

Carnipure™ Focus

Metabolic function

Lonza

Introduction

The history of L-Carnitine starts in the year 1905 when L-Carnitine was discovered in muscle extracts by Russian scientists. Since then extensive research has been conducted on biosynthesis, biological function, and metabolism of this nutrient^{1, 2}. Most of the L-Carnitine benefits have their origin in the energy metabolism and can be related to one or more of the three main functions: Transport of long-chain fatty acids into the mitochondria, availability of free Coenzyme A, and detoxification function. Today it is well known that L-Carnitine plays a crucial role in exercise performance and recovery, cardiovascular and brain health, weight management as well as infant nutrition. The scientific evidence is the reason why Carnipure™ is widely available in dietary supplements and in functional food products today.

What is Carnipure™?

Carnipure™ is a special grade of L-Carnitine, manufactured by the Swiss life-science company Lonza. Thanks to a unique production process based on fermentation, Lonza is the only L-Carnitine manufacturer capable of producing L-Carnitine in the same way as nature. Products carrying the Carnipure™ quality seal on the packaging show the consumer that they contain pure Lonza L-Carnitine.



Carnipure™ offers purest L-Carnitine and is a trademark of Lonza Ltd, Switzerland.

What is Carnitine?

Chemically, L-Carnitine, (γ -trimethylamino-hydroxybutyric acid), is a low-molecular-weight polar molecule and a quaternary amine. It is important to know that only the L-isomer of Carnitine is biologically active. This L-Carnitine form is present in nature and in human bodies. The optical isomer D-Carnitine does not exist in nature and is harmful to the human body because it inhibits the utilisation of L-Carnitine³⁻⁶.

L-Carnitine is naturally occurring in all mammalian species and is found in almost all cells⁷. The human pool of L-Carnitine is around 20 g with 98% of this being within cardiac and skeletal muscle pool⁸⁻¹⁰. L-Carnitine in the body is derived both from endogenous biosynthesis and from dietary intake.

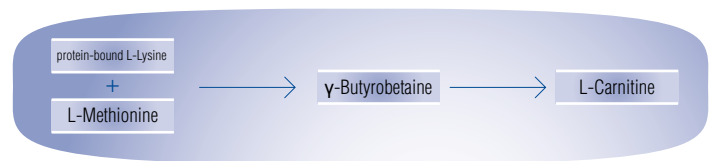


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Endogenous biosynthesis

Humans are able to synthesize L-Carnitine from the two essential amino acids lysine and methionine in a multi-step process. For this endogenous biosynthesis specifically, protein bound lysine is required which arises from turnover of muscle proteins. In addition to these amino acids a sufficient supply of vitamin C, B₃, B₆ and iron are mandatory for the L-Carnitine synthesis¹¹.

In humans, this complex synthesis of L-Carnitine can occur up to the precursor γ -Butyrobetaine in practically all tissues of the body. The last step of the L-Carnitine production occurs almost exclusively in the liver, kidney and brain¹². The endogenous synthesis of L-Carnitine is estimated to be approximately 10–20 mg per day in omnivores who have regular meat consumption⁸.



Uptake with the diet

L-Carnitine is generally available in food products of animal origin. So, products like meat, fish, poultry, and dairy products are the best sources¹³. In general, the redder the meat, the higher its L-Carnitine content. Fruits and vegetables in contrast contain only trace amounts of this substance¹⁴. The average non-vegetarian diet provides about 100 to 300 mg L-Carnitine daily^{15, 16}. However, as many people try to reduce their meat intake, the dietary intake of L-Carnitine has also decreased considerably¹⁷.

L-Carnitine absorption in the gut

In the small intestine the main uptake of L-Carnitine is likely to involve a combination of active transport and passive diffusion^{7, 18, 19}. In the large intestine the L-Carnitine uptake appears to be restricted to a passive component only^{20, 21}. These are the results of a variety of scientific test systems including amongst others animal intestinal preparations, and human intestinal epithelial cell lines^{20, 22–25}.

The absorption of L-Carnitine in the gut is characterized by slow mucosal uptake, prolonged mucosal retention and slow mucosal exit into the blood. Therefore, in humans the time to achieve maximum plasma concentrations after oral administration of L-Carnitine can be up to 4–6h which needs to be considered in case of supplementation^{19, 26–28}. Hence it might be advisable to split the daily dosage of Carnipure™ into several smaller portions.

Homeostasis and excretion

Generally, the L-Carnitine homeostasis in humans is maintained by dietary intake, a modest rate of L-Carnitine biosynthesis and an efficient conservation of L-Carnitine by the kidney.

The intracellular homeostasis of L-Carnitine is controlled by different membrane transporters which manage the entry of L-Carnitine in the cell and therefore in most of the tissues. Most of this transport is facilitated by so called sodium dependent organic cation transporter (OCTN2). This OCTN2 transport protein exists in higher concentrations in kidney, skeletal muscle, heart, placenta, pancreas, and testis and is only weakly represented in liver, lung, and brain^{22, 29}.

The excretion of L-Carnitine through the kidneys contributes considerably to the regulation of the L-Carnitine plasma level. This process is also controlled through OCTN2 proteins. The renal reabsorption is highly efficient when the plasma L-Carnitine concentration is low³⁰. The body probably has a higher tendency to excrete acyl-L-Carnitine than free L-Carnitine. This has been shown for example during exercise³¹. The L-Carnitine plasma level is normally higher in males than in females and decreases in both genders with age³².

L-Carnitine can be considered as a conditionally essential nutrient and therefore under certain circumstances an L-Carnitine deficiency can occur. There exist two types of L-Carnitine deficiencies. In both, an increased dietary intake and supplementation with Carnipure™ can be beneficial.

Primary L-Carnitine deficiency is a genetic disorder characterized by low serum and intracellular concentrations of L-Carnitine. It is caused by mutations in the sodium-dependent organic cation transporter (OCTN2) and manifests often in the first five years of life with symptoms such as for skeletal-muscle weakness or cardiomyopathy^{33, 34}.

Secondary L-Carnitine deficiency is more common than the primary deficiency and can occur under particular conditions: e.g. use of certain drugs or during pregnancy. This kind of L-Carnitine deficiency is also largely related to disorders in fatty acid metabolism^{35, 46}.

Physiological roles of L-Carnitine

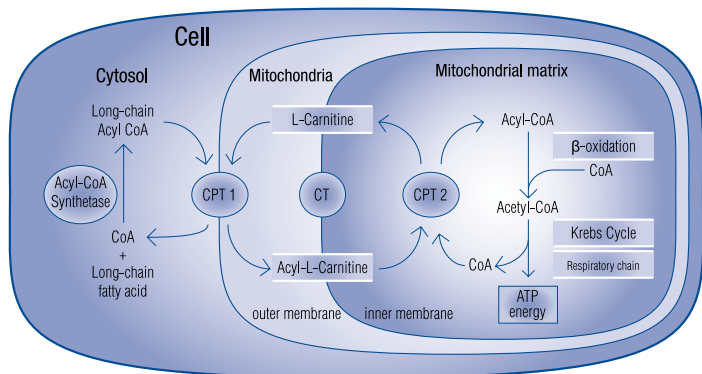
Transport of long-chain fatty acids into the mitochondria

L-Carnitine shuttles long-chain fatty acids across the inner-mitochondrial membrane, so they can be broken down into two carbon chains (acetyl) within a process referred to as β -oxidation. Ultimately these two carbon chains are used for the generation of energy (ATP).

Before this process can start, fatty acids from the diet or from adipose tissue have to reach the cells via circulation. Then they have to be taken up into the cytosol (internal fluid) of the cell. The mitochondria are organelles of a cell which have two membranes separated by a space. The centre of the mitochondria is called the matrix. This is the place where the fatty acids are broken down for energy production.

The transport of the long-chain fatty acids from the cytosol of the cell into the matrix of the mitochondria starts with the activation of the fatty acids on the mitochondrial outer membrane through the enzyme Acyl-CoA-Synthetase to long-chain acyl-CoA compounds. This makes them able to cross the outer mitochondrial membrane.

In order to cross the inner mitochondrial membrane and to reach the matrix, these activated fatty acids are dependent on L-Carnitine. In this context, L-Carnitine can be considered as a shuttle bus for the acyl-CoA compounds. The activated fatty acids bind to L-Carnitine in a form of acyl-L-Carnitine for transport. After reaching the matrix acyl-L-Carnitine has to be reconverted to acyl-CoA compounds which results in the release of free L-Carnitine. The whole process consists of several steps in which three enzymes are involved: Carnitine-palmitoyltransferase 1 (CPT 1), Carnitine-acyl translocase (CT) and Carnitine-palmitoyltransferase 2 (CPT 2)³⁶. Finally, the reactivated acyl-CoA compounds that are located in the matrix of the mitochondria are transformed into energy through multiple cycles of the β -oxidation^{37, 38}.



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This theoretical explanation about the pathway of long-chain fatty acids in the mitochondrial matrix for energy production is the background for the practical applicability of Carnipure™ in everyday life. In two human intervention trials the authors concluded that Carnipure™ is important to all people who exercise, who undergo a weight management program or have a high energy demand:

The first of these two studies was conducted at the University of Leipzig, Germany in 2002. This research group demonstrated that oral Carnipure™ supplementation stimulates *in vivo* long chain fatty acid metabolism in healthy adults without L-Carnitine deficiency³⁹.

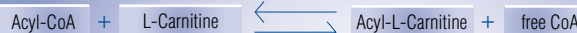
In 2004, these initial findings were confirmed by a research group at the University of Rostock, Germany⁴⁰. The authors used a modified approach by using slightly overweight adults. They received 1.5 g Carnipure™ tartrate daily (equivalent to 3 x 1 g L-Carnitine per day) as an oral supplement. Prior to, and after ten days of Carnipure™ supplementation, the subjects received labelled fatty acids with a meal. Labelled CO₂ as the breakdown product of the labelled fatty acids was then measured in the exhaled air. The Carnipure™ supplementation led to a significant increase in fatty acid oxidation rates (15.8% vs 19.3%) as measured by the percentage of cumulative labelled CO₂ exhalation.

Availability of free Coenzyme A

L-Carnitine helps to maintain an optimal intramitochondrial acetyl-Coenzyme A / free Coenzyme A (CoA) ratio. Inside the mitochondria the energy generation can only continue if there is sufficient free CoA available due to the fact that free CoA is a required cofactor in many cellular reactions^{41, 42}.

The energy required by an organism is produced by metabolizing lipids, carbohydrates and proteins. During these metabolic processes acetyl-CoA eventually emerges which is an important metabolic intermediate. L-Carnitine is released in the mitochondrial matrix after the import of acyl-L-Carnitine and the further reaction of the acyl group to free CoA. Now, L-Carnitine can either exit the mitochondria via the Carnitine-acyl-transferase, or it may be used as a reservoir for excess acetyl residues. In this reaction L-Carnitine

takes over the acetyl group from acetyl-CoA. Thus, the free CoA can participate in other cellular reactions. Based on this fact, L-Carnitine can be regarded as an acetyl buffer or an intermediate depot of acetyl groups^{36, 43, 44}. Therefore, this function of L-Carnitine is often called a buffer function.



Detoxification function

L-Carnitine supports the elimination of certain harmful substances which the body is not able to excrete on its own. Heavy exercise, for example, leads to an excretion of metabolic waste products via ester formation with L-Carnitine. High performance athletes usually have a higher L-Carnitine excretion as acyl-L-Carnitine in urine after exercise³¹. In this case, L-Carnitine acts as a sink for these acyl groups transporting them out of the tissue by excretion via the kidney.

The same happens during a long-term treatment with certain xenobiotic acids (prodrugs) such as pivalic acid. This leads to an accumulation of poorly-metabolizable acyl-CoAs³⁶. Over 90% of the administered pivalic acid is eliminated from the body in the form of pivalonylcarnitine^{45, 46}. An increased loss of L-Carnitine for a prolonged period decreases the plasma and tissue levels of L-Carnitine in the body and can lead to a secondary L-Carnitine deficiency⁴⁷.

And so to conclude

L-Carnitine has an important impact on different cellular biochemical reactions in the body. Its primary function is to facilitate the transport of fatty acids across the inner mitochondrial membrane, making them available for the mitochondrial β -oxidation. The enormous interest in Carnipure™ is also based on the other scientifically proven functions in the intermediate cellular metabolism. Therefore Carnipure™ is able to contribute to different health areas in daily life like for example sports performance and recovery, weight management, cardiovascular and brain health.

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Note: This document is an overview of published scientific information on L-Carnitine and published scientific information on clinical and nutritional trials with L-Carnitine and its derivatives. No claims are made herein for any particular consumer product, nor can these statements be used on such consumer products. The recommended use for Carnipure™ is as a nutrient or dietary supplement.

The statements in this document have not been evaluated by any Food and Drug Administration. Lonza's Carnipure™ is not intended to diagnose, treat, cure or prevent any disease.

No statement is intended or should be construed as a recommendation to infringe any existing patent. The information contained herein is believed to be correct and corresponds to the latest state of scientific and technical knowledge.



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