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Article

Urinary excretion of L-carnitine, acetyl-L-carnitine, propionyl-L-carnitine and their antioxidant activities after single dose administration of L-carnitine in healthy subjects

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The urine excretion of L-carnitine (LC), acetyl-L-carnitine (ALC) and propionyl-Lcarnitine (PLC) and their relations with the antioxidant activities are presently unknown. Liquid L-carnitine (2.0 g) was administered orally as a single dose in 12 healthy subjects. Urine concentrations of LC, ALC and PLC were detected by HPLC. Superoxide dismutase (SOD), total antioxidative capacity (T-AOC), malondialdehyde (MDA) and nitrogen monoxidum (NO) activities were measured by spectrophotometric methods. The 0~2 h, 2~4 h, 4~8 h, 8~12 h, 12~24 h excretion of LC was 53.13±31.36 μmol, 166.93±76.87 μmol, 219.92±76.30 μmol, 100.48±23.89 μmol, 72.07±25.77 μmol, respectively. The excretion of ALC was 29.70±14.43 μmol, 80.59±32.70 μmol, 109.85±49.21 μmol, 58.65±18.55 μmol, and 80.43±35.44 μmol, respectively. The urine concentration of PLC was 6.63±4.50 μmol, 15.33±12.59 μmol, 15.46±6.26 μmol, 13.41±11.66 μmol and 9.67±7.92 μmol, respectively. The accumulated excretion rate of LC was 6.1% within 24h after its administration. There was also an increase in urine concentrations of SOD and T-AOC, and a decrease in NO and MDA. A positive correlation was found between urine concentrations of LC and SOD (r = 0.8277) or T-AOC (r = 0.9547), and a negative correlation was found between urine LC excretions and NO (r = -0.8575) or MDA (r = 0.7085). In conclusion, a single oral LC administration let to a gradual increase in urine L-carnitine excretion which was associated with an increase in urine antioxidant enzymes and the total antioxidant capacities. These data may be useful in designing therapeutic regimens of LC or its analogues in the future.

Uniterms: L-carnitine/antioxidant activity. Acetyl-L-carnitine/antioxidant activity. Propionyl-Lcarnitine/antioxidant activity. Antioxidants. Urine excretion/analysis.

A excreção urinária de L-carnitina (LC), acetil-L-carnitina (ALC) e propionil-L-carnitine (PLC) e as suas relações com as atividades antioxidantes são presentemente desconhecidos. Líquido de L-carnitina (2,0 g) foi administrada por via oral como uma dose única em 12 indivíduos saudáveis. As concentrações urinárias de LC, PLC e ALC foram detectados por HPLC. Atividades superóxido dismutase (SOD), a capacidade antioxidante total (T-AOC), malondialdeído (MDA) e óxido nítrico (NO) foram medidas por métodos espectrofotométricos. O 0~2 h, 2~4 h, 4~8 h, 8~12 h, 12~24 h excreção de LC foi 53,13±31.36 μmol, 166,93±76.87 μmol, 219,92±76.30 μmol, 100,48±23.89 μmol, 72,07±25.77 μmol, respectivamente. A excreção de ALC foi 29,70±14.43 μmol, 80,59±32.70 μmol, 109,85±49.21 μmol, 58,65±18.55 μmol, e 80,43±35.44 μmol, respectivamente. A concentração de urina de PLC foi 6,63±4.50 μmol, 15,33±12.59 μmol, 15,46±6.26 μmol, 13,41±11.66 μmol e 9,67±7.92 μmol, respectivamente. A taxa de excreção acumulada de LC foi de 6,1% 24 horas após sua administração. Houve também um aumento nas concentrações de urina de SOD e T-COA e diminuição de NO e de MDA. Correlação positiva foi encontrada entre as concentrações de urina de LC e SOD (r = 0,8277) ou T-AOC (r = 0,9547) e correlação negativa entre a excreção de LC e NO (r = -0,8575) ou MDA (r = 0,7085). Em conclusão, a administração oral única de LC leva ao aumento gradual na excreção urinária de L-carnitina, que foi associada com o aumento das enzimas antioxidantes na urina

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e as capacidades antioxidantes totais. Estes dados podem ser úteis no futuro para o planejamento de esquemas terapêuticos de LC ou os seus análogos, no futuro.

Unitermos: L-carnitina/atividade antioxidante. Acetil-L-carnitina/atividade antioxidante. Antioxidantes. Urina/excreção/análise.

INTRODUCTION

L-carnitine (3-hydroxy-4-*N*-trimethylammonium butyrate, LC) is an endogenous compound which has several physiological functions. LC is involved in the transfer of long-chain fatty acids across the inner matrix membrane of mitochondria (Mancinelli *et al.,* 2007). It also regulates acetyl storage and transfer in mitochondria, cells, and between organs, and the transport of potentially toxic, activated acids out of mitochondria (Bellinghieri *et al.,* 2003). LC is believed to be important for acting as an osmo protectant in organs such as the kidney, and as a general cell membrane stabilizer (Lahjouji *et al.,* 2004; Biolo *et al.,* 2008). LC homeostasis is maintained by a modest biosynthesis in the liver and kidney, absorption from dietary sources (eg, meat and dairy products), and efficient renal tubular reabsorption from glomerular filtrate (Rebouche, Seim 1998). Short-chain carnitine esters, including acetyl-Lcarnitine (ALC) and propionyl-L-carnitine (PLC), are produced by esterification of the hydroxyl group of LC. LC, ALC and PLC form components of the endogenous carnitine pools in humans and experimental animals (Mancinelli *et al.,* 2000). There is a reciprocal transformation among the three carnitine analogues (LC, ALC and PLC) (Cao *et al.,* 2009). Acetylation of L-carnitine and the transformation to ALC or PLC can take place during the absorption process (Gross, Henderson, 1984; Gudjonsson *et al.* 1985).

LC is administered clinically for the treatment of primary and secondary carnitine deficiency syndromes. Available biochemical and clinical information provides a strong rationale for carnitine supplementation to patients on hemodialysis (Guarnieri *et al.,* 2007). Bioavailability of dietary LC in individuals adapted to low-carnitine is between 54% to 72% (Rebouche, Chenard, 1991). However, the bioavailability of L-carnitine from oral supplements was lower than dietary LC, ranging from 14%-18% of the total dose (Rebouche, 2004). ALC supplementation has been reported to reduce the progression of Alzheimer's disease (Gavrilova *et al.*, 2011; Pettegrew, McClure 2002). Patients with intermittent claudication exhibited improved walking capacity after the administration of PLC (Brevetti *et al.*, 1995).

Apart from the physiological roles in intermediary metabolism, LC has also been found to possess antioxidant properties, such as prevention of DNA damages and increase of non-enzymatic and enzymatic antioxidant levels (Ribas *et al.,* 2012; Derin *et al.,* 2004). LC also raises the activities of blood antioxidant enzymes and total antioxidant capacity in a concentration-dependent manner (Cao *et al.,* 2011). However, there has been limited information about the relationships between the urine concentrations of LC and and anti-oxidation in in healthy humans. The aim of this study was to investigate the urine concentration of LC, ALC and PLC after a single oral administration of L-carnitine solution in healthy volunteers, and to evaluate their urine antioxidant status through the measurement of superoxide dismutase (SOD), total antioxidative capacity (T-AOC), nitrogen monoxidum (NO), and malondialdehyde (MDA) activities in the urine.

MATERIALS AND METHODS

Drugs, reagents and apparatus

Standard preparations of L-carnitine (purity 99%, batch No. 060708, 10 ml: 1 g) were obtained from Northeast Pharmaceutical Group Co., China. 1-Ethyl-3-(3-dimethyllaminopropyl) carbodiimide hydrochloride (EDC-HCL) and 1-aminoanthracen (1-AA) were supplied by Sigma. Acetonitrile (HPLC grade reagent) was purchased from Honeywell international INC. Other reagents (hydrochloric acid, acetone, ammonium acetate, aether, glacial acetic acid, chloroform) were of analytical grade.

Study participants

This study was approved by the Institutional Review Board of Qingdao University. Informed written consent was obtained from all participants. Healthy volunteers were invited from the staff working at the hospital clinics and those who attended the clinics for annual health check-ups. All subjects were free from pulmonary, neurologic, hematologic and gastrointestinal diseases. None of the participants were past or current smokers. A thorough physical examination was performed, and the

following laboratory tests were conducted: blood cell counts, biochemistry profile, liver and renal function tests and electrocardiogram. The volunteers were not permitted to consume alcohol for 72 h before or during the study, and were asked to abstain from any medications for at least 1 week before and during the study. All subjects were prescribed a similar diet commencing two weeks before the study. In the prescribed diet there were green vegetables, rice, 50 g/day of cooked chicken meat, but no milk, other forms of meat or diary product such as cheeses.

Study design

A single dose of LC (2.0 g in 200 mL warm water) was administered orally to all participants. The Urine was collected just before (0 h) and at 0~2 h, 2~4 h, 4~8 h, 8~12 h, and 12~24 h after the oral administration of LC. The urine volume at each time point was recorded. Five ml of the urine was transferred into a polypropylene tube and kept at -20 ^{o}C for analysis.

Chromatographic conditions and extraction procedure

The analytes were precolumn derivatived with l-aminoanthracene (1-AA). The fluorescent derivatives were separated on a Hypersil C_{18} column, and the mobile phase consisted of acetonitrile-0.1 mol.L^{-1} ammonium acetate (34:66), the flow rate was 1.0 mL.min^{-1}. The derivatives were monitored with a fluorimetric detector set at 248 nm excitation wavelength and 418 nm emission wavelength. We have previously reported the extraction procedure and validation of the methodologies (Cao *et al.,* 2009, 2011).

Determination of urine excretion and accumulated excretion rate

The urine excretion was a summation of excretion through multiplying the concentration and volume in 0~2 h, 2~4 h, 4~8 h, 8~12 h, 12~24 h, respectively. The accumulated excretion rate of LC was calculated by dividing accumulated excretion of LC with the oral dose (2.0 g).

Determination of antioxidant index

The urine samples were subjected to the measurement of SOD, T-AOC, NO and MDA by spectrophotometric methods according to the procedures provided by the assay kits (purchased from Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Statistical analysis

Data are expressed as means ± SD. SPSS15.1 software was used for data analysis. Numerical data were analyzed with one-way ANOVA. Categorical data were analyzed with Chi-square test. Pearson correlation was used to analyze the correlations between LC and the concentrations of SOD or T-AOC, NO or MDA. $P<0.05$ was considered statistically significant.

RESULTS

Urine excretion of LC, ALC, PLC and accumulated excretion rate of LC

The 0~2 h, 2~4 h, 4~8 h, 8~12 h, 12~24 h urine excretion of LC was 53.13±31.36 μmol, 166.93±76.87 μmol, 219.92±76.30 μmol, 100.48±23.89 μmol and 72.07±25.77 μmol, respectively. The excretion of ALC was 29.70±14.43 μmol, 80.59±32.70 μmol, 109.85±49.21 μmol, 58.65±18.55μmol, and 80.43±35.44 μmol, respectively, and the urine excretion of PLC was 6.63±4.50 μmol, 15.33±12.59 μmol, 15.46±6.26 μmol, 13.41±11.66 μmol, and 9.67±7.92 μmol, respectively (Figure 1). The accumulated urine excretion rate of LC was 6.1% within 24 h after its administration.

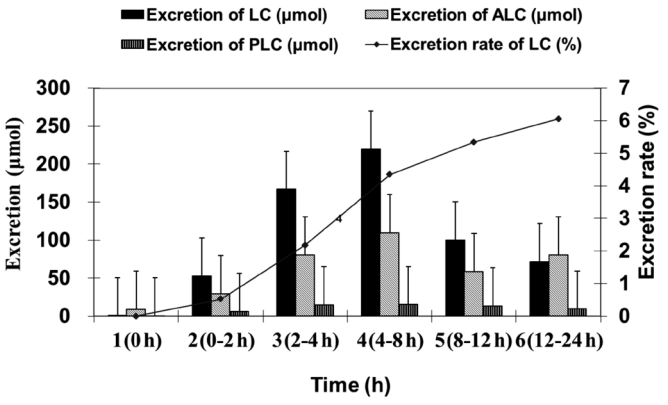

FIGURE 1 - The urinary excretion of LC, ALC, PLC and the urinary excretion rate of LC after single oral administration.

Urinary antioxidant status

As shown in Table I, after single oral administration of LC, the excretion of LC increased gradually from 0~2 h to 4~8 h, and reached the peak at 4~8 h. The antioxidant index of SOD and T-AOC had the same transmutation as the excretion, however NO and MDA had a conversely changing tendency. The mean concentrations of SOD and T-AOC in 2~4 h,4~8 h were higher than in 0~2 h (*P*

TABLE I - The urine excretion of L-carnitine and the antioxidative parameters

Time (h)	Excretion (μmol)	SOD U (mL^{-1})	T-AOC (U mL^{-1})	NO (μmol L^{-1})	MDA (μmol mL^{-1})
0	0.94±0.82	17.49±5.69	28.67±7.08	3.69±1.98	3.05±1.99
0~2	53.13±31.36	22.53±10.01	40.13±16.70	2.12±0.68	2.86±1.62
2~4	166.93±76.87**	39.70±10.46*	64.92±22.86*	0.40±0.10*	0.16±0.10*
4~8	219.92±76.30**	33.31±10.95*	64.12±30.77*	0.72±0.39*	0.65±0.42*
8~12	100.48±23.89**	26.19±12.18	46.90±22.84	1.05±0.79*	0.67±0.62*
12~24	72.07±25.77*	24.08±8.37	43.44±15.28	1.70±0.88	1.26±1.09

SOD, superoxide dismutase activity; T-AOC, total antioxidative capacity; NO, nitrogen monoxidum; MDA, malondialdehyde. *$P<0.05$ and **$P<0.01$, compared with 0~2h.

<0.05), however the mean concentrations of NO and MDA in 2~4 h, 4~8 h and 8~12 h were lower than in 0~2 h (P <0.05).

Correlation analysis

A positive correlation was found between excretion of LC and urine concentrations of SOD (r = 0.8277) or T-AOC (r = 0.9547). A negative correlation was found between LC excretion and NO (r = -0.8575) or MDA (r = -0.7085).

DISCUSSION

The present study found that urine excretion of LC, ALC, and PLC started within one hour and reached its peak between 4-8 h after a single oral administration in healthy subjects. This study also demonstrated a gradual increase in the urine antioxidant index of SOD and T-AOC within the first 8h of LC administration. Furthermore, a positive correlation was found between urine LC excretion and urine concentrations of SOD or T-AOC.

In 1991, Rebouche (1991) published a pivotal paper that provided a quantitative estimation of the fate of an oral tracer dose of L-[*methyl*-3H]-carnitine in five men who were receiving a high-carnitine diet and L-carnitine supplementation. It was found that the absorption of oral L-[3H]-carnitine was slow and incomplete, with t_{max} values of 2–4.5 hours. This suggests a prolonged retention of that fraction of the dose that had been incorporated into the body's carnitine pool. In their study, only 6.3% of the oral LC dose was recovered unchanged in the urine, with a further 34% recovered in urine as metabolites, mostly [3H]-trimethylamine-*N*-oxide (Rebouche, 1991). About 22% of the dose was recovered in feces, mostly as labeled γ-butyrobetaine (Rebouche, 1991). In our study, after a single dose of LC, the urine excretion of LC increased gradually from 0~2 h to 4~8 h, and reached the peak at 4~8 h. The excretion rate of L-carnitine was only 6.1%, which was consistent with Rebouche's report (Rebouche, 1991). The excretion of ALC and PLC also increased and reached the peak within 8h following LC administration, which suggests that acetylation of LC and the transformation to ALC or PLC can take place *in vivo*. One notable variation was that the excretion of ALC between 12-24 h was greater than that between 8-12 h (80.4 vs 58.7 μmol). The reason for this is unclear, but whether there is a second phase of urinary ALC excretion 12 h after LC administration requires further investigation.

In kidneys, LC decreased the severity of renal cortical proximal tubular necrosis and improved renal function in rats with gentamicin-induced or doxorubicin-induced renal injury (Boonsanit *et al.,* 2006; Kopple *et al.,* 2002). LC reversed the increases in blood BUN and creatinine following the doxorubicin or gentamicin caused renal injuries. LC has been shown to reduce the severity of glycerol-induced myoglobinuric kidney damages, indicating that LC may be a beneficial agent in the prevention and treatment of glycerol-induced myoglobinuric acute renal failure (Ustundag *et al.,* 2009). The mechanisms of the renal protective effect of LC are not entirely clear. In previous studies, LC has been shown to have antioxidant effects against oxidative damage in different organs or tissues, including the kidney (Aydogdu *et al.,* 2006; Chang *et al.,* 2002). It has been demonstrated that LC administration inhibits both serum and kidney tissue MDA formation in response to renal ischaemia–reperfusion injury (Ergün *et al.,* 2001). Carnitine supplementation has been found to enhance the activities of antioxidant enzymes, such as SOD, CAT and GPx, and decrease the MDA concentration in kidney tissues of 24-month-old rats (Kalaiselvi, Panneerselvam, 1998). The direct antioxidant effects of LC might contribute to attenuation of oxidative stress in kidney tissues (Sener *et al.,* 2004). Antioxidant effects of carnitine were also shown *in vitro* studies, and in patients on hemodialysis (Guarnieri *et al.,* 2007; Pertosa *et al.,* 2005).

These effects could in turn reduce oxidative stress–induced inflammation and insulin resistance (Evans *et al.,* 2003). We have also previously reported that aadministration of liquid LC could raise the activities of plasma antioxidant enzymes and total antioxidant capacity in a concentration-dependent manner in healthy human volunteers (Cao *et al.,* 2011). In the present study, the transmutation of urine SOD, T-AOC, NO, and MDA provides further evidence to confirm that LC could increase the antioxidant activities in healthy subjects.

There have been some studies to compare the effect of LC with other antioxidant biomolecules. In hypoxia-induced lipid peroxidation in the brain during postnatal ontogenesis, the protective effect of LC is comparable with the effect of tocopherol, well-known reactive species scavenger (Rauchová *et al.,* 2012). In the obstructed kidney of rats subjected to 24-hr of unilateral ureteral obstruction (UUO), LC reduced oxidative stress and suppressed energy metabolism, while α-tocopherol only prevented redox imbalance (*Moosavi SM et al.,* 2011). The effect of LC on superoxide anion radical scavenging and hydrogen peroxide scavenging seems comparable with alpha-tocopherol and trolox (Gülçin, 2006). L-carnitine seems to have more protective effects than selenium on the electromagnetic radiation-induced blood toxicity by inhibiting free radical supporting antioxidant redox system (Gumral *et al.,* 2009).

In this study, there was a moderate increase in urinary SOD within 2-8 hr of LC administration. The reasons for this SOD increase are unclear. SOD is a large molecule which is usually reabsorbed in the kidney and urine SOD should be negligible in healthy subjects. Whether LC increased kidney injury leading to higher SOD releaser requires further investigation.

In summary, this study in healthy Chinese subjects has demonstrated that following oral administration of LC, there was a gradual increase in the urine excretion of L-carnitine, ALC and PLC, with a peaking excretion occurring between 4 and 8 h after the drug administration. This study also showed that there was an increase in the antioxidant activities in the urine after LC administration. The antioxidant activities were closely correlated with the urine LC excretion. These data may be useful in designing therapeutic regimens of L-carnitine or its analogues in the future.

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CONFLICT OF INTEREST

None to declare.

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