Review Article

Effects of L-carnitine on obesity, diabetes, and as an ergogenic aid

Youn-Soo Cha PhD

Department of Food Science & Human Nutrition and Obesity Research Center, Chonbuk National University, Jeonju, Jeonbuk, Korea

Data on the functionalities of L-carnitine on obesity, diabetes, and as an ergogenic aid are summarized as follows: Obesity: Total lipid, triglyceride, and total protein increased during the 3T3-L1 cell differentiation. However, nonesterified carnitine (NEC), acid-soluble acylcarnitine (ASAC), and acid-insoluble acylcarnitine (AIAC) concentrations were lower in the differentiated 3T3-L1 cells. In addition, the exogenously added carnitine inhibited the increases in triglyceride and total lipid levels. In an animal study, L-carnitine supplementation reduced serum leptin and abdominal fat weight caused by high-fat diet in C57BL/6J mice. Diabetes: In an animal study, streptozptpcin-induced diabetic rats had markedly lower IGFBP-3 than normal rats, and IGFBP-3 was increased by L-carnitine treatment, demonstrating that L-carnitine treatment of diabetic rats modulates the IGFs/IGFBPs axis. A study of Korean diabetics indicated that there is a remarkable abnormality in lipid and carnitine metabolism in Korean diabetic patients. Ergogenic aids: We investigated the separate and combined effects of L-carnitine and antioxidant supplemenation on carnitine and lipid concentrations in trained and non-trained animal and humans. Supplementation of L-carnitine and antioxidants improve lipid profiles and exercise ability in exercise-trained rats. Also, both exercise training and supplementation of carnitine and antioxidants improved lipid profiles and carnitine metabolism in humans, suggesting that carnitine and antioxidant supplementation may improve exercise performance.

Key Words: L-carnitine, obesity, diabetes, ergogenic aids, animal, human

INTRODUCTION

Carnitine, is a quaternary amine (β-hydroxy-γ-N-trimethy-ammonium butyric acid-M.W. 161.2), and is known as a vitamin like and amino acid like substance.[1] Synthetic carnitine occurs as both D & L isomers; however, only L-carnitine is physiologically active. The main function of carnitine in the body is facilitation lipid oxidation by transporting long-chain fatty acids into the inner mitochondria region where they undergo β-oxidation.[2] In order for fatty-acids (from food intake or adipose tissue) to produce energy they must be changed into acylCoAs prior to β-oxidation; however, since acylCoAs can not cross cell walls, carnitine comes into place to help with the transportation through the mitochondrial wall.[3] Therefore, without carnitine, most of the dietary lipids cannot be used as an energy source and our body would accumulate fatty-acids resulting in obesity. In humans, carnitine is absorbed in the small intestinal mucosa by sodium-dependent active transport and by passive transpoet.[4] In blood, carnitine does not need protein for a carrier, and is present in the free or acylcarniitne form.[5]

Some previous studies have shown the effects of L-carnitine on obesity, blood glucose control and exercise or specific metabolites. However, they have yielded inconsistent results and the usefulness of carnitine as a functional food remains uncertain. Data from our laboratory on the functionalities of L-carnitine on obesity, diabetes, and as an ergogenic aid are discussed.

The effects of carnitine on obesity and fat metabolism

1) Carnitine Profiles During Differentiation and Effects of Carnitine on Differentiation of 3T3-L1 Cells.[6] To induce cell differentiation, undifferentiated 3T3-L1 cells were treated with dexamethasone, 1-methyl-3-isobutylxanthine, and d-biotin. Carnitine was also exogenously added to the cells to test its effect on cell differentiation. Triglyceride, total lipid, total protein, nonesterified carnitine, acid-soluble acylcarnitine, and acid-insoluble acylcarnitine were analyzed during the differentiation of 3T3-L1 cells. Total lipid, triglyceride, and total protein increased during the 3T3-L1 cell differentiation. However, nonesterified carnitine, acid-soluble acylcarnitine, and acid-insoluble acylcarnitine concentrations were lower in the differentiated 3T3-L1 cells. In addition, the exogenously added carnitine inhibited the increases in triglyceride and total lipid levels. These results suggest that carnitine may have an inhibitory role on the early stage of 3T3-L1 cell differentiation.

2) L-carnitine reduces obesity caused by high-fat diet in C57BL/6J mice.[7] The mice were fed a normal diet (ND), high-fat diet (HD), or carnitine-supplemented (0.5% of diet) high-fat diet (HDC) for 12 weeks.

Corresponding Author: Dr. Youn-Soo Cha, Dept. of Food Science and Human Nutrition, Chonbuk National University, 664-14 Duckjin-dong 1-ga, Jeonju, Jeonbuk, 561-756, South Korea.
Tel: + 82 63 270 3822; Fax: +82 63 270 3854
Email: cha8@chonbuk.ac.kr
Manuscript received 9 September 2007. Accepted 3 December 2007.

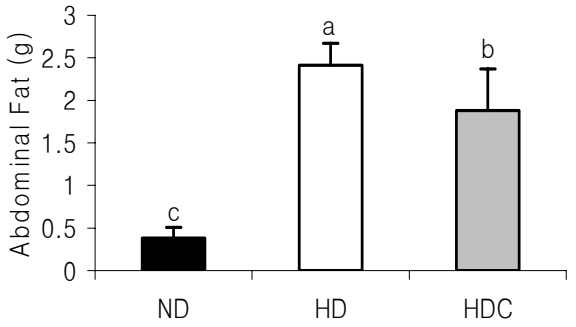

Figure 1. Abdominal fat weight of mice Mean±S.D of 6 mice per group. Bars with different letters are significantly different at $p<0.05$ by Duncan's multiple range test. ND, AIN-93 modified diet with 4% fat (10% fat calorie) content; HD, AIN-93 modified diet with 35% fat (60% fat calorie) content; HDC, 35% fat diet containing 0.5% L-carnitine.

The results showed that body weight, energy intake, and feed intake were lower in the HDC group than the control groups. As expected, in the current study a high-fat diet resulted in increased abdominal fat deposits, as well as serum leptin levels. However, the weight of white adipose tissue and serum leptin levels in the carnitine-supplemented group were notably lower (Fig. 1). Acid-soluble acylcarnitine (ASAC), acid-insoluble acylcarnitine (AIAC), and total carnitne (TCNE) in the serum and liver were significantly higher in the HDC group. Hepatic carnitine palmitoyl transferase-I (CPT-1) activity was significantly higher in the HDC group than the control groups. Acyl-coA synthetase (ACS) and CPT-I mRNA expression in the liver was highest in the HDC group, however hepatic acetyl-coA carboxylase (ACC) mRNA expression in this group was lowest. Serum leptin levels and abdominal fat weight were lowest in the HDC group. We concluded that L-carnitine supplementation diminished the risk of obesity caused by a high-fat diet.

3) Effect of Genistein with carnitine administration on lipid parameters and obesity in C57BL/6J mice fed a high-fat diet.[8] We investigated the effect of dietary genistein (the principal soy isoflavone) alone and combined with L-carnitine to evaluate possible synergistic effects on the intentionally induced pre-diabetic state characterized by insulin resistance and obesity in C57BL/6J mice fed a high-fat diet (HD). In the HD-alone group, abdominal and back fat relative to total body weight were significantly higher compared with other groups, including those fed normal diets (ND). Among the HD groups, final weight gains of the HD plus genistein (HD+G) and HD plus genistein plus L-carnitine (HD+G+C) groups were lower compared with that of the control (HD-alone). Especially in liver, the results showed that genistein with carnitine transcriptionally up-regulated expression of ACS and CPT-I by approximately 50% and 40%, respectively, compared with genistein alone. However, the up-regulation of CPT-I transcription was not directly reflected in the enzyme activity of CPT-I. Our study suggests that genistein with carnitine exerts anti-obesity effects, probably by modulating peroxisome proliferator-activated receptor-associated genes.

Carnitine effects on carbohydrate metabolism

L-carnitine improves lipid metabolism and insulin-like growth factors (IGFs) and IGF binding proteins in rat.[9, 10] Diabetes was induced in 24 of the rats by single intraperitoneal injection of STZ (50mg/kg b.w.). Each rat in the three L-carnitine-treated groups was injected subcutaneously with L-carnitine, 50 (D50), 100 (D100), or 200 (D200) mg/kg body weight every other day for four weeks, and animals in normal (N) and diabetic (DM) groups received saline by the same method. Diabetic rats had significantly lower carnitine concentrations in serum and liver compared with normal rats. Total carnitine concentrations were increased dose-dependently by carnitine treatment. Total IGF-I in serum from diabetic rats was increased dose-dependently by carnitine treatment, but was statistically significant only in the D200 group. The expression of liver IGF-I mRNA was lower in diabetic rats than in normal rats and increased by L-carnitine treatment. These results demonstrate that L-carnitine treatment of diabetic rats modulates the IGFs/IGFBPs axis. Especially note-worthy is that L-carnitine at a dose of 200 mg/kg/48 h for four weeks was able to restore serum total IGF-I in STZ-induced diabetic rats to nearly normal levels.

Plasma and urinary carnitine in Korean diabetic patients.[11] The study subjects included 108 Korean diabetic patients (64 males and 44 females) who were hospitalized in Chonbuk National University Hospital and 27 subjects were also hospitalized as non-diabetic controls (10 males and 17 females). Korean diabetic patients had significantly higher total cholesterol (187 vs. 237 mg/dL), triglyceride (179 vs. 257 mg.dL), LDL-cholesterol (168 vs. 237 mg/dL) in plasma than normal controls, but had significantly lower HDL-cholesterol (55.6 vs. 32.1mg/dL). Plasma NEC (57.7 vs. 38.0 nmol/ml) and TCNE (60.9 vs. 42.5 nmol/ml) concentrations were significantly lower in diabetics. Urinary NEC (131 vs. 415 nmol/ml) and TCNE (288 vs. 769 nmol/ml) concentrations were significantly higher in diabetics. The ratios of serum and urinary acylcarnitine/NEC were also significantly higher in diabetics than in controls. This study suggested that there was a remarkable abnormality in lipid and carnitine metabolism in Korean diabetic patients, and that further study on carnitine metabolism and the effects of carnitine supplementation in Korean diabetic patients are needed.

Carnitine as an ergogenic aid

1) Exercise-trained but not untrained rats maintain free carnitine reserves during acute exercise.[12] Sprague-Dawley rats(age 7weeks) were divided into two groups, one of which was exercised daily (60min/day, 10°incline, 25m/min) and one not exercised. At the end day of the study, the two groups were each divided into two subgroups, one of which was exercised (single exercise) and one that was not exercised before decapitation. Animals that were exercised daily (long-term trained, LT) had lower serum triacylglycerols and total cholesterol compared with untrained animals, but there was no difference in serum total lipids between the groups. Acute-exercised animals in the not exercised (non-trained, NT) group had higher liver triacylglycerol levels, but total lipids were higher in both groups following acute exercise. Serum acyl- and total carnitine was significantly higher in the trained animals, whether exercised or not, suggesting an exercise-induced increase in a renal threshold for

carnitine. Untranined rats had significantly higher acyl-carnitine in skeletal muscle and an acyl/free carnitine ratio of 0.63 compared with 0.31 in trained animals receiving an identical acute bout of exercise, demonstrating that untrained animals utilized a significantly higher percentage of free carnitine reserves during exercise. This study suggests that free carnitine reserves may be reduced during exercise in untrained rats, and effect that has the potential to impair both carbohydrate and fat metabolism during exercise.

2) Exercise training and supplementation with carnitine and antioxidants increases carnitine stores, triglyceride utilization, and endurance in exercising rats.[13] Thirty-two male SD rats, age 7 wk were divided into four groups according to exercise training and modified AIN-76 diets NTNS (non-trained non-supplemented), NTS (non-trained supplemented), LTNS (long-trained non-supplemented) and LTS (long-trained supplemented). The trained rats were run on a treadmill for 60 min per day (10^0 incline, 20 m/min for 8 wk). LTNS and LTS rats had significantly lower serum total lipid, triglyceride, total cholesterol and liver triglycerides, but had higher serum HDL-cholesterol. There were no changes in exercise endurance time by supplementation in untrained animals, however endurance times were longer in LTS animals than in LTNS (Fig. 2). The supplementation and training tended to increase CPT-I activities, although the differences were not statistically significant. Likewise, CPT-I mRNA levels were higher in both supplemented and exercise trained rats. These results suggest that supplementation of carnitine and antioxidants may improve lipid profiles and exercise ability in exercise-trained rats.

3) Effect of carnitine and antioxidant supplementation on carnitine and lipid profiles in trained and non-trained humans.[14] The volunteers were divided into four groups; PN (placebo-non exercised), SN (supplement-non exercised), PE (placebo-exercised) and SE (supplement-exercised). The exercised groups were run on a treadmill for 50 min per day at 75% VO2 max. The supplemented groups were fed carnitine (4g/day), vitamin C (1000mg/day), vitamin E (500 IU/day) and melatonin (0.1mg/kg b.w) for 6 weeks. SN, PE and SE groups had significantly lower serum total cholesterol and LDL-cholesterol, but had higher HDL-cholesterol levels than the PN group. Serum non-esterified (NEC) and acid-soluble acylcarnitine (ASAC) increased in the SN, PE and SE group. The SN and SE groups had significantly higher urinary excretion of NEC and acid-insoluble acylcarnitine (AIAC) than the PN and PE groups. CPT-1 mRNA expression in skeletal muscle, obtained by biopsy, was enhanced by both supplementation and exercise. These results suggest that both exercise training and supplementation of carnitine and antioxidants improve lipid profiles and carnitine metabolism in people, and suggests that carnitine and antioxidant supplementation may improve exercise performance.

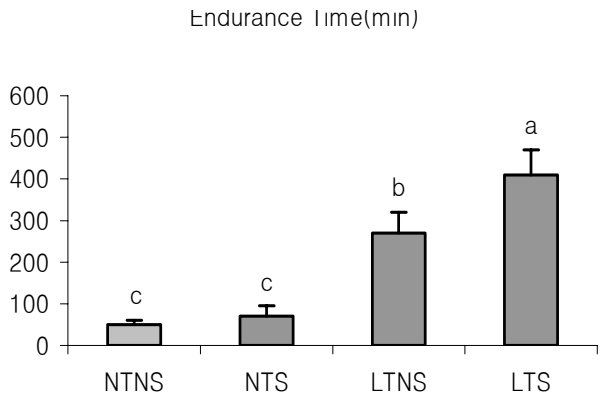

Figure 2. Endurance time (min). NTNS, non-trained non-supplemented; NTS, non-trained supplemented; LTNS, long-trained non-supplemented; LTS, long-trained supplemented. The error bars show the standard deviations of the means (n=8). Bars that have different letters (a, b, c) are significantly different (p<0.05) among the four groups by F-test. When the F-test indicated differences between groups, the differences were separated using Tukey's test.

AUTHOR DISCLOSURES

Youn-Soo Cha, no conflicts of interest.

REFERENCE

1. Cerretelli P, Marconi C. L-carnitine supplementation in human. The effects on physical performance. Int J Sports Med. 1990;11:1-14.
2. Bieber LL. Carnitine. Ann Rev Biochem. 1998;57:261-83.
3. Borum PR. Clinical aspects of human cartine deficiency. New York: Pergamon press, 1986. p. 1-271.
4. Hamilton J, Li B, Shug A, Olsen W. Studies of L-carnitine absorption in man. Gastroenterology. 1983;85:1180.
5. Broquist HP. Carnitine. In: Modern Nutrition in health and disease (Shils ME, Olson JA, Shike M). Philodelphia: Lea & Febiger, 1994. p. 459-465.
6. Cha YS, Eun JS, Oh SH. Carnitine Profiles during differentiation and effects of carnitine on differentiation of 3T3-L1 cells. J Med Food. 2003;6:163-7.
7. Mun EG, Soh JR, Cha YS. L-carnitine reduces obesity caused by high-fat diet in C57BL/6J mice. Food Sci Biotechnol. 2007;16:228-33.
8. Yang JY, Lee SJ, Park HW, Cha YS. Effect of genistein with carnitine administration on lipid parameters and obesity in C57BL/6J mice fed a high-fat diet. J Med Food. 2006;9:459-67.
9. Heo YR, Lee Y, Cha YS. L-carnitine adminstration improves lipid metabolism in Streptozotocin-induced Diabetic rat. Nutr Sci. 2002;5:3-8.
10. Heo YR, Kang CW, Cha YS. L-carnitine changes the levels of insuline-like growth factors (IGFs) and IGF binding proteins in streptozotocin-induced Diabetic rat. J Nutr Sci Vitaminol. 2001;47:329-34.
11. Lee Y, Heo YR, Cha YS. The plasma and urinary carnitine system in Korean diabetic patients. Nutrl Sci. 2005;8:97-103.
12. Cha YS, Kim HY, Daily JW. Exerciae-trained but not untrained rat manitain free carnitine reserves during acute exercise. Asia Pacific J Clin Nutr. 2003;12:120-6.
13. Kim E, Park H, Cha YS. Exercise training and supplement with carnitine and antioxidants increases carnitine stores, triglyceride utilization, and endurance in exercising rats. J Nutr Sci Vitaminol. 2004;50:335-43.
14. Cha YS, Soh JR, Kim CK, Park H. Effect of carnitine and antioxidant supplementation on carnitine and lipid profiles in trained and non-trained humans. FASEB J. 2003;17: A733-447.