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L-Carnipure® in Human Nutrition

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Abstract: L-Carnitine (β-hydroxy-γ-trimethylaminobutyric acid) plays a crucial role in fat and carbohydrate metabolism and is required for the proper functioning of heart and muscle. In 1905, L-carnitine was isolated for the first time from muscle tissue and its structure was established in 1927. L-Carnitine was shown to be an essential nutrient for a meal worm (*Tenebrio molitor*) and was therefore called vitamin B_T.
In the search for the perfect physique, consumers are discovering the health benefits of L-carnitine. Studies show that L-carnitine supplements not only help with weight management programs, but also optimize performance during exercise, delay the onset of fatigue and improve the recovery process. Extensive clinical data indicate that supplemental L-carnitine can positively support cardiovascular health, while other studies show beneficial effects for pregnant women, elderly people or people who follow a vegetarian or meat-reduced diet and thus miss out on natural L-carnitine in the diet. L-Carnipure® is a special grade of L-carnitine, manufactured by the Swiss life sciences company Lonza. Thanks to a unique natural fermentation process with an integrated biotransformation step, Lonza is the only L-carnitine manufacturer capable of supplying pure L-carnitine without any unnatural D-isomer, hence the brand name and sign of quality assurance, L-carnipure®.

Keywords: L-Carnipure® · L-Carnitine · Fatty acid oxidation · Fermentation · Health ingredients

Introduction

The growth in sectors such as functional food clearly shows that the consumer's demand for a healthy diet is increasing. A healthy lifestyle and feelgood food are today recognised as priorities in most people's lives.

The vast majority of the health-ingredients used in functional food are of plant origin. But there are some exceptions to this, one being L-carnitine (β-hydroxy-γ-trimethylaminobutyric acid), an active component discovered in meat extract in 1905. After its chemical structure had been established in 1927 (Fig. 1) [1], Prof. Strack from the University of Leipzig in Germany published his first article about L-carnitine in 1935 [2] and initiated decades of investigations into the physiological functions of this substance.

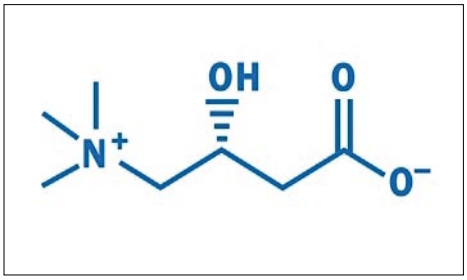

Fig. 1. Chemical structure of L-carnitine (β-hydroxy-γ-trimethylaminobutyric acid)

By the 1960s the essential role of L-carnitine in utilisation of long-chain fatty acids for energy was confirmed [3], and the latest research has found that L-carnitine can actually increase fatty acid oxidation in healthy adults. Numerous clinical studies have reported upon the beneficial effects of L-carnitine supplementation, and the number of publications per year on this substance still is increasing (Fig. 2).

L-Carnitine functions in the transport of activated fatty acids over the mitochondrial

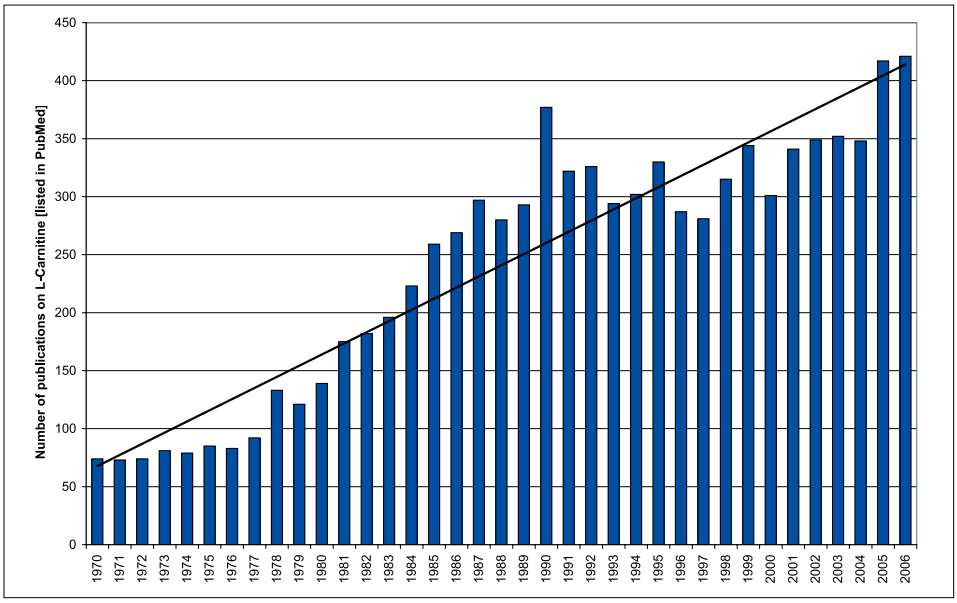

Fig. 2. Number of publications on L-carnitine listed in PubMed

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inner membrane in eukaryotes. Its presence is indispensable for the β-oxidation of long-chain fatty acids by mitochondria. Thus it has key functions in substrate flux and energy production [4]. In animals and man, L-carnitine is synthesized mainly in the liver from where it is transported into muscle tissue [5]. In addition, it can be taken up from food, with products of animal origin containing the highest concentration of L-carnitine, plant products containing only trace amounts [6]. L-Carnitine in the body is always a mixture from both sources. Since the synthesis of L-carnitine in the body requires the essential amino acids lysine and methionine as well as the micronutrients iron, vitamin C, B_6 and niacin, a too low intake in one of these nutrients will lead to a diminished L-carnitine synthesis and consequently to muscle fatigue [7]. Therefore, an incomplete diet, physiological stress situations and also some clinical cases can create a need for external L-carnitine supplementation in the form of functional food or dietary supplements [8].

What is L-Carnipure®?

L-Carnipure® is an ingredient brand of Lonza, indicating a special quality of L-carnitine which is produced *via* a biotechnological production process that imitates the endogenous synthesis of L-carnitine in our body.

L-Carnipure® has a host of applications, ranging from approved pharmaceutical indications and nutritional supplementation to animal feed formulations. In contrast, D-carnitine, as pure substance or in the form of racemic D,L-carnitine, has been found to be not only physiologically inactive but also inhibits the uptake and functions of the natural isomer L-carnitine [9–11], which can then lead to a functionally relevant depletion of L-carnitine in skeletal and cardiac muscle [12]. Serious side effects to animal as well as human health have been observed with applications of racemic D,L-carnitine [13–19]. Results of experimentation with racemic D,L-carnitine, and subsequently also with the pure isomers D-carnitine and L-carnitine have been reviewed by Borum and Fisher [8] and also by Meier [20]. The US FDA has long maintained that D-carnitine and D,L-carnitine are not generally recognized as safe and are, therefore, illegal food additives.

Lonza has been supplying L-Carnipure® products to the dietary supplement, pharmaceutical and infant formula industries globally for many years. More recently, an increasing number and variety of functional food products such as dairy, bakery, confectionary and beverages supplemented with L-Carnipure® have entered the market. The L-Carnipure® brand name and logo are registered trademarks and used on product labels, to indicate the highest Lonza quality.

Contribution to the Quality of Life

Extensive clinical research has discovered that L-carnitine has a beneficial role to play in a broad array of applications.

Studies in athletes have shown that L-Carnipure® supplementation may foster exercise performance [21]. Both an increase in maximal oxygen consumption and a lowering of the respiratory quotient indicate that L-carnitine has the potential to stimulate lipid metabolism. Supplementation with L-carnitine prior to high intensity exercise is significantly effective in assisting recovery. Volek *et al*. [22] observed a decrease in the production of free radicals, less tissue damage and reduced muscle soreness after exercise and a better utilization of fat as an energy source during recovery.

Studies also indicate that L-carnitine is useful as part of a weight management program when combined with exercise and calorie restriction [23–25]. In 2002, researchers from the University of Leipzig, Germany, were the first to conclusively show that oral L-Carnipure® supplementation stimulates *in vivo* long-chain fatty acid metabolism in healthy adults without L-carnitine deficiency [26]. Prior to, and after ten days of L-Carnipure® supplementation, the subjects received labelled fatty acids with a meal. Labelled CO_2 as the breakdown product of the labelled fatty acids was then measured in the exhalation air. A significant increase in exhalation of labelled CO_2 was observed, indicating a significant increase in fatty acid oxidation in healthy adults following L-Carnipure® supplementation. In 2004, these initial findings were confirmed by another research group at the University of Rostock, Germany [27]. Set up to verify the results of the first study by using a modified approach in slightly overweight adults, oral supplementation with L-Carnipure® tartrate was found to significantly increase long-chain fatty acid oxidation. The researchers concluded that these studies are important to all people who exercise, those undergoing a weight management program and those who have a high energy demand.

Further, it is widely accepted that L-carnitine has significant cardioprotective properties. L-Carnitine supplements have a favourable effect on blood lipid levels, and have demonstrated to be helpful for people with angina, arrhythmias and heart failure [28–30].

L-Carnitine is considered to be an essential nutrient for infants because, unlike adults, infants are unable to synthesize sufficient L-carnitine in their bodies to meet their requirements [31]. L-Carnitine is present in breast milk and for many years now, manufacturers of soy-based infant formula have been fortifying their products with L-Carnipure®, which would otherwise be devoid of this conditionally essential nutrient [32].

As the intake of dietary L-carnitine is directly linked to meat intake, and meat is the richest source of this nutrient, vegetarians and anybody who reduces his meat intake gets very little L-carnitine with the diet. If L-carnitine intake is low, however, the body has to rely almost entirely on endogenous synthesis to meet the needs. A vegetarian diet, however, is frequently also low in some of the nutrients that are essential for L-carnitine biosynthesis in the body [33]. Indeed, humans following a lacto-ovo or a strict vegetarian diet over years have been shown to have decreased plasma L-carnitine concentrations and may benefit from supplementary L-Carnipure® [34].

With a twofold increase in the world's elderly predicted between 1998 and 2025, it is not surprising that the market for anti-aging foods and supplements will see increased levels of activity and opportunity for manufacturers. Various studies in elderly subjects show improved mental status and learning ability, improved immune function or an increase in muscle mass after supplementation with L-carnitine [35–37]. Thus, L-carnitine can be regarded as the ideal nutrient for a long life, as it comprises all the benefits that seniors need to stay fit and healthy in both mind and body.

Manufacturing Principles

Although L-carnitine was originally discovered in meat extract, the vast majority of L-carnitine on the market to date comes from synthesis rather than from extraction from meat. For many years, the only available large-scale production process of L-carnitine consisted of L-carnitine separation from the racemic mixture of synthetically produced D,L-carnitine. This situation changed when Lonza described the synthesis of enantiomerically pure L-carnitine from an optically inactive precursor molecule based on fermentation, using a biotransformation step for stereoselective introduction of the optical centre [38].

Lonza researchers were successful in removing the enzyme carnitine dehydrogenase from the organism by mutagenesis. The resulting strain of *Rhizobia* imitates L-carnitine synthesis in the liver of mammals using the same enzyme 4-butyrobetaine hydroxylase (Fig. 3). This enzyme adds a chiral hydroxyl group to the natural L-carnitine precursor 4-butyrobetaine to directly and selectively form L-carnitine, which is excreted into the medium in stoichiometric amounts. Only growing cells produce L-carnitine, but very slow growth seems to

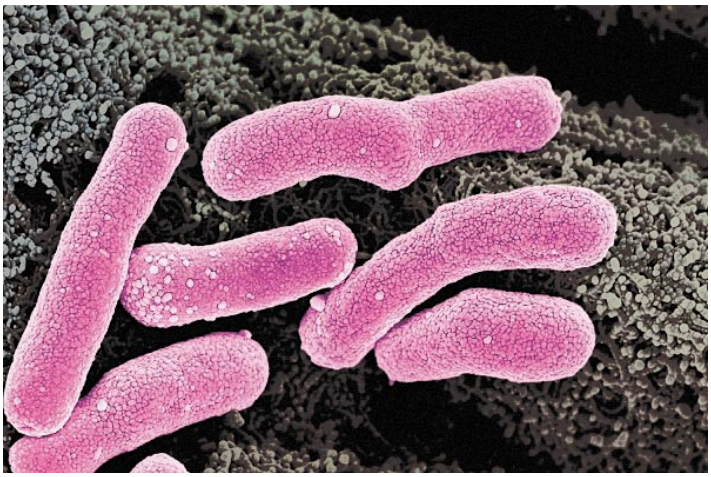

Fig. 3. Photograph of the L-carnitine production strain, a bacterium isolated from soil samples. The production strain is a natural soil isolate and not genetically modified. It is taxonomically related to *Agrobacterium* and *Rhizobium*. The strain was assumed to belong to a new, as yet unidentified genus. The bacterium is a non-sporulating, Gram negative and motile microorganism, which metabolises substrates aerobically (chemoorganotrophs).

be sufficient. The 4-butyrobetaine is almost completely converted into L-carnitine [39]. The natural and biological L-Carnipure® process does neither involve genetically modified organisms nor any products of animal origin.

Lonza produces all of its L-Carnipure® products in fermenters of 15–75 m^3 size in compliance with current Good Manufacturing Practices (cGMP) guidelines for Bulk Active Ingredients using state-of-the-art, ISO 9002 certified production facilities. Lonza's plants have been inspected and approved for the production of pharmaceuticals by the United States Food and Drug Administration (FDA) and national authorities. Lonza's L-Carnipure® crystalline meets the requirements of the United States Pharmacopoeia (USP) and the Food Chemical Codex (FCC). Both L-Carnipure® crystalline and L-Carnipure® tartrate are HACCP certified and manufactured according to OU-kosher principles. Because L-Carnipure® does not contain any D-carnitine, it is Generally Recognized As Safe (GRAS) in the USA.

Summary

The growing interest in L-Carnipure® can be attributed to a number of factors including its basic function in helping convert fat into energy, its efficacy, its excellent safety profile and, of course, its suitability for processing.

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