Quantitative Estimation of Absorption and Degradation of a Carnitine Supplement by Human Adults

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Results of kinetic and pharmacokinetic studies have suggested that dietary carnitine supplements are not totally absorbed, and are in part degraded in the gastrointestinal tract of humans. To determine the metabolic fate of dietary carnitine supplements in humans, we administered orally a tracer dose of [*methyl*-^{3}H]L-carnitine with a meal to five normal adult males, who had been adapted to a high-carnitine diet plus carnitine supplement (2 g/d) for 14 days. Appearance of [*methyl*-^{3}H]L-carnitine and metabolites in serum, and urinary and fecal excretion of radiolabeled carnitine and metabolites was monitored for 5 to 11 days following administration of the test dose. Maximum concentration of [*methyl*-^{3}H]L-carnitine in serum occurred at 2.0 to 4.5 hours after administration of the tracer, indicating relatively slow absorption from the intestinal lumen. Total radioactive metabolites excreted in urine and feces ranged from 47% to 55% of the ingested tracer. Major metabolites found were [^{3}H]trimethylamine *N*-oxide (8% to 49% of the administered dose; excreted primarily in urine) and [^{3}H]γ-butyrobetaine (0.44% to 45% of the administered dose; excreted primarily in feces). Urinary excretion of total carnitine was 16% to 23% of intake. Fecal excretion of total carnitine was negligible (less than 2% of total carnitine excretion).

DIETARY SUPPLEMENTATION with carnitine has been recommended for treatment of a variety of genetic and acquired disorders, including chronic hemodialysis associated with renal disease,[1] organic acidemias,[2] genetic defects in acyl-CoA dehydrogenation,[3] hypertrophic cardiomyopathy,[4] renal Fanconi syndrome,[5] anticonvulsant (valproic acid) therapy,[6] and other less well-defined disorders.[7]

Segre et al[8] and Harper et al[9] have examined the pharmacokinetics of L-carnitine in humans. In both studies, bioavailability of oral L-carnitine in pharmacological amounts (26 to 111 mg/kg; single bolus dose) was less than 20%. However, no attempt was made to account for the greater than 80% of the doses that was not absorbed as carnitine. In this study, we have examined the metabolic fate of carnitine ingested as a diet supplement in humans, using a radioactive tracer to identify and quantify metabolites of carnitine formed by the action of microbial flora in the gastrointestinal tract.

MATERIALS AND METHODS

Study Participants

Five normal, adult male volunteers were recruited from the university and Iowa City communities. Prior to entry into the study, each subject was screened for chronic and recent acute illnesses and use of medications. All were judged to be in good health. Characteristics of the five participants are summarized in Table 1. The protocol was reviewed and approved by the University of Iowa Institutional Review Board, the General Clinical Research Center Protocol Review Committee, and the Human Use Subcommittee of the Radiation Protection Committee prior to the start of the study. All participants gave informed consent before entry into the study.

Materials

[*methyl*-^{3}H]L-Carnitine was synthesized by the method of Stokke and Bremer.[10] Radiochemical purity was greater than 98% by thin-layer and high-performance ion-exchange chromatography.[11] [^{3}H]Methyl iodide and [^{3}H]toluene were obtained from Dupont New England Nuclear Division (Boston, MA). Carnitine acetyltransferase, trimethylamine *N*-oxide dihydrate, and (3-carboxypropyl)trimethylammonium chloride (γ-butyrobetaine hydrochloride) were obtained from Sigma Chemical (St Louis, MO).

L-Carnitine capsules (GNC brand) were obtained from the General Nutrition Corporation (Pittsburgh, PA). All capsules were from manufacturer lots 9906G8 and 990668. Each capsule contained tricalcium phosphate (filler) and silica, magnesium stearate, and talc (excipients). Thin-layer chromatography (see Table 2) of a methanolic extract of the capsule contents revealed only two substances, corresponding to carnitine and stearic acid (from magnesium stearate). Densitometric analysis of chromatograms indicated that each capsule contained approximately 175 mg of carnitine · HCl, in agreement with the radioenzymatic analysis (176 mg/capsule). Thus, the capsules contained no detectable D-carnitine, γ-butyrobetaine, or other compounds structurally related to L-carnitine.

Diets

Each participant consumed a prescribed diet for 15 days. All meals were prepared in the Clinical Research Center and weighed to the nearest gram. A 2-day rotating menu was prepared for each individual. Subjects were fed a diet high in carnitine (8.0 to 9.6 μmol [kg body wt]$^{-1}$ · d^{-1}).[11] In addition, subjects received a carnitine supplement in capsule form (10.6 mmol · d^{-1}; see below). Normal carnitine intake is 50 to 600 μmol · d^{-1} for a nonvegetarian adult.[11-13] Diets were designed to meet each participant's energy requirement as determined from his height, weight, age, and usual physical activity level.[14] Macronutrient composition and sample menus have been reported previously.[11] Carnitine intake was approximately equally divided among breakfast, lunch, and dinner. During the course of the study duplicate meals for one 2-day cycle for each individual were prepared for analysis of carnitine content.

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Table 1. Characteristics of Participants

Subject No.	Age (yr)	Weight (kg)	Height (cm)	Serum Carnitine* (μmol/L) Free	Serum Carnitine* (μmol/L) Total	Creatinine Excretion† (mmol/d)
1	40	106	190	77.6 (3.2)	93.3 (3.4)	16.6 (2.9)
2	27	68.8	178	69.8 (2.9)	85.5 (3.7)	15.3 (0.8)
3	29	94.7	178	64.3 (3.3)	76.7 (3.7)	14.7 (2.8)
4	23	84.4	183	63.4 (5.3)	72.5 (5.0)	16.5‡
5	22	76.6	180	51.4 (2.9)	60.9 (2.5)	15.6 (1.5)

*Mean (SD) for 12 days.

†Mean (SD) for 15 days.

‡This subject's creatinine excretion was unusually low on 5 of the 15 days, suggesting noncompliance with the urine collection protocol; therefore, true creatinine excretion was estimated from values obtained during the 2 days when the subject was an inpatient in the Clinical Research Center.

Protocol

Each participant began the dietary regimen on day 1 of the study. Subjects were given carnitine supplements (four capsules per meal, three times a day) for 10 days before starting the dietary regimen, and continued to consume the supplement until the end of the study (day 15). On the morning of day 5, a single dose of [*methyl*-^{3}H]L-carnitine (3.7×10^5 Bq/kg body wt; 180 to 370 Bq/pmol) was given orally with 25 g of D-xylose (to assess intestinal absorptive function). These materials were dissolved in fruit juice and consumed about midway through ingestion of the normal breakfast meal. The usual carnitine supplement was consumed with the meal. Blood samples were obtained from an indwelling, forearm venous catheter over 48 hours for assessment of D-xylose absorption and appearance of radiolabeled carnitine and metabolites in the circulation. Additional blood samples were obtained via venipuncture twice daily for the remainder of the study. Complete 24-hour fecal excretions were collected for 5 days after administration of the test dose. Complete 24-hour urine collections were obtained from day 1 until the end of the study. Urine was stored at −80°C until analyzed. Feces were stored at −80°C until dried by lyophilization. The dried feces were stored at −20°C until extracted and analyzed.

Analytical Methods

Radioactivity in fecal extracts and urine was determined by liquid scintillation counting of 0.2-mL (fecal extract) or 1.0-mL (serum or urine) aliquots in 5 mL of Ready Gel (Beckman Instruments, Fullerton, CA). Counting efficiency was determined with a [^{3}H]toluene internal standard. Aliquots of urine and food homogenates were prepared and assayed for free and total carnitine as previously described.[15] Carnitine in feces was measured following extraction, hydrolysis, and anion-exchange chromatography.[11] The method of standard additions was used to correct for interference of the enzymatic reaction equilibrium by contents of the fecal extract.[11] Urinary creatinine was measured by an automated Jaffe-based method.[13] D-Xylose in serum and urine was determined by the method of Eberts et al.[16]

Urine and feces were prepared for and analyzed by cation-exchange chromatography and liquid scintillation counting, as described previously.[11] Urinary and fecal metabolites were purified for analysis by desalting of the appropriate column fractions following cation-exchange column chromatography.[17] The urinary metabolite was further purified by high-performance cation-exchange chromatography[11] and desalting before analysis. [*methyl*-^{3}H]L-Carnitine and radiolabeled metabolites in serum were separated by high-performance cation-exchange chromatography and quantified by liquid scintillation counting of effluent fractions.[11]

Mass spectra of the major urinary and fecal metabolites were provided by the University of Iowa High Resolution Mass Spectrometry Facility, using a ZAB-HF high-resolution mass spectrometer (VG Instruments, Stamford, CT). Spectra for the urine metabolite and the standard compound were generated by mass spectrometry in the electron ionization mode, using a direct insertion probe. Spectra for the fecal metabolite and the standard compound were obtained by fast atom bombardment mass spectrometry.

RESULTS

None of the participants reported any adverse affects during or following completion of the study. D-Xylose concentration in serum was highest 0.75 to 1.75 hours (mean, 1.2 hours) following ingestion of the test dose (Fig 1). Urinary recovery of the test dose was 23% to 34% (mean, 27%) by 24 hours. Based on these results, all participants were judged to have normal intestinal absorptive function.

Table 2. Intake and Excretion of Carnitine by Human Subjects

Subject No.	Carnitine Intake (μmol/kg/d)	Urinary Carnitine Excretion* (μmol/kg/d)	Urinary Carnitine Excretion* (mmol/mol creatinine)	Fecal Carnitine Excretion† (μmol/kg/d)	Total Carnitine Excretion (μmol/kg/d)
1	114	25.8 (3.17)	166 (19.3)	0.160	26.0
2	171	32.7 (4.39)	147 (16.6)	0.0996	32.8
3	125	19.8 (3.15)	128 (16.7)	0.0931	19.9
4	141	25.3‡	129 (28.9)	0.220	25.6
5	154	27.1 (6.42)	134 (27.2)	0.495	27.6
Mean (SD)§	141 (22.5)	26.1 (4.61)	144 (14.2)	0.214 (0.166)	26.4 (4.62)

*Mean (SD) for 11 days (study days 5 through 15).

†Mean (SD) for 5 days (study days 5 through 9).

‡Mean of values for days 5 and 6; see footnote ‡ of Table 1.

§Mean (SD) of means for all five subjects.

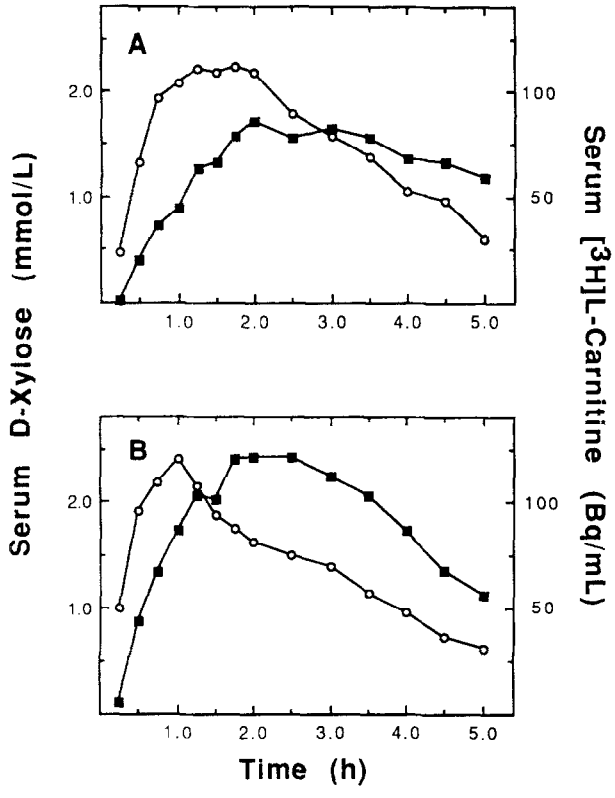

Fig 1. Appearance of D-xylose (○) and [^{3}H]L-carnitine (■) in serum following oral administration with a morning meal. Twenty-five grams of D-xylose was dissolved in a fruit drink and administered with the tracer dose of [*methyl*-^{3}H]L-carnitine and a carnitine supplement, all ingested with the morning meal. (A) Subject no. 2; (B) subject no. 5.

Oral administration of a single tracer dose of [*methyl*-^{3}H]L-carnitine with a meal was used to assess the metabolic fate of dietary carnitine. [*methyl*-^{3}H]L-Carnitine appeared in serum within 15 minutes after ingestion of the test dose; however, the peak of radiolabeled carnitine did not occur for 2.0 to 4.5 hours (mean, 3.0 hours; Figs 1 and 2) following administration of the tracer. Thus, carnitine was absorbed relatively slowly, compared to the rapidly absorbed sugar D-xylose. One major metabolite of [*methyl*-^{3}H]L-carnitine was detected in serum. The chromatographic properties of this metabolite were identical with those of trimethylamine oxide. Appearance of the metabolite was biphasic in four of five subjects, with maxima occurring at 1.25 to 6.0 hours (mean, 2.6 hours) and 16 to 30 hours (mean, 24 hours) following administration of the tracer (Fig 2).

All participants in the study excreted less carnitine than they consumed (mean, 18%; Table 2). This result is consistent with the data obtained by Segre et al[8] and Harper et al[9] by pharmacokinetic analysis. For all subjects, fecal carnitine excretion accounted for less than 2% of total carnitine excretion. Cation-exchange chromatography and liquid scintillation counting revealed two major radioactive species in urine of all subjects (Table 3 and Fig 3A). One radioactive metabolite eluted from the column coincident with carnitine. A second, more basic, peak of radioactivity behaved chromatographically like trimethylamine *N*-oxide (Table 4), and was positively identified by mass spectrometry ($[M\cdot]^+$ at $m/z = 75$ and $[M - OH]^+$ at $m/z = 58$; identical with authentic trimethylamine *N*-oxide].

One major metabolite was excreted in feces, which accounted for as much as 45% of the administered dose (Table 3 and Fig 3B). This metabolite was tentatively

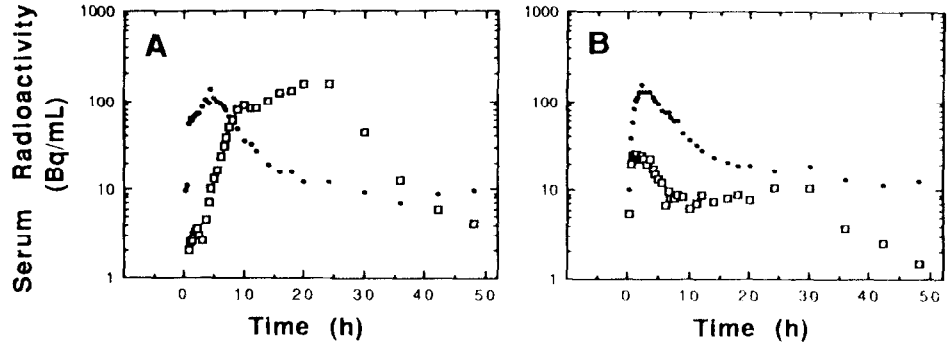

Fig 2. Appearance of [^{3}H]L-carnitine (●) and [^{3}H]trimethylamine oxide (□) in serum following oral administration of [*methyl*-^{3}H]L-carnitine. (A) Subject no. 1; (B) subject no. 4.

Table 3. Excretion of Radiolabeled Carnitine and Metabolites by Human Subjects Following Ingestion of [methyl-^{3}H]L-Carnitine

	Percent of Dose Administered						
	Urine			Feces			
Subject No.	Carnitine	Trimethylamine Oxide	Other Metabolites	Carnitine	γ-Butyrobetaine	Other Metabolites	Total Excretion as Metabolites
1	6.64	49.1	2.96	0.161	5.76	0.172	58.0
2	4.01	42.5	2.79	0.101	12.0	2.10	59.4
3	6.82	47.0	3.18	0.053	0.441	0.586	51.2
4	7.63	8.39	2.38	0.121	39.8	1.08	51.6
5	6.40	7.76	2.94	0.242	44.7	1.86	57.3
Mean (SD)	6.30 (1.36)	31.0 (21.0)	2.85 (0.30)	0.136 (0.071)	20.5 (20.3)	1.16 (0.82)	55.3 (3.8)

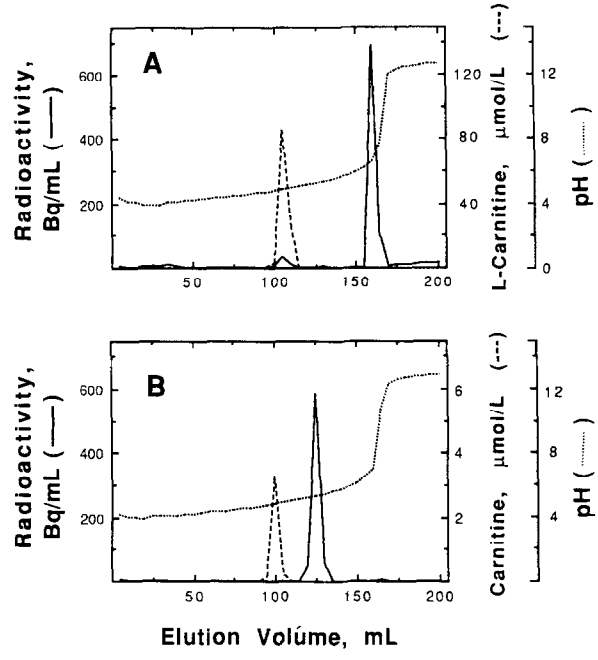

Fig 3. Cation-exchange column chromatography of urine and fecal extracts following administration of [*methyl*-^{3}H]L-carnitine. Preparation of urine and fecal extracts, and chromatographic conditions, were as previously described.[11,17] Urine chromatogram (A) shown is from subject no. 2; specimens collected 0 to 24 hours after administration of the tracer. The fecal extract chromatogram (B) shown is from subject no. 4, specimens collected 48 to 72 hours after administration of the tracer.

identified by chromatographic comparisons as γ-butyrobetaine (Table 4). Positive identification was obtained by mass spectrometry (positive ion at $m/z = 146$; identical with authentic γ-butyrobetaine). A peak of radioactivity coincident with carnitine was observed in all fecal chromatograms, but accounted for less than 0.5% of the isotope administered in all subjects (Table 3).

For all subjects, greater than 5% of the administered dose of [*methyl*-^{3}H]L-carnitine appeared in urine as [^{3}H]trimethylamine *N*-oxide within 24 hours (Figure 4A). Excretion of this metabolite, as a percentage of the administered dose, rapidly declined but was still detectable in urine after 11 days. Fecal [^{3}H]γ-butyrobetaine accounted for a mean of approximately 20% of the dose of [*methyl*-^{3}H]L-carnitine within 48 hours of administration, but rapidly declined to virtually undetectable levels after 3 days (Fig 4B).

For three subjects, cumulative excretion of [^{3}H]trimethylamine *N*-oxide in urine was high (42% to 49% of the administered dose) and fecal [^{3}H]γ-butyrobetaine excretion was relatively low (0.4% to 12% of the administered radioactivity). However, for the remaining two subjects, urinary [^{3}H]trimethylamine *N*-oxide excretion was relatively low (8%) and fecal [^{3}H]γ-butyrobetaine excretion was high (40% to 45% of the administered dose). For all subjects, excretion of all radioactive metabolites accounted for 51% to 59% (mean, 55%) of the administered [*methyl*-^{3}H]L-carnitine.

DISCUSSION

It has been known for a number of years that microorganisms of the rat gastrointestinal tract metabolize dietary carnitine.[17,18] We have shown previously that carnitine ingested by humans at levels normally found in the diet is significantly degraded, presumably by intestinal microflora.[11] Those results are consistent with inferences from previous kinetic studies in humans.[12] In this report, we quantitate the extent to which non-absorbed dietary carnitine supplements are degraded, and show that the rate of absorption of carnitine in humans is relatively slow. The latter observation is consistent with data reported by Gross and Henderson[19] and Gudjonsson et al,[20] in which they showed that in the rat carnitine is rapidly taken up by the intestinal mucosa, but is only slowly released into the circulation.

Table 4. Chromatographic Analysis of Major Urinary and Fecal Metabolites of [methyl-^{3}H]L-Carnitine

	Thin-Layer Chromatography (R_f)		Paper Chromatography‡ (R_f)	Ion-Exchange Liquid Chromatography§ (elution volume [mL])	High-Performance Cation-Exchange Liquid Chromatography¶ (elution volume [mL])
	System 1*	System 2†			
Major urinary metabolite	68	59	59	160	15
Trimethylamine *N*-oxide	68	61	59	—	—
Major fecal metabolite	43	42	44	125	10
γ-Butyrobetaine	43	44	44	125	10
L-Carnitine	35	56	32	100	7

*Mobile phase: methanol/concentrated NH_4OH (75:25); stationary phase: silica gel G (Analtech, Newark, DE), 250-μm layer on glass plate developed to 15 cm; visualized with I_2 vapor.

†Mobile phase: methanol/acetone/concentrated HCl (90:10:4); stationary phase and conditions as above.

‡Mobile phase: 1-butanol/glacial acetic acid/water (60:15:25); stationary phase: Whatman 3MM paper; developed to 25 cm (descending); visualized with I_2 vapor.

§Stationary phase: AG50W-X8 cation exchange resin (200 to 400 mesh, Bio-Rad; Na^+ form, equilibrated with buffer A) packed in a water-jacketed glass column, 9 × 500 mm; mobile phase: linear gradient of 100% A (sodium citrate, pH 4.08 [0.25 mol/L in Na^+], 1% polyethylene glycol 400 [Carbowax PEG 400; Fisher]) to 100% B (0.25 mol/L NaOH) over 8 h; flow rate 30 mL/h at 50°C.

¶Stationary phase: Aminex A-9 cation exchange resin packed in stainless steel column, 4 × 250 mm (Bio-Rad, Richmond, CA); mobile phase: linear gradient of 75% A (sodium citrate, pH 4.25 [0.2 mol/L in Na^+], 0.1% phenol), 25% B (0.2 mol/L NaOH, 0.1% phenol) to 25% A, 75% B over 20 min; flow rate 1.0 mL/min at ambient temperature.

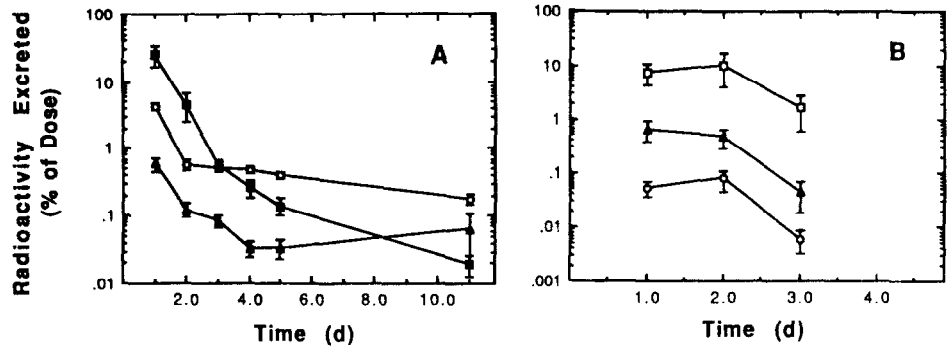

Fig 4. Excretion of radiolabeled carnitine and metabolites in urine (A) and feces (B). ○, [^{3}H]L-carnitine; ■, [^{3}H]trimethylamine oxide; □, [^{3}H]γ-butyrobetaine; ▲, all other radiolabeled metabolites. Bars indicate SEM (n = 5).

The biphasic appearance of [^{3}H]trimethylamine oxide in the circulation suggests that a portion of ingested carnitine may have been degraded prior to entry into the large intestine. Thus, we propose that the early peak (1.25 to 6 hours) of radioactivity in trimethylamine oxide appearing in the circulation arose from degradation of the tracer in the oral cavity, stomach and/or the small intestine, by the action of indigenous bacteria (oral cavity) or bacteria ingested with the meal. The late peak (16 to 30 hours) of [^{3}H]trimethylamine oxide in the circulation most likely arose from large-intestinal bacterial degradation of the ingested tracer. Alternatively, the biphasic nature of [^{3}H]trimethylamine oxide may have been due to tissue trapping of the metabolite and its subsequent slow release.

In an earlier report,[11] we quantified the extent of carnitine degradation at two different levels of carnitine normally found in western diets (2 and 10 μmol/[kg body wt] · d). We found that at these two levels of dietary carnitine, 25.3% and 36.7% of a tracer dose of [*methyl*-^{3}H]L-carnitine was excreted as metabolites other than carnitine. In this study, we found that at a carnitine intake of 141 μmol/[kg body wt] · d, 55% of the tracer dose was excreted as metabolites. These results further support the conclusion that the extent of absorption (percent absorbed) of carnitine is inversely proportional to the level of intake, and conversely, the degree to which carnitine is degraded in the intestinal tract is directly proportional to the quantity ingested.

Further suggestion of the extent of carnitine degradation in the gastrointestinal tract arises from the discrepancy between the amount of radioactive metabolites recovered in urine and feces as a percent of administered dose, and the percent of total carnitine ingested that was not accounted for by excretion in urine and feces. For subjects receiving the carnitine supplement, these results were 55% and 82%, respectively. Thus, in addition to the 55% recovered as nonvolatile metabolites in urine and feces, another 27% of the administered dose of [*methyl*-^{3}H]L-carnitine may have been excreted as volatile metabolite(s). In our previous study of rats,[17] we found no $^{14}CO_2$ or [^{14}C]trimethylamine in expired air from rats given [*methyl*-^{3}H]L-carnitine orally. Thus, we considered it unlikely that these metabolites would be excreted in humans. However, in conventional rats we accounted for only 61% to 86% of the administered radioactivity, whereas in germ-free rats 91% of the radioactivity was recovered.[17] Thus, it is likely that in both rats and humans, other metabolite(s) (perhaps methane) were excreted following oral administration of methyl group-radiolabeled carnitine.

Quantitatively, the degree to which oral carnitine is metabolized to other compounds is greater in humans than in rats. For example, in human subjects receiving the carnitine supplement, at least 55% of the dose was degraded, compared to 35% in rats receiving a comparable amount (relative to body weight) of dietary carnitine. Because virtually all of the nonabsorbed carnitine must have been degraded (very little appeared in feces in either species), these results suggest that the human small intestine (on a body weight basis) may not possess as high an absorptive capacity for carnitine as does that of the rat.

The use of oral carnitine supplementation for treatment of a variety of disorders has been efficacious in many cases. However, the very large doses now prescribed in these treatments may be unnecessary and perhaps unwarranted. In view of the findings of Segre et al[8] and Harper et al[9] and those presented here, it would seem that increasing the level of carnitine supplementation beyond a certain point may not produce an increased therapeutic effect, due to the inefficiency of absorption of carnitine at very high intakes. Moreover, metabolites of carnitine produced by the gastrointestinal flora may have as yet undetermined deliterious effects.

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