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Review

L-carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders

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ABSTRACT

In recent years increasing evidence has emerged suggesting that oxidative stress is involved in the pathophysiology of a number of inherited metabolic disorders. However the clinical use of classical antioxidants in these diseases has been poorly evaluated and so far no benefit has been demonstrated. L-Carnitine is an endogenous substance that acts as a carrier for fatty acids across the inner mitochondrial membrane necessary for subsequent beta-oxidation and ATP production. Besides its important role in the metabolism of lipids, L-carnitine is also a potent antioxidant (free radical scavenger) and thus may protect tissues from oxidative damage. This review addresses recent findings obtained from patients with some inherited neurometabolic diseases showing that L-carnitine may be involved in the reduction of oxidative damage observed in these disorders. For some of these diseases, reduced concentrations of L-carnitine may occur due to the combination of this compound to the accumulating toxic metabolites, especially organic acids, or as a result of protein restricted diets. Thus, L-carnitine supplementation may be useful not only to prevent tissue deficiency of this element, but also to avoid oxidative damage secondary to increased production of reactive species in these diseases. Considering the ability of L-carnitine to easily cross the blood–brain barrier, L-carnitine supplementation may also be beneficial in preventing neurological damage derived from oxidative injury. However further studies are required to better explore this potential.

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Abbreviations: LC, L-Carnitine; ALC, acetyl-L-carnitine; ATP, adenosine triphosphate; ROS, reactive oxygen species; H_2O_2, hydrogen peroxide; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; HNE, 4-hydroxy-2-nonenal; GSH, reduced glutathione; HSP, heat shock protein; PI3K, phosphoinositol-3 kinase; CNS, central nervous system; PLC, propionyl-L-carnitine; MCAD, medium-chain acyl-coenzyme A dehydrogenase; LCAD, long-chain acyl-CoA dehydrogenase; VLCAD, very-long-chain acyl-CoA dehydrogenase; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; CPT, carnitine palmitoyltransferase; PKU, phenylketonuria; TBARS, thiobarbituric acid reactive species; TAR, total antioxidant reactivity; MSUD, maple syrup urine disease; BCKAD, branched-chain α-keto acid dehydrogenase complex; BCAA, branched-chain amino acids; MDA, malondialdehyde; HD, Huntington's disease.

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1. Introduction

L-Carnitine (LC, β-hydroxy-y-trimethylaminobutyric acid) is a water soluble molecule important in mammalian metabolism, especially for the normal mitochondrial oxidation of fatty acids. LC exists in the organism as free LC, acetyl-L-carnitine (ALC) and other carnitine esters. About 25% of carnitine in the body is obtained by endogenous biosynthesis from methionine and protein bound lysine in the liver and kidney, but most LC is supplied by the diet, particularly from red meat and milk (Walter, 1996). Furthermore, over 99% of body carnitine is intracellular. High tissue concentrations are observed in the liver (800–1500 mmol/kg), but also in skeletal muscle (2–3 mmol/kg). Circulating carnitine accounts for only about 0.5% of body carnitine, and plasma levels can vary between 40 and 60 μmol/L (Stanley, 2004). The uptake of LC into most tissues involves carrier-mediated transport systems, which maintain high tissue/plasma concentration ratios (Pochini et al., 2013). Carnitine cannot be metabolized and is excreted as free carnitine, in the urine, but also as acylcarnitine (Stanley, 2004).

LC performs important cellular functions in the mitochondrial and peroxisomal metabolism. Cellular energy metabolism is largely sustained by mitochondrial β-oxidation of fatty acids, especially when carbohydrate stores are depleted after fasting or prolonged exercise. LC acts as a mediator of long chain fatty acid transport into the mitochondria, thus facilitating β-oxidation cycle and ATP production. Therefore, any deficiency in carnitine availability or in the carnitine-dependent mitochondrial transport system results in the curtailment of fatty acid oxidation (Stanley, 2004; Walter, 1996).

Besides, LC improves recycling of CoA by shuttling the short-chain acyl groups from the inside of the mitochondria to the cytosol, thus raising the levels of mitochondrial free CoA (Evangeliou and Vlassopoulos, 2003). Consequently, a reduced availability of carnitine induces an increase in the acetyl Coa/CoASH ratio, and this change may interfere in other ways in the intermediary metabolism, particularly gluconeogenesis, glycolysis, amino acid catabolism and ketone body production (Fig. 1).

In addition to its intrinsic interaction with bioenergetic processes, LC is also involved in the transesterification and excretion of acyl-CoA esters and removal of organic acids and xenobiotics from the mitochondria. Short-chain acylcarnitines, produced in the mitochondrial matrix by the action of carnitine acetyltransferase, can diffuse across cellular membranes and be eliminated in the urine. This action helps to protect cells from the toxic effects caused by the accumulation of organic acids in the organism (Chapela et al., 2009).

2. Neuroprotective effects of L-carnitine

In addition to its role in energy metabolism, LC may exert cytoprotective effects. In the last years, numerous neuroprotective, neuromodulatory, and neurotrophic properties have been demonstrated for this molecule. Despite the low level of β-oxidation in the brain, under metabolically compromised conditions the blood levels of free acetyl-CoA and ketosis may become important for brain functioning (Virmani and Binienda, 2004). In this particularly, fatty acids are also needed for incorporation into brain structural lipids. LC is actively transported through the blood–brain barrier by the organic cation transporter OCTN2 and accumulates in neural cells especially as acetyl-L-carnitine (ALC) (Mroczkowska et al., 1997; Shug et al., 1982). Although the actions of LC in the brain are not yet fully established, it is known that ALC can mediate the transfer of acetyl groups for acetylcholine synthesis in neurons (Nałecz and Nałecz, 1996) and also influence signal transduction pathways and gene expression (Binienda and Ali, 2001). ALC was shown to be able to prevent decay and accelerate regeneration of neurons in various in vitro and in vivo studies (Manfridi et al., 1992). Palmitoylcarnitine, other ester of carnitine, can also stimulate the expression of GAP-43 (named also B-50, neuromodulin, F1, pp45) (Nałecz et al., 2004), a protein involved in neural development, neuroplasticity, and neurotransmission (Masliah and Terry, 1993; Nałecz et al., 2004) (Fig. 2).

Recent studies have reported that LC may protect cells against oxidative damage in important neurodegenerative disorders, such as in Parkinson's and Alzheimer's diseases (Abdul and Butterfield, 2007; Beal, 2003). Underlying deleterious process in neurodegeneration is the increased metabolic stress due to mitochondrial dysfunction and formation of reactive oxygen species (ROS) (Abdul and Butterfield, 2007; Hinerfeld et al., 2004). In this context, it is well established that

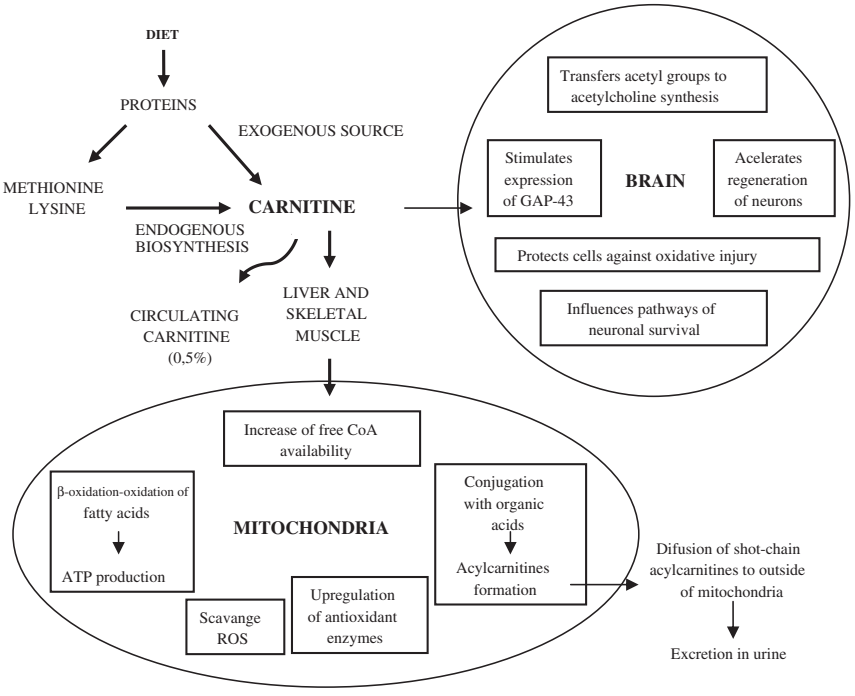

Fig. 1. Carnitine biosynthesis, distribution and main functions in the cells under physiological conditions.