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A VIEW OF L- CARNITINE IN HEALTH AND DISEASES

N. Santhosh Kumar[1*], K. N. Kalaivanam[1], R. Bheemasen[1], M. Subhas Chandrappa[2], Dinesha Ramadas[3]

[1]Department of Biochemistry, Shridevi Institute of Medical Science & Research Hospital, Tumkur, Karnataka, India.*

[2]Department of Biochemistry, Basaveshwara Medical College, Chitradurga, Karnataka, India.

[3]Adichunchanagiri Biotechnology & Cancer Research Institute, B.G. Nagara, Karnataka, India.

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ABSTRACT

Carnitine is essential nutrient obtained from the diet and also biosynthesized from the essential amino acids lysine and methionine. The established function of carnitine is as a carrier of activated fatty acids and activates acetate across the inner mitochondrial membrane. Other roles of carnitine include buffering of the acyl coenzyme A - CoA ratio, removal of excess acyl groups, and peroxisomal fatty acid oxidation and also influences carbohydrate metabolism. Primary carnitine deficiency (PCD) is an autosomal recessive disorder of fatty acid oxidation caused by deficiency of plasma membrane carnitine resulting from impairment in the plasma membrane transporter, leading to decreased accumulation in the skeletal muscle, heart and potentiates increased renal loss leading to systemic carnitine depletion. Recent studies have revealed Secondary carnitine deficiencies (SCD) occur due to an accumulation of organic acids, characterized by carnitine increased excretion in urine in the form of acyl-carnitine and SCD associated with more common disorders like Diabetes mellitus, hemodialysis, trauma, malnutrition, cardiovascular diseases, obesity, Alzheimer's disease, AIDS and cancer. Allow us to tease out additional pathways dependent on carnitine functions. In this review, we present current knowledge of carnitine biology in health and disease. This article is part of a special issue entitled: Metabolic Functions and Biogenesis of Carnitine in Health and Disease.

Corresponding author

Santhosh Kumar .N

Assistant Professor
Dept. of Biochemistry,
Shridevi Institute of Medical Sciences & Research Hospital,
Tumkur, Karnataka, India.
nune.santhosh@gmail.com

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INTRODUCTION

Carnitine was detected very long back, but it was nearly forgotten among biochemists until its importance in fatty acid metabolism was established. In the recent years, interest in the study of metabolism and functions of carnitine has steadily increased. Carnitine (L-3-hydroxy-4-N-trimethyl amino butyrate) is an endogenous compound present in most mammalian tissues and performs many heterogeneous functions [1].

Chemistry

L-Carnitine is highly polar, water soluble, small quaternary amine derived from essential amino acids, is found in all cells of the body [2]. Synthetic carnitine occurs as D & L isomers; L-carnitine is physiologically active [3, 4].

Absorption, transport and metabolism of Carnitine

In humans, Free L- carnitine (active form) is absorbed in the small intestinal mucosa by sodium-dependent active transport and by passive transport, reaches the blood stream and the extracellular fluid. Carnitine does not need protein for a carrier, and is present in the free or acyl carnitine form [5, 6].

Plasma concentration of free carnitine is in dynamic balance with acyl carnitines. The acyl to free carnitine ratio is ≤ 0.4 being considered normal [7]. Acetyl carnitine esters are formed intracellularly during regular metabolic activity in both anabolic and catabolic pathways in cellular metabolism [8] and also participate in the removal of organic acids [9].

In mammals protein-bound lysine is enzymatically methylated to form tri-methyl lysine [10], converted to butyrobetaine in all tissues; the butyrobetaine is finally hydroxylated to endogenous L-carnitine by γ-butyrobetaine hydroxylase, requires ascorbic acid, ferrous iron, pyroxidine, niacin [11], these enzyme are absent in cardiac muscle, skeletal muscle and high concentration in liver, testes, and kidneys [12-15] (see Fig. 1).

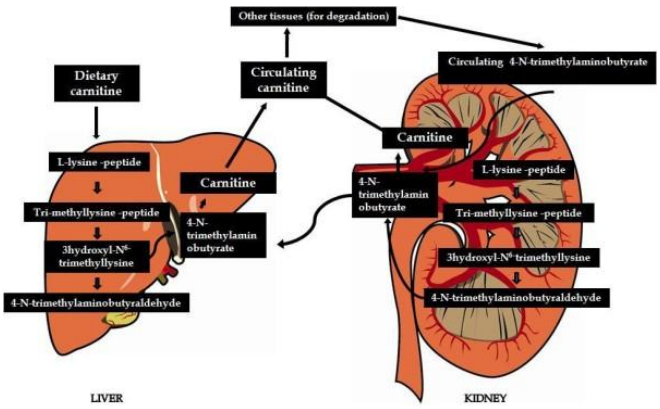

Figure 1: Biosynthesis of carnitine [15].

Degradation

99% of carnitine is intracellular. Liver is the major site for release of carnitine into circulation. Humans cannot degrade carnitine. It is excreted in the urine in free form and also acyl-carnitine. Kidneys reabsorb carnitine with high efficiency, and play a crucial role in whole-body homeostasis. They are responsible for the retention of the whole-body carnitine pool [16, 17].

Functions:

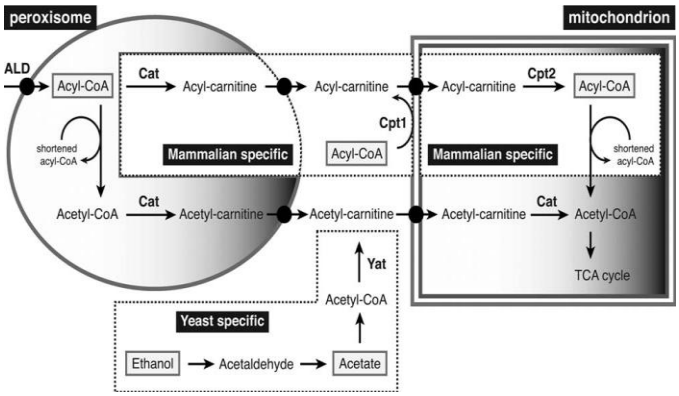

Figure 2: Function of carnitine in intracellular transport of acyl- and acetyl-CoA. Yeast and mammalian specific pathways are depicted in dashed boxes [18].

LC essentially plays a key role in the mitochondrial β-oxidation of long chain free fatty acids, providing a shuttle system for free fatty acids and derivatives of acyl-CoA within the mitochondria. During this passage through the cell membrane, acyl groups are temporarily transferred to LC, producing ALC. In a similar way, carnitine facilitates the transport of Acetyl groups via ALC (Figure 2). This is modulation of mitochondrial conc. of CoA implicated in various metabolic ways such as the Tricarboxylic acid cycle (Krebs cycle) [18].

During growth on the carbon sources of fatty acids, acetyl units are produced in the cytosol and are to be transported to the mitochondria(TCA cycle) and into the peroxisomal or cytosol (glyoxylate cycle) [19-21].

In addition to its metabolic role, LC and its esters such as acetyl-L-carnitine (ALC) posses' unique neuroprotective, neuromodulatory and neurotrophic properties and plays an important role in counteracting various disease [22].

Assays

In DTNB method, the sulfhydryl groups of the liberated free CoA further react with 5,5'-dithiobis-2-nitro benzoic acid (DTNB) producing a thiophenolate ion which absorbs at 412 nm. This spectrophotometric method, developed for rat tissues, needs blank tissue to compensate for sulfhydryl groups present in biological tissues and vastly improved specificity and sensitivity for carnitine [23].

$$\text{Carnitine + acetyl CoA} \xleftrightarrow{\text{Carnitine acetyl transferase}} \text{acetyl carnitine +CoASH}$$

$$\text{CoASH + DTNB} \longrightarrow \text{TNB (412nm) + CoAS-SNB}$$

A radioactive method is based upon a similar reaction with ^{14}C-acetyl-CoA and its conversion into ^{14}C-acetyl carnitine, which is purified on a column. The –SH group of the CoASH formed is oxidized by N-ethyl maleimide [24].

Carnitine dehydrogenase method is a spectrophotometric method. Free carnitine is measured with purified bacterial carnitine dehydrogenase and NAD^+. Acyl carnitine is hydrolyzed with bacterial acyl carnitine hydrolases before the determination of total carnitine [25].

Tandem mass spectrometric method to measures carnitine and individual acyl carnitine species. It is developed for diagnostic screening purposes; the occurrence of acyl carnitine species in urine or blood is highly suggestive of inborn errors and is in addition to the GC-MS screening for the organic acidurias [26, 27].

Role in Disorder:

Carnitine deficiency represents a heterogeneous group of diseases with widely varying clinical symptoms. Based on the etiologies carnitine deficiencies can be classified as primary and secondary.

Primary Carnitine Deficiency

Primary carnitine deficiency (PCD) is a rare genetic, autosomal recessive disorder of fatty acid oxidation caused by deficiency of plasma membrane carnitine resulting from impairment in the plasma membrane transporter (OCTN2 carnitine transporter), occurs in most commonly manifests between ages 1 to 7 [28, 29]. This deficiency diminished tissue uptake, leading to decreased accumulation in the muscles (heart and skeletal) and potentiates increased renal loss leading to systemic carnitine depletion [30- 34]. Due to defective renal absorption (free) carnitine is excreted in the urine of patients with primary deficiency and can result in tissue carnitine levels drop ping to below 10% of normal [35]. Mainly three organs are affected by PCD: cardiac muscle which leads to progressive cardiomyopathy; central nervous system which is affected by encephalopathy, and skeletal muscle which is affected by myopathy [36, 37].

Secondary Carnitine deficiency (SCD)

Secondary deficiency is characterized by increased carnitine excretion in urine in the form of acyl-carnitine due to an accumulation of organic acids [38]. SCD is less severe, occurs due to association with other disorders such as liver or kidney disease and defects in fatty acid metabolism. SCD is seen in patients with renal tubular disorders, in which there may be excessive excretion of carnitine [39-42] and also in fanconi syndrome, hemodialysis, peritoneal dialysis and increased excretion of acyl carnitine with certain drugs [43,44].

Role in other diseases:

In cardiovascular disease, heart is one of the organs most affected by catalyzing the exchange of carnitine - acyl carnitine; is the major source of energy (β-oxidation of FAs) for the heart [45]. LC has been shown to have favorable effects in patients with severe cardiovascular disorders such as Cardiomyopathy, cardiac arrhythmia, cardiac insufficiency [46], coronary heart disease, heart failure and peripheral vascular disease [47,48], arise from carnitine-acyl carnitine carrier (CAC) deficiency. In ischemia, L-carnitine reduces myocardial injury mainly by improving carbohydrate metabolism and reducing free fatty acid levels [49]. L-carnitine supplementation also prevents ventricular enlargement and dysfunction [50].

In obesity, carnitine supplementation improves glucose tolerance and total energy expenditure [51]. Carnitine palmitoyl transferase (CPT)-1 is the rate- limiting step of the fatty acid oxidation pathway and a target for the treatment of obesity. Modulation of CPT-1 may affect energy metabolism and food intake [52, 53].

Early research in Type 2 Diabetes suggests that supplementation with L-carnitine intravenously improves insulin sensitivity by decreasing fat levels in muscle and lower glucose levels in the blood by increasing its oxidation in the cells [54]. A recent analysis, either Type 1 or Type 2 Diabetes found that treatment with acetyl-L-carnitine (3 grams/day orally) for one year provided significant relief of nerve pain and improved vibration perception in those with diabetic neuropathy [55]. The treatment was most effective in subjects with Type 2 Diabetes of short duration [56, 57].

Hyperthyroidism patients exhibit higher urinary carnitine concentrations compared with hypothyroid patients [58].
L-acyl-carnitine has been suggested in liver disorders, as a potent, low-cost, and safe alternative therapy for patients with cirrhosis [59] & minimal hepatic encephalopathy (MHE) [60, 61].

Kidney disorders leading to decreased carnitine clearance and resulting in elevated plasma levels [62]. Uremic patients have elevated levels of AC, FC and total carnitine [63], due to accumulation of metabolic intermediates, impaired carnitine biosynthesis, reduced protein intake [64, 65]. Supplementation of LC leads to improvement in several complications of uremic patients through normalizing the reduced carnitine palmitoyl transferase activity in red cells [66, 67].

The metabolic process in sepsis, carnitine levels are reduced in patients suffering from Gram-Negative sepsis and urinary loss of carnitine is proportional to the degree of injury. There has even been suggestion that maintenance of normal carnitine levels reduces complications seen in sepsis [69-72]. A study suggests supplementation of micro nutrients including carnitine aid wound healing in Diabetics and in burns [73, 75].

In malnutrition conditions like Kwashiorkor and Marasmus (PEM) carnitine is low but reaches normal levels following protein repletion. There is a positive correlation between albumin and plasma carnitine levels in PEM [76- 78].

In Alzheimer's disease (AD) and dementia, several studies indicate that Acetyl-L-carnitine (ALC) has several neurobiological properties that promotes synthesis and release of acetylcholine (ACh) & modulation of brain energy metabolism, synaptic transmission and neurotrophic factors [79]. All investigators noted some improvement in cognitive function and positive effects of neuropsychological parameters in elderly patients with dementia subsequent to the administration of acetyl-L-carnitine [80]. Use of nutritional antioxidants such as carnitine/acetyl-L-carnitine has been advocated to counteract the oxidative stress- induced brain damage in AD [81, 82]. Colluci and colleagues used an in vitro model to suggest that carnitine supplementation in the elderly may stimulate osteoblast activity and decrease age-related bone loss [83, 84].

Dry eye and retinal disorders, Use of carnitine (compatible solute) in artificial tears has demonstrated rapid and consistent improvements in signs and symptoms in patients with dry eye [85] suggesting an intrinsic homeostatic role for carnitine in the eye [86, 87]. Under hyper osmolar conditions, LC was found to protect against stress activation of corneal epithelial cells [88, 89].

Fatigue resulting from chemotherapy, radiation treatment, and poor nutritional status is common in cancer patients [90]. In one study, treatment with carnitine supplements (4 gm/day for one week) ameliorated fatigue in most chemotherapy-treated subjects and restored normal blood levels of carnitine [91]. In another trial, terminal cancer patients supplemented with carnitine (doses ranged from 250 mg to 3 gm/day) experienced less fatigue and improved mood and quality of sleep [92].

HIV-infected individuals preliminary research suggests that supplementation with carnitine both intravenously and orally (at doses of 2–6 gm/day for weeks or months) in HIV-infected individuals may slow the death of lymphocytes (which in turn may slow HIV progression), reduce neuropathy [93- 95], and favorably affect blood lipid levels [96-99].

In male infertility, LC and ALC are highly concentrated in the epididymis and play a crucial role in sperm formation, maturation and the metabolic processes as an energy source following ejaculation [100] and protect spermatozoa from oxidative damage [101]. Some studies demonstrated low conc. of LC seen in azoospermia [102]. Carnitine acetyl transferase useful marker enzyme for germ cell differentiation in the testis & epididymis [103-104].

CONCLUSION

Carnitine is essential vehicle for carrying activated fatty acids and activated acetate, across the inner mitochondrial membrane. Even though its importance is established half a century back, it has come to lime light in recent 30years. L- Carnitine essentially plays a key role in the mitochondrial β-oxidation of long chain free fatty acids, removal of excess acyl groups and peroxisomal fatty acid oxidation. Acyl CoA and CoA ratio works as buffer. It also has role in cardiovascular, renal, liver diseases, Type 2 Diabetes, Alzheimer's diseases, Dementia, HIV infected persons, burns and wound healing [105].

The nature of the potentially important regulatory mechanism is still unknown and represents a challenge for further research. The purpose of L-carnitine review is useful for complete understanding of its role in human health, diseases and highlights the major areas of research in this field. There is still a great deal to be revealed.

ABBREVIATIONS

PCD: Primary carnitine deficiency, SCD: Secondary carnitine deficiencies, Ach: Acetylcholine, AD: Alzheimer's disease. PEM: Protein-energy malnutrition. Cat: carnitine acetyl-transferase, Cpt: carnitine palmitoyl transferase, TCA cycle: tricarboxylic acid cycle, Yat: yeast carnitine acetyl-transferase.

Authors' Statements

Competing Interests:

No conflict of interest.

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