

Figure (1): Chemistry of l-carnitine [3].

Physical properties:

The white, extremely water-soluble powder known as pure L-carnitine has good thermostability (up to 200 ℃). It has very low toxicity with a LD50 in rodents of 9 g/kg weight in the body. The substance's inherent hygroscopicity restricts its application in chemically pure form [4].

L-Carnitine Biosynthesis in Humans:

Because 6-N-trimethyllysine is a byproduct of protein degradation during lysosomal proteolysis, it provides the carbon backbone of L-carnitine [5]. 6-N-trimethyllysine undergoes a series of reactions supported by enzymes present in many tissues to become γ-butyrobetaine. Next, the conversion of γ-butyrobetaine to L-carnitine is catalyzed by γ-butyrobetaine dioxygenase, an enzyme that is exclusive to the kidney, liver, and brain [6]. Thus, only the kidney, liver, and brain have full endogenous carnitine production. These organs can also synthesize L-carnitine from γ-butyrobetaine that is imported from other cells lacking γ-butyrobetaine dioxygenase **(Figure 2)** [5].

Dietary Intake of L-Carnitine:

Meat, especially red meat, and dairy products are the primary dietary sources of L-carnitine, while fruit and vegetables have very small levels of the substance [7].

Symptoms of L-carnitine deficiency:

The disruption of the L-carnitine shuttle may be the cause of many symptoms seen in congenital or experimentally induced L-carnitine insufficiency. These symptoms include severe muscle weakness, fast weariness, discomfort in the muscles, and lipid drops, which are accumulations of fat in the muscles. If the main L-carnitine shortage is the cause of the sickness, then L-carnitine treatment can alleviate all these symptoms [8].

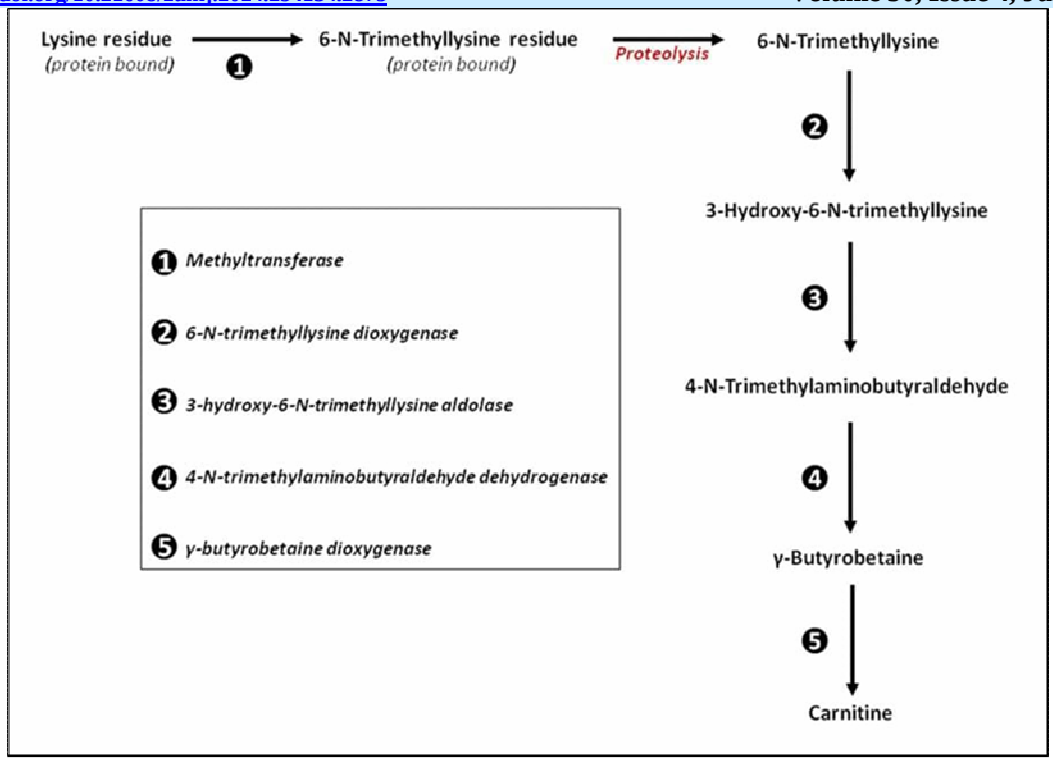

Figure (2): L-Carnitine biosynthesis in humans [6].

Pharmacology & Pharmacokinetics:

Absorption

L-carnitine enters the small intestine's epithelium partially by carrier-mediated transport and partially through passive diffusion. sluggish mucosal uptake, extended mucosal retention, and sluggish mucosal escape into circulation are the characteristics of L-carnitine absorption. Therefore, in humans, it may take up to 4-6 hours or more after oral administration to reach the peak plasma concentrations [7].

Volume of distribution

Initial volume of distribution = 0.2–0.3 L/kg [9].

Protein binding

L-carnitine and its short-chain esters don't bind to plasma proteins (fraction unbound =1). The rate and amount of plasma dispersion into erythrocytes appear to be very low or nonexistent [7].

Route of elimination

L-carnitine is mostly eliminated by the kidneys following intravenous injections because it is not bound to plasma proteins [10].

Half-life

LC has a half-life of 0.5–1 hour initially and 3–12 hours terminally [11].

Clearance:

LC's filtration clearance is comparable to glomerular filtration rate (GFR) at 100–120 mL/min since it is not bound to plasma proteins. At a typical plasma concentration of 40–50 µmol/L, around 8–9 mmol of L-carnitine are filtered daily [7].

Mechanism of action:

L-carnitine, a naturally produced antioxidant that is essential to the metabolism of long-chain fatty acids, which produces energy. It exhibits a multitude of biological actions, including anti-inflammatory, anti-apoptotic, neuroprotective, cardioprotective, and gastroprotective properties [12].

L-carnitine prevents oxidative stress, regulates nitric oxide, cellular respiration and the activity of enzymes included in defense against oxidative damage [13].

Furthermore, the reason for all these

effects is its antioxidative and free radical scavenging activity. It also acts on DNA and cell membranes to protect them from damage caused by free oxygen radicals [12].

L-Carnitine and Fatty Acid Oxidation:

L-carnitine is well acknowledged for its important role in fatty acid β-oxidation-mediated energy production, maintenance of normal mitochondrial function by elimination of toxic intermediates from fatty acyl-CoA metabolism, and control of the cellular acyl-CoA/CoASH ratio [14]. Fatty acid oxidation (FAO) occurs in peroxisomes and mitochondria, two cellular compartments important in lipid regulation **(Figure 3)** [15].

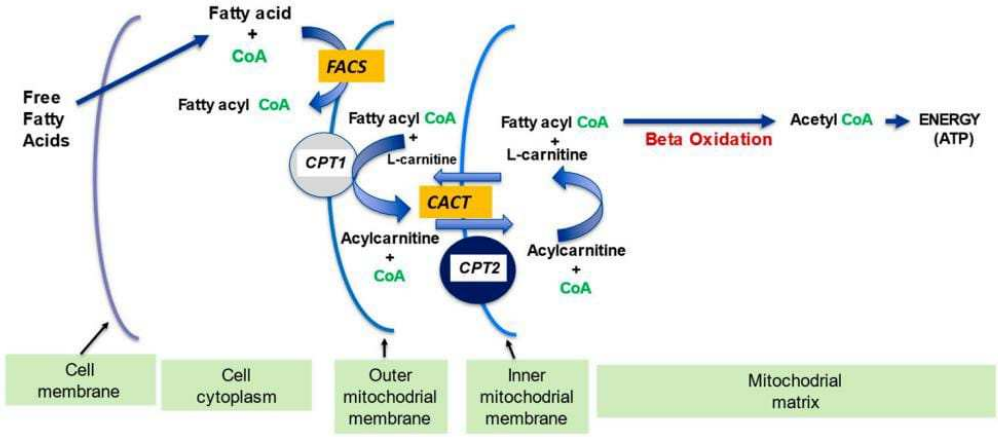

Figure (3): The Role of L-carnitine in fatty acid transport and β -oxidation in mitochondria [16].

L-Carnitine Antioxidant Properties:

L-carnitine's ability to shield cells from oxidative damage is related to its antioxidant properties. The direct radical oxygen species (ROS) scavenging action of L-carnitine is most likely caused by a carboxylate group that has a carbonyl unit to stabilize the generated radical [12]. Indeed, the L-carnitine molecule could scavenge hydrogen peroxide, superoxide anion, and 1,1-diphenyl-2-picryl-hydrazyl free radicals [17]. L-carnitine's antioxidant action comes from both its scavenging activity and its capacity to control the enzymes that produce free radicals. One such enzyme is NADPH oxidase, an oxidoreductase that produces ROS by transferring electrons from NADPH to molecular oxygen. According to reports, L-carnitine indirectly regulates this enzyme by inhibiting Protein kinase C (PKC) in a dose-dependent manner, which subsequently phosphorylates NADPH to a significant level in the cytosol [18]. Mitochondria, which are susceptible to damage, are one of the primary targets of oxidative damage in cells. ROS have the power to damage mitochondrial respiratory chains, DNA, and membrane permeability. They can also change the equilibrium of calcium [19]. L-Carnitine demonstrates the protective benefits of mitochondrial function and structure. Following L-carnitine therapy, the electron transport chain enzymes also show improvement **(Figure 4)** [17].

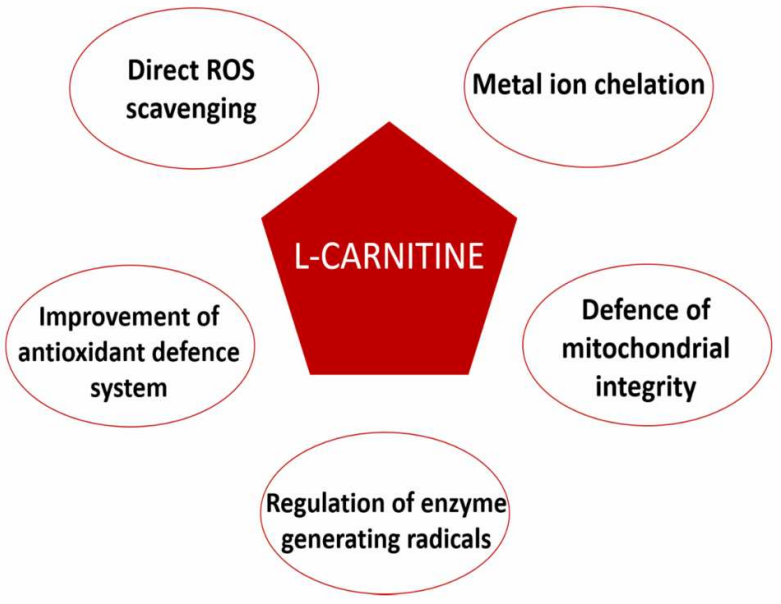

Figure (4): An overview of the antioxidant properties of L-carnitine [17].

Role of L-Carnitine in disease:

L-Carnitine and insulin resistance

L-carnitine has been demonstrated to enhance insulin sensitivity and glucose tolerance by several theories that report why carnitine has such a positive impact on glucose metabolism. Among them are:

• Better long chain acyl CoA oxidation in the mitochondria, as their accumulation is connected to insulin resistance.

• Increasing the pyruvate dehydrogenase complex (PDHC) activity as indicated by an increase in intramitochondrial acetyl-CoA/CoA.

• Increasing the expression of gluconeogenic and glycolytic enzymes.

• Improved insulin signaling cascade gene expression.

• Improved IGF-1 and the insulin-like growth factor-1 (IGF-1) axis signaling cascade [20].

L-Carnitine and endocrine imbalances

Low levels of L-carnitine are seen in women with polycystic ovary syndrome (PCOS), men with oligoasthenospermia, and women experiencing ovarian hyperstimulation. According to studies, males preparing for intracytoplasmic sperm injection (ICSI), women with PCOS, and women having in vitro fertilization (IVF) superovulation procedures can all benefit from L-carnitine medication. Additionally, it has been shown to enhance insulin sensitivity and the lipid profile in PCOS women [21].

L-Carnitine and fatty liver disease

When there is an imbalance between the uptake, production, and excretion of fatty acids from the liver of very low-density lipoprotein (VLDL) and fatty acid oxidation, fatty liver disease, sometimes referred to as steatosis, occurs. Several investigations have demonstrated that by enhancing hepatic mitochondria β-oxidation and lowering oxidative stress, L-carnitine supplementation can mitigate or avoid liver damage brought on by a variety of stressors. It has been shown that L-carnitine increases the expression of genes in the liver related to antioxidant enzymes, β-oxidation, and fatty acid transport [22].

L-Carnitine in neurodegenerative diseases

It seems that mitochondrial failure has an early underlying role in the onset of neurodegenerative illnesses such as dementia, Parkinson's disease, Alzheimer's disease, and Huntington's disease. One possible explanation for the central nervous system (CNS) toxicity is that there may be more harm to neurons and glia due to metabolic impairment caused by malfunctioning

mitochondria. Increased excitotoxicity decreased energy production, and decreased antioxidant potential would be the outcome of this. L-carnitine and acetyl-L-carnitine have been shown to alleviate Alzheimer's disease symptoms and reduce the harmful effects of beta amyloid (Aβ). The neuroprotective properties of carnitines may be associated with a decrease in ROS levels and amyloid-related mitochondrial dysfunction [23].

Clinical uses:

L-Carnitine is a vital part of the human body that supports the heart's and the muscles' healthy operation. Additionally, it helps the cell use glucose appropriately, enhancing glucose metabolism in diabetic patients and lowering symptoms including fatigue, insomnia, and mental activity [24].

L-Carnitine supplementation offers a therapeutic regimen that is helpful in reducing erythropoietin-resistant anemia, oxidative and inflammatory stress, and muscle weakness. It also avoids comorbidities including fatigue, poor cognitive function, myalgia, and muscle wasting [12].

It may benefit these patients because it promotes the oxidation of fatty acids, which may cause skeletal muscle insulin resistance. It has been established that LC is beneficial for the management of diabetes, insulin resistance, hypertension, and dyslipidemia [25].

L-Carnitine supplements can be helpful for those with heart disease since they help restore cardiac energy stores. It has been shown that long-term oral LC supplementation lowers risk factors for metabolic syndrome and cardiovascular disease [26].

L-Carnitine is an endogenous cofactor that could be linked to an increase in myocardial energy generation and mitochondrial oxidation [27].

L-Carnitine supplementation can help with certain types of male infertility and erectile dysfunction as well as enhance male reproductive functioning [28].

Patients who are overweight or obese see a decrease in their body weight and body mass index (BMI) when taking LC, suggesting that LC has anti-obesity effects **(Figure 5)** [29].

Adverse effects:

Long-term LC supplementation is probably safe at doses of 2 g/day, but greater doses may result in indigestion, nausea, vomiting, diarrhea, or a fishy body odor of 3 g/day [31].

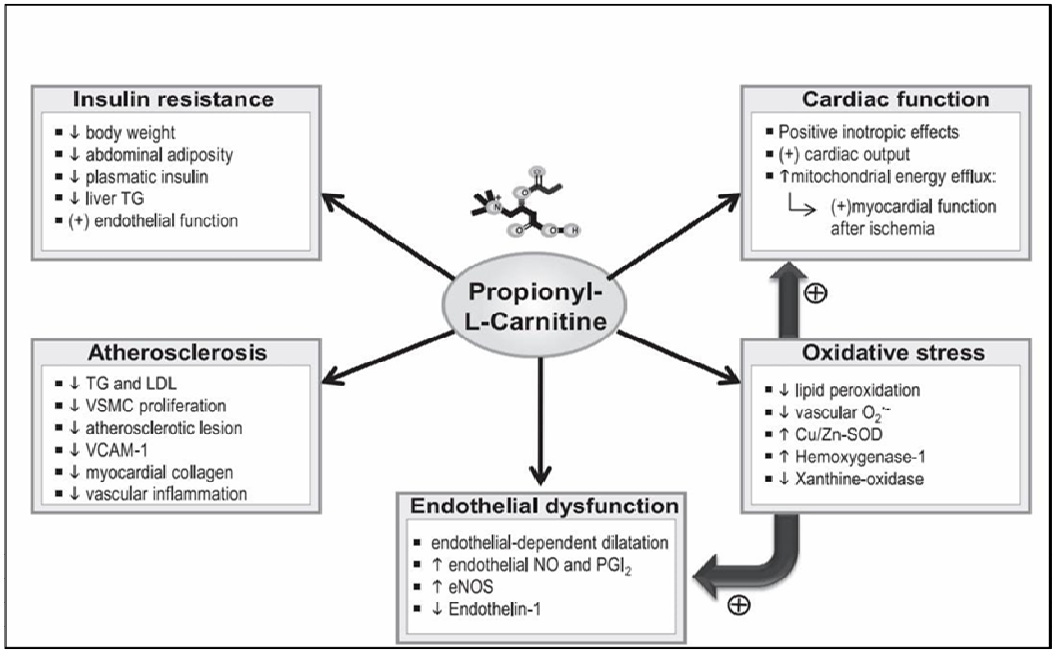

Figure (5): Pharmacological effects attributed to propionyl-l-carnitine [30].

CONCLUSIONS

Specialists have repeatedly underlined the need for L-carnitine supplementation as the primary defense against a range of illnesses. L-carnitine, a crucial element facilitates the transport of long-chain fatty acyl CoA in the metabolism of fatty acids, supporting mitochondrial β-oxidation and preserving the energy balance inside cells. Research indicates that L-carnitine is essential for regulating brain function.

Recommendations:

On the light of the information provided by the current review, the following guidelines are recommended: L-Carnitine can be used as a prophylactic treatment against various diseases. Consuming natural compounds as daily doses of L-Carnitine could help in regulation of biological activities, mitochondrial energy production and control of brain functions. Further studies are needed for assessment of the mechanisms of action, role, and applications of L-carnitine.

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