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Free and Total Carnitine Concentrations in Pig Plasma after Oral Ingestion of Various L-Carnitine Compounds

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Abstract: This study was undertaken to investigate the bioavailability of various L-carnitine esters (acetyl-L-carnitine and lauroyl-L-carnitine) and salts (L-carnitine L-tartrate, L-carnitine fumarate, L-carnitine magnesium citrate) relative to base of free L-carnitine. Six groups of five or six piglets each were administered orally a single dose of 40 mg L-carnitine equivalents/kg body weight of each of those L-carnitine compounds. A seventh group served as a control. Free and total plasma carnitine concentrations were determined 1, 2, 3.5, 7, 24, and 32 hours after administration of the single dose. Area-under-the-curve (AUC) values were calculated to assess the bioavailability of the L-carnitine compounds. AUC values, calculated for the time interval between 0 and 32 hours, for both free and total carnitine were similar for base of free L-carnitine and the three L-carnitine salts (L-carnitine L-tartrate, L-carnitine fumarate, L-carnitine magnesium citrate) while those of the two esters (acetyl-L-carnitine, lauroyl-L-carnitine) were lower. Administration of L-carnitine L-tartrate yielded a higher plasma free carnitine AUC value for the time interval between 0 and 3.5 hours than administration of the other compounds. The data of this study suggest that L-carnitine salts have a similar bioavailability to that of free L-carnitine while L-carnitine esters have a lower one. The study also suggests that L-carnitine L-tartrate is absorbed faster than the other L-carnitine compounds.

Key words: L-carnitine compounds, pig, plasma carnitine concentration

Introduction

L-Carnitine (L-β-hydroxy-4-N-trimethylaminobutyric acid) is an important compound in mammals. Its primary function lies in the transport of long-chain fatty acids across the inner mitochondrial membrane to the place of their ß-oxidative degradation; e.g., energy production [1]. The endogenous synthesis of L-carnitine requires lysine and methionine as precursors. About 98% of body L-carnitine is present in skeletal and cardiac muscle. Because carnitine synthesis depends on the availability of different vitamins (C, B_6) and the micronutrient iron, a deficiency of these compounds and physiological stress situations can require an exogenous L-carnitine supplementation [2, 3]. Previous reports indicate also that physical exercise or diseases such as ischemia, neuropathy, AIDS, or hemodialysis develop a need for additional L-carnitine [4–7]. To meet the requirement under these conditions, dietary supplements can be helpful. Base of free L-carnitine is the compound commonly used for L-carnitine supplementation. It has been well established that maximum plasma concentrations after oral administration of base of free L-carnitine can be up to 4–6 hours or longer. Twenty-four hours after administration, the plasma carnitine concentration

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returns to its baseline level in humans [8, 9]. Although base of free L-carnitine is highly water soluble, the absolute bioavailability is relatively low, being in the range between 15 and 20% [9, 10]. It is largely unknown whether chemical modification of free base of L-carnitine into its salts or esters influences its absorption kinetics, therefore, the aim of the present study was to compare absorption rate and kinetics of various L-carnitine compounds (ester and organic salts). To establish whether these L-carnitine compounds influence free and esterified carnitine in a different manner, we determined the response of plasma free and total carnitine concentrations after a single dose of each of them in piglets, which were used as model animals. As proposed by others [8, 9, 11–13], we calculated area under the curve (AUC) values to determine the bioavailability of L-carnitine esters and salts relative to that of base of free L-carnitine.

Table I: Properties of the L-carnitine compounds used in this study

Compound	Properties
Base of free L-carnitine	R-(3-Carboxy-2-hydroxypropyl)trimethylammoniumhydroxide ($C_7H_{15}NO_3$); purity: 99%; white crystalline powder; MW: 161.2 g
L-carnitine L-tartrate	R-(3-carboxy-2-hydroxypropyl)trimethylammoniumhydroxide salt with [R-(R*, R*)]-2,3-dihydroxy L-tartrate (2:1) ($C_{18}H_{36}N_2O_{12}$); purity: 68%; white, crystalline powder; MW: 472.5 g
L-carnitine fumarate	R-(3-carboxy-2-hydroxypropyl)trimethylammoniumhydroxide salt with fumarate ($C_{18}H_{34}N_2O_{12}$); purity: 58%; white crystalline powder; MW: 470.0 g
L-carnitine magnesium citrate	R-(3-carboxy-2-hydroxypropyl)trimethylammoniumhydroxide salt with magnesium citrate ($C_{13}H_{21}NO_{10}Mg$); granulate; purity: 43%; white powder; MW: 375.6 g
Acetyl-L-carnitine	Acetyl-L-carnitine hydrochloride ($C_9H_{18}ClNO_4$); purity: 98%; crystalline powder; MW: 239.7 g
Lauroyl-L-carnitine	3-O-lauroyl-L-carnitine hydrochloride ($C_{19}H_{38}ClNO_4$); purity: 98%; white crystalline powder; MW: 380.0 g

Materials and Methods

Animals and treatment: Forty male crossbred piglets with an average body weight of 13.3 ± 0.3 kg and an age of 6 to 8 weeks were used for this study. Prior to the experiment, these piglets were fed nutritionally adequate piglet diets. Three days before the beginning of the experiment the piglets were transferred into separate metabolic cages to allow individual control of the animals. They were allotted to seven treatment groups of five or six each. Twelve hours before the bioavailability test, the animals were deprived of food. Six groups of piglets received various carnitine compounds as a single oral single dose of 40 mg L-carnitine equivalents/kg. To facilitate the supply of the exact amount of each of the L-carnitine compounds, we mixed them in 25 g of wheat bran. This portion of wheat bran was administered to the piglets. It was completely consumed by the animals within one minute after administration. The control group (group 1) received the same amount of wheat bran without L-carnitine supplement. The six other groups received wheat bran supplemented with base of free L-carnitine, L-carnitine L-tartrate, L-carnitine fumarate, L-carnitine magnesium citrate, acetyl-L-carnitine, or lauroyl-L-carnitine. During the following 32 hours, the animal did not receive any other food. All carnitine compounds were supplied in powder form by Lonza GmbH, Wuppertal, Germany. Some information about the preparations used is given in Table I. The protocol was approved by the local committee for animal welfare.

Sample collection: Blood samples were collected from *vena carotis communis* into heparinized tubes at 0, 1, 2, 3.5, 7, 24, and 32 hours after administration of the carnitine supplement. Plasma was obtained by centrifugation of the blood at 1800 × g for 10 minutes at 4° C. Plasma samples were stored at –18° C until analysis.

Carnitine analysis: The determination of the concentration of carnitine was based on procedures of Maeda and Stanley [14] as well as Wieland *et al* [15]. 400 µL of plasma samples were deproteinized with 160 µL of trichloroacetic acid (10%) and centrifuged at 15,000 × g (Biofuge 13, Heraeus, Sepatech) for 15 minutes at room temperature. 200-µL aliquots of the supernatants were used to determine the concentration of free carnitine; the remaining 200-µL aliquot of the supernatant was hydrolyzed with 100 µL of potassium hydroxide (1 mol/L) at 56 °C for 45 minutes. After termination of the hydrolysis by the addition of 100 µL hydrochloric acid (1 mol/L), the sample was used to determine the concentration of total carnitine. Prior to carnitine analysis, the samples were adjusted to pH 6.5 to 7.0 with potassium hydroxide solution (1 mol/L) and centrifuged at 4000 × g for 5 minutes at ambient temperature. 200 µL of each supernatant were passed through a column filled with 0.7 g of Dowex (1-X4 ion exchange resin). Carnitine was eluted with 4.0 mL of distilled wa-

ter from the column. The solvent was evaporated in a vacuum centrifuge (Centrifugal Evaporator, Jouan, France) and the residue was reconstituted in 400 µL of deionized-distilled water. This solution was used for the carnitine assay. The carnitine assay was based on the principle that, in the presence of acetyl-CoA and carnitine acetyltransferase, free carnitine is acetylated and coenzyme A is formed, which reacts with 5,5'-dithio-bis-(2 nitrobenzoic acid) (DTNB) to form the yellow anion 5-thio-2-nitrobenzoate (TNB). The concentration of TNB was measured spectrophotometrically at a wavelength of 405 nm by a Spectrafluor plus plate reader (Tecan, Crailsheim, Germany), at ambient temperature. 200 µL of samples or standards were pipetted into 96-well plates. After addition of 20 µL DTNB buffer (DTNB, 2.7 mmol/L; HEPES, 0.5 mol/L; EDTA, 10 mmol/L; pH 7.5) and 10 µL of acetyl-CoA (2 mmol/L), the absorbance (A1) was measured after 10 minutes. Then 10 µL of carnitine acetyltransferase (400 kU/L) was added to the reaction mixture and the absorbance (A_2) was read after 30 minutes. The difference between the two readings ($\Delta A = A_2 - A_1$) was used to calculate the concentration of carnitine.

Calculations and statistical analysis: The determination of the area under the curve (AUC) was calculated with the software Origin 5.0, Microcal. The relative bioavailability of the L-carnitine compounds (related to that of base of free L-carnitine) was calculated from the AUC values:

$$\text{Relative bioavailability} = (AUC_{\text{Compound}} / AUC_{\text{Base of free L-carnitine}}) \times 100$$

Data were analyzed using one-factorial analysis of variance (ANOVA). Results of plasma peak L-carnitine concentrations, ratio of plasma concentration between free and total L-carnitine, AUC values, and calculated relative bioavailability were evaluated with carnitine compound as treatment factor. Results of the ratio of plasma concentration between free and total L-carnitine was also evaluated with time as treatment factor. For statistically significant F-values, means of the groups were compared by Fisher's multiple range test. Means were considered significantly different at $p < 0.05$.

Results

Concentrations of free and total L-carnitine in plasma: Single-dose administration of all the L-carnitine compounds caused a time-dependent increase of free and total carnitine in plasma (Fig. 1 and 2). Peak concentrations and the time at which they were achieved, however, were different for the various compounds. At administration of L-carnitine L-tartrate, peak levels of free and total carnitine were already reached after 3.5 hours; at administration of all the other carnitine compounds, peak levels of free and total carnitine were reached after 7 hours. Peak concentrations of free carnitine after administration of base of free L-carnitine (18.7 ± 5.6 µmol/L) and the L-carnitine salts, L-carnitine L-tartrate (19.3 ± 6.2 µmol/L), L-carnitine fumarate (15.9 ± 2.6 µmol/L), and L-carnitine magnesium citrate (16.3 ± 3.9 µmol/L) were similar. Peak concentrations of free L-carnitine after administration of

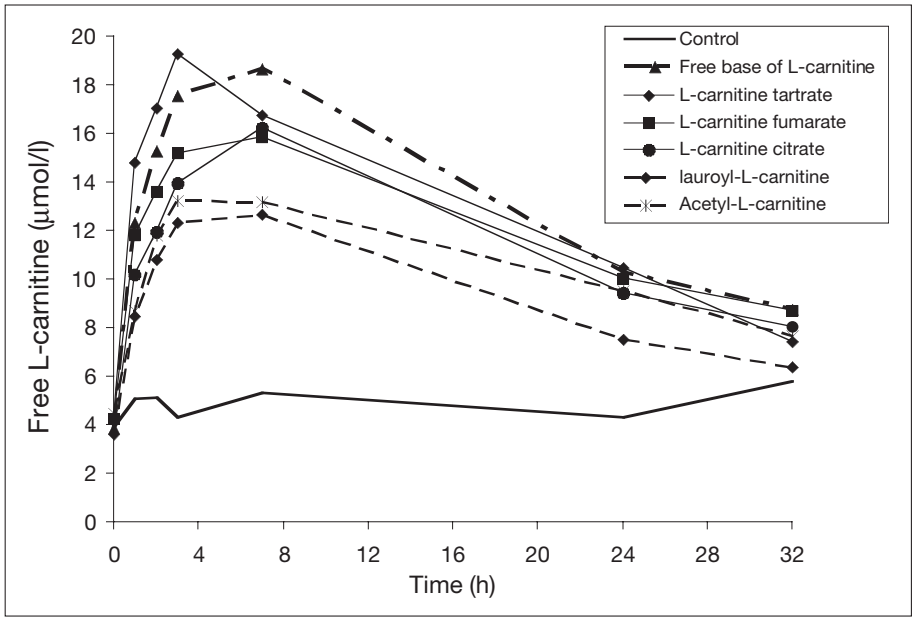

Figure 1: Concentration of free L-carnitine in plasma of pigs at various time points after oral administration of various L-carnitine compounds. Data are means, n = 5–6 per group.

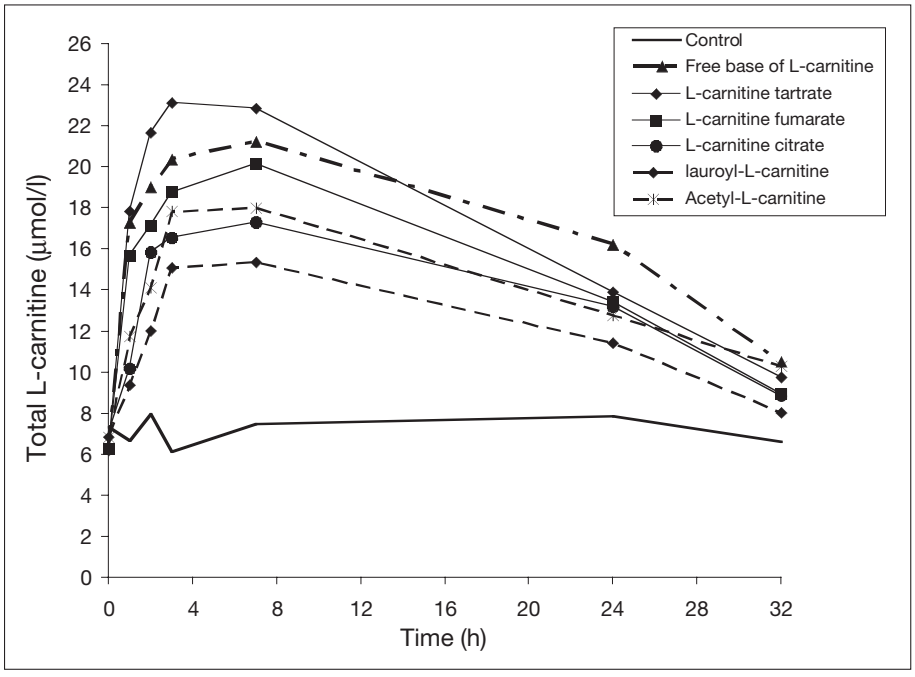

Figure 2: Concentration of total L-carnitine in plasma of pigs at various time points after oral administration of various L-carnitine compounds. Data are means, n=5–6 per group.

the L-carnitine esters, acetyl-L-carnitine (13.2 ± 2.9 µmol/L) and lauroyl-L-carnitine (12.7 ± 3.6 µmol/L), were lower ($p < 0.05$) than those achieved after administration of the other carnitine compounds. Peak concentrations of total carnitine in plasma were similar after administration of base of free L-carnitine (21.3 ± 6.9 µmol/L), acetyl-L-carnitine (18.0 ± 5.9 µmol/L), L-carnitine L-tartrate (23.2 ± 4.5 µmol/L), L-carnitine fumarate (20.2 ± 2.7 µmol/L), and L-carnitine magnesium citrate (17.3 ± 3.5 µmol/L). The peak concentration of total carnitine after administration of lauroyl-L-carnitine (15.4 ± 5.1 µmol/L) was lower ($p < 0.05$) than that after administration of L-carnitine L-tartrate.

After reaching their peak level, the concentrations of free and total carnitine declined to the control level. Treatment levels of free L-carnitine in plasma were no longer significantly different from the control level after 24 hours (for lauroyl L-carnitine) or 32 hours (for all the other carnitine compounds). Similarly, treatment levels of total L-carnitine were no longer different from control levels after 24 hours (for acetyl L-carnitine, L-carnitine fumarate, L-carnitine magnesium citrate, and lauroyl L-carnitine) or 32 hours (for base of free L-carnitine and L-carnitine L-tartrate).

The ratio of the concentrations between free L-carnitine and total L-carnitine in plasma after oral administration of various L-carnitine compounds was higher ($p < 0.05$) after 3.5 hours (0.82 ± 0.18 mol/mol, means ± SD, n = 34) and 7 hours (0.81 ± 0.15 mol/mol, n = 34) than at baseline (0.60 ± 0.16 mol/mol, n=34). This ratio, however, was not different at various times points between piglets orally administered the various L-carnitine compounds (Table II).

AUC values: The base-line corrected AUC values for free carnitine in plasma, calculated for the ranges between 0 and 2 hours and 0 and 7 hours, did not differ between pigs administered the six carnitine compounds (Table II). However, the baseline corrected AUC values for free L-carnitine, calculated for the range between 0 and 3.5 hours, was significantly higher in pigs administered L-carnitine L-tartrate than in pigs administered any of the other carnitine compounds, with the exception of L-carnitine fumarate. The baseline corrected AUC for free carnitine, calculated for the period between 0 and 32 hours, was similar for free base of L-carnitine and the three L-carnitine salts (L-carnitine L-tartrate, L-carnitine fumarate, and L-carnitine magnesium citrate); AUC values for L-carnitine esters (acetyl L-carnitine and lauroyl L-carnitine) were significantly lower than those of the others.

Free base of L-carnitine and L-carnitine L-tartrate yielded the highest baseline corrected AUC values for total carnitine in plasma in the time intervals between 0 to 2, 0 to 3.5, and 0 to 7 hours; L-carnitine magnesium citrate, lauroyl-L-carnitine, and acetyl-L-carnitine yielded the lowest AUC values for these time intervals; AUC values for L-carnitine fumarate were intermediate (Table III). Base of free L-carnitine, L-carnitine L-tartrate, and L-carnitine fumarate yielded the highest AUC values for total carnitine in plasma over the whole period of 0 to 32 hours;

Table II: Ratio between the concentration of free L-carnitine and that of total L-carnitine in plasma of piglets after oral administration of free base of L-carnitine, L-carnitine salts, and L-carnitine esters at various time points and in average of the time interval between 1 and 32 hours

Compound	Free base	L-carnitine salts			L-carnitine esters	
	L-carnitine (6)	L-carnitine L-tartrate (6)	L-carnitine fumarate (6)	L-carnitine magnesium citrate (5)	Acetyl L-carnitine (5)	Lauroyl L-carnitine (6)
Time	Free L-carnitine/total L-carnitine (mol/mol)					
0 h (Baseline)	0.61 ± 0.13	0.70 ± 0.17	0.68 ± 0.10	0.51 ± 0.20	0.66 ± 0.24	0.53 ± 0.14
3.5 h	0.87 ± 0.12	0.84 ± 0.31	0.81 ± 0.20	0.85 ± 0.09	0.75 ± 0.09	0.82 ± 0.27
7 h	0.72 ± 0.27	0.74 ± 0.17	0.79 ± 0.11	0.93 ± 0.12	0.87 ± 0.12	0.82 ± 0.13
24 h	0.63 ± 0.06	0.76 ± 0.09	0.75 ± 0.11	0.72 ± 0.09	0.74 ± 0.04	0.66 ± 0.13
Average 1-32 h	0.78 ± 0.11	0.79 ± 0.05	0.81 ± 0.09	0.84 ± 0.16	0.76 ± 0.05	0.82 ± 0.14

Values are means ± SD. Number of animals is given in parenthesis.
h = hours

Table III: Baseline corrected areas under the curve (AUCs) for plasma free and total carnitine, calculated for various time intervals after oral administration of free base of L-carnitine, L-carnitine, salts and L-carnitine esters

Compound	Free base	L-carnitine salts			L-carnitine esters	
	L-carnitine (6)	L-carnitine L-tartrate (6)	L-carnitine fumarate (6)	L-carnitine magnesium citrate (5)	Acetyl L-carnitine (5)	Lauroyl L-carnitine (6)
Time interval	AUC (free carnitine, µmol * h * L^{-1})					
0–2 hours	8 ± 10	14 ± 9	11 ± 6	7 ± 4	8 ± 5	6 ± 6
0–3.5 hours	18^{b} ± 18	37^{a} ± 13	26^{ab} ± 12	19^{b} ± 8	19^{b} ± 9	16^{b} ± 12
0–7 hours	57 ± 41	82 ± 27	63 ± 21	55 ± 19	49 ± 18	43 ± 26
0–32 hours	269^{a} ± 68	255^{a} ± 67	255^{a} ± 25	264^{a} ± 70	166^{b} ± 64	159^{b} ± 45
Time interval	AUC (total carnitine, µmol * h * L-1)					
0–2 hours	17^{a} ± 8	18^{a} ± 11	14^{ab} ± 9	8^{b} ± 8	9^{ab} ± 7	4^{b} ± 7
0–3.5 hours	36^{a} ± 18	41^{a} ± 16	30^{ab} ± 14	21^{b} ± 14	21^{ab} ± 13	16^{b} ± 12
0–7 hours	85^{a} ± 44	98^{a} ± 31	76^{ab} ± 23	56^{b} ± 23	58^{ab} ± 25	46^{b} ± 25
0–32 hours	288^{ab} ± 72	307^{a} ± 129	301^{ab} ± 63	241^{ab} ± 74	190^{b} ± 135	201^{ab} ± 65

Values are means ± SD. Number of animals is given in parenthesis. Different superscripts in a row denote significant differences ($p < 0.05$) between the treatment groups.
h = hours

due to a large standard deviation, these values, however, were not significantly different from those of L-carnitine magnesium citrate and lauroyl L-carnitine. Only the AUC of acetyl-L-carnitine was lower than that of L-carnitine L-tartrate ($p < 0.05$).

Calculated bioavailabilities: The three L-carnitine salts (L-carnitine L-tartrate, L-carnitine fumarate, and L-carnitine magnesium citrate) had a similar bioavailability as base of free L-carnitine, based on AUC values of both free and total plasma carnitine (Table IV). Bioavailabilities of L-carnitine esters (acetyl L-carnitine and lauroyl L-carnitine) were lower than those of base of free L-carnitine and the L-carnitine salts.

Discussion

The aim of this study was to compare the bioavailability of various L-carnitine compounds. According to several other studies [8, 9, 11–13] dealing with the bioavailability of L-carnitine, we calculated AUC values of plasma L-carnitine concentrations to assess the relative bioavailability of these compounds after a single dose orally applied to piglets. The basal plasma L-carnitine concentrations in these piglets were in a similar range as those reported in the literature for pigs [16–18]. These basal L-carnitine concentrations of pigs, however, are lower than those of humans [8, 9, 19–21]. To exclude an interfering effect of native L-carnitine from the diet on plasma L-carnitine concentrations, we fasted animals for 12 hours before administration of the L-carnitine compounds to be tested for their bioavailability, and did not supply food un-

Table IV: Relative bioavailability of various L-carnitine salts and L-carnitine esters compared to base of free L-carnitine (= 100) based on the areas under the curve values (AUCs) for plasma free and total carnitine at the time interval between 0 and 32 hours

Compound	L-carnitine salts			L-carnitine esters	
	L-carnitine L-tartrate (6)	L-carnitine fumarate (6)	L-carnitine magnesium citrate (5)	Acetyl L-carnitine (5)	Lauroyl L-carnitine (6)
Base (AUC of)	Bioavailability (%, relative to Base of free L-carnitine)				
Free carnitine	$92^{a} \pm 19$	$93^{a} \pm 9$	$84^{a} \pm 17$	$61^{b} \pm 14$	$43^{b} \pm 16$
Total carnitine	$106^{a} \pm 20$	$104^{a} \pm 13$	$89^{ab} \pm 15$	$66^{b} \pm 20$	$70^{b} \pm 26$

Values are means ± SD. Number of animals is given in parenthesis. Different superscripts in a row denote significant differences ($P < 0.05$) between the treatment groups.

til termination of the experiment after 32 hours. As shown by others [8, 9], oral application of L-carnitine leads to an increase in the plasma L-carnitine concentration. Our study, moreover, shows that the time course of the increase of the plasma concentration is similar for free L-carnitine and total L-carnitine. The data of this study also show that oral administration of L-carnitine causes a temporary increase of the ratio between free L-carnitine to total L-carnitine in the plasma, while different L-carnitine esters and salts do not influence this ratio. The exact mechanism of the absorption of L-carnitine from various compounds has not yet been fully explored [22]. The data of our study suggest that most of the L-carnitine absorbed from different dietary L-carnitine compounds enters the blood as free L-carnitine. The absolute amount of L-carnitine absorbed in the intestine, however, cannot be elucidated from AUC values alone.

Consideration of the AUC values for free and total L-carnitine in plasma suggests that the three L-carnitine salts (L-carnitine L-tartrate, L-carnitine fumarate, and L-carnitine magnesium citrate) were equivalent to base of free L-carnitine free in their bioavailability while the L-carnitine esters (acetyl L-carnitine and lauroyl L-carnitine) had a lower bioavailability. To assess the speed of the absorption, we determined the time points at which maximum L-carnitine concentrations in plasma were reached. In this respect, a certain inaccuracy resulted from the relatively large intervals between the time points of blood sampling. It is probable that maximum L-carnitine concentrations might have been reached between two time points. However, for technical reasons, it was not possible to draw blood samples at shorter time intervals. The observation that the AUC value calculated for the time interval between 0 and 3.5 hours was higher for L-carnitine L-tartrate than for all other L-carnitine compounds suggests that L-carnitine tartate was absorbed faster than the other L-carnitine compounds; according to the AUC values, the speed of the absorption of the other L-carnitine compounds was equivalent to that of base of free L-carnitine.

Peak concentrations of free and total L-carnitine in plasma were observed in the time range between 3.5 hours (L-carnitine L-tartrate) and 7 hours (L-carnitine free base, L-carnitine fumarate, acetyl-L-carnitine, L-carnitine magnesium citrate, and lauroyl-L-carnitine) after administration. These values are higher than others reported in the literature for humans. Peak levels of L-carnitine were observed in the ranges between 3.1 and 3.4 hours [9] or between 3.0 and 3.5 hours [8] after administration of base of free L-carnitine. The basal concentrations of total carnitine in pigs, ranging between 6 and 8 µmol/L, are lower than those in humans, which are in the range between 50 and 60 µmol/L. Maximum increase of plasma L-carnitine which ranged between 8 and 17 µmol/L, was also lower than in humans. In the study of Rizza *et al* [8], administration of 30 mg base of free L-carnitine/kg body weight increased plasma L-carnitine concentration by 26 µmol/L.

This study was not designed to determine the mechanism by which the various L-carnitine compounds are absorbed. To date, two carnitine transporters are known. One of them, the organic cation transporter (OCTN2) that is widely expressed in mammalian tissues is a Na^{+}-dependent transporter for carnitine with a high affinity [23, 24]. The second one, named $ATB^{0,+}$, is an energy-coupled carnitine transporter. $ATB^{0,+}$ transports both L-carnitine and propionyl-L-carnitine with lower affinity than does OCTN2 [25, 26]. To date, little is known about transport characteristics of those transporters. But it has been shown that $ATB^{0,+}$ is a poor transporter of acetyl-L-carnitine. This could be a reason for the observation that both acetyl-L-carnitine and lauroyl-L-carnitine were obviously less efficiently absorbed than the other compounds.

In conclusion, this study suggests that L-carnitine salts have a similar bioavailability as base of free L-carnitine while L-carnitine esters have a lower one. The study also suggests that L-carnitine L-tartrate is absorbed faster than the other L-carnitine compounds.

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