Kinetics, Pharmacokinetics, and Regulation of 
L-Carnitine and Acetyl-L-carnitine Metabolism

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ABSTRACT: In mammals, the carnitine pool consists of nonesterified L-carnitine and many acylcarnitine esters. Of these esters, acetyl-L-carnitine is quantitatively and functionally the most significant. Carnitine homeostasis is maintained by absorption from diet, a modest rate of synthesis, and efficient renal reabsorption. Dietary L-carnitine is absorbed by active and passive transfer across enterocyte membranes. Bioavailability of dietary L-carnitine is 54–87% and is dependent on the amount of L-carnitine in the meal. Absorption of L-carnitine dietary supplements (0.5–6 g) is primarily passive; bioavailability is 14–18% of dose. Unabsorbed L-carnitine is mostly degraded by microorganisms in the large intestine. Circulating L-carnitine is distributed to two kinetically defined compartments: one large and slow-turnover (presumably muscle), and another relatively small and rapid-turnover (presumably liver, kidney, and other tissues). At normal dietary L-carnitine intake, whole-body turnover time in humans is 38–119 h. In vitro experiments suggest that acetyl-L-carnitine is partially hydrolyzed in enterocytes during absorption. In vivo, circulating acetyl-L-carnitine concentration was increased 43% after oral acetyl-L-carnitine supplements of 2 g/day, indicating that acetyl-L-carnitine is absorbed at least partially without hydrolysis. After single-dose intravenous administration (0.5 g), acetyl-L-carnitine is rapidly, but not completely hydrolyzed, and acetyl-L-carnitine and L-carnitine concentrations return to baseline within 12 h. At normal circulating L-carnitine concentrations, renal L-carnitine reabsorption is highly efficient (90–99% of filtered load; clearance, 1–3 mL/min), but displays saturation kinetics. Thus, as circulating L-carnitine concentration increases (as after high-dose intravenous or oral administration of L-carnitine), efficiency of reabsorption decreases and clearance increases, resulting in rapid decline of circulating L-carnitine concentration to baseline. Elimination kinetics for acetyl-L-carnitine are similar to those for L-carnitine. There is evidence for renal tubular secretion of both L-carnitine and acetyl-L-carnitine. Future research should address the correlation of supplement dosage, changes and maintenance of tissue L-carnitine and acetyl-L-carnitine concentrations, and metabolic and functional changes and outcomes.

KEYWORDS: L-carnitine; acetyl-L-carnitine; kinetics; pharmacokinetics; absorption; reabsorption; degradation; kidney; liver; skeletal muscle; human

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INTRODUCTION

Carnitine homeostasis in humans is maintained by acquisition of carnitine from dietary sources, a modest rate of endogenous carnitine biosynthesis, and efficient reabsorption of carnitine. Distribution of carnitine and its esters among tissues and the extracellular compartment and maintenance of substantial concentration gradients between some tissues and the extracellular compartment are regulated by cell membrane transporters and by intracellular enzymes that interconvert carnitine and its esters. L-Carnitine and acetyl-L-carnitine provided as pharmaceuticals or dietary supplements perturb normal endogenous carnitine kinetics. However, because carnitine kinetics and pharmacokinetics are complex, it is difficult to predict the ultimate disposition of these compounds in cellular and extracellular compartments and thus their impact on cellular metabolism. Nevertheless, studies in humans and experimental animals now provide a window, albeit incomplete, into the metabolic fate of endogenous and exogenous carnitine and its esters.

CARNITINE ABSORPTION, SYNTHESIS, AND ELIMINATION

Dietary carnitine intake by humans ranges from <1 to ~15 µmol/kg body wt/day. Vegans typically acquire very little carnitine from diet, usually <1 µmol/kg body wt/day. Individuals who consume dairy products, some chicken and fish, but little or no red meat, acquire ~1 to 8 µmol carnitine/kg body wt/day. Humans who regularly consume red meat acquire 6 to 15 µmol carnitine/kg body wt/day from their diet. Bioavailability of dietary carnitine for humans consuming a low-carnitine diet (1.53

FIGURE 1. Bioavailability of dietary carnitine. Dietary carnitine intake (full bars) and carnitine absorbed from diet (filled portion of bars) are shown for 12 normal human adults. Numbers above bars are percent of dietary carnitine absorbed. Data are from reference 1.
to 2.12 µmol/kg body wt/day) was 66–86%; for humans consuming a high-carnitine diet (8.40 to 11.8 µmol/kg body wt/day), it was 54–72% of intake (Fig. 1). Studies of carnitine absorption and its components in humans, experimental animals, and cell culture models suggest that carnitine is transported from the intestinal lumen into the enterocyte, but passes across the serosal membrane into the circulation by simple diffusion. In live rats and in vascularly perfused rat small intestine, carnitine is rapidly taken up from the lumen, but is only slowly released into the circulation. High-affinity, saturable, sodium-gradient-driven transport of carnitine into Caco-2 cells and human muscle biopsy specimens was observed. In Caco-2 cells, this activity was located in the brush border membrane, but not in the serosal membrane. Extensive intracellular acetylation of carnitine (50–60%) occurs in rat and guinea pig intestine and in isolated guinea pig enterocytes. In rat and guinea pig intestine, acetyl-L-carnitine is more readily released across the serosal membrane than is nonesterified carnitine. Intracellular acetylation of carnitine may facilitate its diffusion across the serosal membrane. In guinea pig intestine, luminal acetyl-L-carnitine was taken up by intestinal mucosa at about the same rate as nonesterified carnitine, but the calculated efflux of total carnitine into the circulation was 4-fold greater for acetyl-L-carnitine compared to nonesterified carnitine.

Carnitine that is not absorbed in the small intestine is almost completely degraded by indigenous flora of the large intestine. In rats and humans, identified products of degradation of methyl group–labeled carnitine were γ-butyrobetaine, primarily excreted in feces, and trimethylamine, which is absorbed, converted to trimethylamine oxide in the liver, and excreted in urine. Carnitine is synthesized from the amino acid precursors, lysine and methionine. A unique feature of the pathway is the requirement for methylation only of protein-bound lysine. This process and the accessibility of ε-N-trimethyllysine to the mitochondrial site of ε-N-trimethyllysine hydroxylase apparently limit the overall rate of carnitine synthesis. Enzymes catalyzing the several steps in carnitine biosynthesis are ubiquitous, with the exception of the last enzyme, γ-butyrobetaine hydroxylase. This enzyme is not found in skeletal muscle and heart, and is most active in liver, kidney, and testis. The rate of carnitine biosynthesis in humans has been estimated to be about 1 to 2 µmol/kg body wt/day.

Carnitine is eliminated from the body primarily by renal excretion of nonesterified carnitine and acylcarnitine esters. However, under normal conditions, only a very small fraction (usually <5%) of filtered carnitine is excreted. At normal circulating concentrations, carnitine is efficiently conserved via reabsorption, a process facilitated by active transport of carnitine and its short-chain esters by the transporter OCTN2 in the renal brush border membrane. The efficiency of carnitine reabsorption increases as dietary intake of carnitine decreases, independent of glomerular filtration rate and filtered load. This adaptive response serves to maintain circulating carnitine concentration in the face of decreased input from dietary intake. Conversely, the rate of carnitine excretion increases rapidly, and the efficiency of carnitine reabsorption decreases as the filtered load of carnitine increases above normal, as for example following ingestion of a dietary carnitine supplement or by intravenous infusion of carnitine. A “threshold” effect is observed at near-normal plasma carnitine concentrations, above which the rate of carnitine excretion soon parallels the increase of filtered load. This homeostatic mechanism serves to maintain circulating carnitine concentrations in a narrow “normal” range.
Radiotracer methodology and kinetic compartmental analysis were used to develop a model for carnitine metabolism in humans.\footnote{11} Disappearance of radioactive tracer from the central extracellular fluid compartment (Fig. 2) mathematically described a three-compartment open system (Fig. 2, inset). Tracer data from 6 human adults were used to calculate carnitine pool sizes and fractional rate constants (Table 1). By comparison to experimentally measured carnitine concentrations and physiological estimates of masses, the mathematically defined compartments corresponded to (A) extracellular fluid, (B) slow-turnover tissues with large mass (e.g., skeletal muscle), and (C) other tissues with limited mass and relatively rapid turnover (likely to include liver and kidney). Mean turnover time for the central compartment was 1.1 h. Mean turnover times for compartments B and C were 191 and 12 h, respectively. Mean whole-body turnover time was 66 h, but the range was wide, 38 to 119 h. The model predictions are mostly consistent with and validated by measured pool sizes and fluxes in individual human subjects. The model was initially applied to carnitine metabolism in dogs, where more extensive validation was obtained.\footnote{12}

**FIGURE 2.** Carnitine kinetics in humans. [Methyl-\(^3\)H]-carnitine tracer (681 µCi) was administered intravenously to a normal human adult. Tracer loss from the extracellular fluid compartment as a function of time (circles) was used to construct a three-compartment open model (inset) for carnitine metabolism in humans. Data are from reference 11.
PHARMACOKINETICS OF L-CARNITINE

Exogenous L-carnitine administered intravenously is rapidly distributed into a central compartment similar to the extracellular fluid volume. Its pharmacokinetics are characterized by rapid elimination by the kidneys, consistent with homeostatic equilibria for endogenous, small, polar substances,\textsuperscript{13,14} which restore baseline conditions. In the case of L-carnitine, saturability of renal carnitine reabsorption and perhaps active secretion of carnitine and its esters into urine return circulating carnitine concentrations to normal within 12 to 24 h of dosing. Large, exogenous, intravenously administered doses of carnitine do to some extent enter intracellular compartments before irreversible elimination because the acylcarnitine ester pool in extracellular fluid increases following intravenous administration of L-carnitine (FIG. 3).\textsuperscript{15}

Single-dose (92.5 or 185 $\mu$mol/kg body wt) intravenous L-carnitine administration had no effect on muscle total carnitine content in exercising adult males.\textsuperscript{16} It is noted that the amounts of carnitine infused in this study and in other single-dose intravenous pharmacokinetic studies in humans are less than 10\% of the endogenous pool of carnitine, most of which is in skeletal muscle. This fact, coupled with rapid renal elimination of the dose, suggests that a single intravenous dose of carnitine should not perturb the skeletal muscle carnitine pool in a measurable way. On the other hand, kinetics of carnitine transport \textit{in vitro} and observations in rats \textit{in vivo}, when extended to humans, suggest that 10–20\% of the dose may enter the liver (net uptake) during the first 2 h after dose administration.\textsuperscript{16}

Bioavailability of oral L-carnitine supplements (600 mg to ~7 g) was in the range of 0.05 to 0.25 (TABLE 2).\textsuperscript{15,17–20} For an oral dose of L-carnitine at 30 mg/kg body wt, peak plasma carnitine concentration ($C_{\text{max}}$) above baseline was 27 $\mu$mol/L\textsuperscript{18} and 29 $\mu$mol/L\textsuperscript{16} at 3 h and 6 h postdose, respectively. At the 100 mg/kg body wt dose, peak plasma carnitine concentration was 91 $\mu$mol/L (baseline subtracted) at 3 h postdose.\textsuperscript{16,18} After single-dose administration, plasma carnitine concentrations returned to baseline within 24 h.

<table>
<thead>
<tr>
<th>TABLE 1. Kinetic parameters for carnitine metabolism in humans</th>
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<tr>
<td>Carnitine pool sizes (mmol)</td>
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<tr>
<td>$Q_a$</td>
</tr>
<tr>
<td>$Q_b$</td>
</tr>
<tr>
<td>$Q_c$</td>
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<tr>
<td>Fractional rate constants (h$^{-1}$)</td>
</tr>
<tr>
<td>$k_{ab}$</td>
</tr>
<tr>
<td>$k_{ac}$</td>
</tr>
<tr>
<td>$k_{ba}$</td>
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<tr>
<td>$k_{ca}$</td>
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<td>$k_{oa}$</td>
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</tbody>
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\textit{Note:} Values are the mean ± SD for 6 healthy human adults. Data from reference 11.
Bioequivalence of oral dosage forms (330-mg tablet, 1-g chewable tablet, and enteral solution) was demonstrated in a multiple-dose pharmacokinetic study of 15 healthy adult males. Each subject received 2 g of L-carnitine every 12 h. Steady-state conditions, based on plasma carnitine concentrations, were achieved by the third day. $C_{\text{max}}$, $t_{\text{max}}$, and $C_{\text{min0}}$ for plasma total carnitine were 89 to 93 µmol/L, 3.0 to 3.4 h, and 64 to 65 µmol/L, respectively.

### TABLE 2. Bioavailability of oral carnitine supplements

<table>
<thead>
<tr>
<th>Dose</th>
<th>Bioavailability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 &amp; 6 g</td>
<td>0.04–0.25</td>
<td>Harper et al.\textsuperscript{17}</td>
</tr>
<tr>
<td>30 &amp; 100 mg/kg body wt</td>
<td>0.15</td>
<td>Rizza et al.\textsuperscript{18}</td>
</tr>
<tr>
<td>100 mg/kg body wt</td>
<td>0.18</td>
<td>Segre et al.\textsuperscript{15}</td>
</tr>
<tr>
<td>2 g every 12 h</td>
<td>0.14–0.16</td>
<td>Sahajwalla et al.\textsuperscript{19}</td>
</tr>
<tr>
<td>600 mg, 3 times/day</td>
<td>0.17</td>
<td>Rebouche\textsuperscript{20}</td>
</tr>
</tbody>
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**FIGURE 3.** Carnitine and short-chain acylcarnitine concentrations in plasma after bolus intravenous administration of carnitine. L-Carnitine (30 mg/kg body wt) was administered intravenously to 6 healthy adult males. Nonesterified carnitine (open circles) and short-chain acylcarnitine ester (filled circles) concentrations in plasma were obtained. Baseline concentrations are subtracted from the data shown. Data are from reference 15.
The effect of an oral multiple-dose L-carnitine supplement on steady-state circulating carnitine concentrations and urinary carnitine excretion was studied in 11 healthy adult males. All were fed standard balanced diets providing maintenance energy requirements and 8.0–11.9 µmol L-carnitine/kg body wt/day. All subjects consumed these diets for 15 days. Five subjects consumed an L-carnitine supplement, 2 g/day, divided approximately equally in three doses and taken with meals at approximately 8 A.M., 12 noon, and 6 P.M. Blood was collected fasting before the morning meal and immediately before the evening meal. Serum total carnitine concentrations for days 6 to 15 are shown. Triangles, no supplement; circles, plus dietary supplement; open symbols, morning blood samples; filled symbols, evening blood samples. Lines are regressions for the four groups of data.

The effect of an oral multiple-dose L-carnitine supplement on steady-state circulating carnitine concentrations and urinary carnitine excretion was studied in 11 healthy adult males. All were fed standard balanced diets providing maintenance energy requirements and 8.0–11.9 µmol L-carnitine/kg body wt/day. All subjects consumed these diets for 15 days. Five subjects were given oral L-carnitine supplements, 2 g each day, in 3 approximately equal doses, with meals at approximately 8 A.M., 12 noon, and 6 P.M. These supplements were begun 10 days before start of the standard dietary regimen and continued until the completion of the study. On days 6 through 15 of the dietary regimen, serial blood specimens (one fasting before the morning meal and the second before the evening meal) and complete 24-h urine voids were collected and analyzed for nonesterified and total carnitine. Those individuals consuming the supplement maintained plasma total carnitine concentrations on average about 25 µmol/L higher than the unsupplemented group (FIG. 4). Trough total carnitine concentrations (from morning fasting blood specimens) were 22 µmol/L higher in the supplemented group than in the unsupplemented group. Steady-state urinary carnitine excretion was 304 µmol/g of creatinine and
1257 µmol/g of creatinine for the unsupplemented and the supplemented groups, respectively. These results demonstrate that multiple-dose oral carnitine supplements can maintain circulating carnitine concentrations above normal even when the capacity to reabsorb carnitine is saturated.

A single oral dose of a carnitine supplement (up to 4 g) does not increase skeletal muscle carnitine concentration because its impact on the total carnitine pool is very small. However, repeated-dose carnitine supplements may modestly increase the skeletal muscle carnitine concentration. For example, in long-distance runners given 2 g of carnitine per day for 28 days and subjected to a 4-week training period, skeletal muscle carnitine concentration increased ~13%. In a comparison group given a placebo, skeletal muscle carnitine concentration decreased by 10% after 4 weeks of training. Similarly, a group of long-distance runners and sprinters were given 1 g of carnitine per day for 120 days, during which time all participants underwent a physical training program. In the group receiving the placebo, skeletal muscle total carnitine content decreased 5–6%; however, in the group receiving the carnitine supplement, skeletal muscle total carnitine content increased 8–10%. On the other hand, in two studies conducted with individuals performing submaximal exercise or high-intensity sprint cycling, skeletal muscle total acid-soluble carnitine content was not changed after 14 days of supplementation with 4 or 6 g of L-carnitine per day.

**PHARMACOKINETICS OF ACETYL-L-CARNITINE**

Acetyl-L-carnitine, as a dietary supplement, appears to slow or reverse the effects of aging in rats. Clinical studies in humans demonstrating positive effects of acetyl-L-carnitine on brain function, cognition, and memory led to the suggestion that acetyl-L-carnitine may slow or reverse mild cognitive impairment and the progression of dementia in Alzheimer’s disease. A therapeutic benefit of acetyl-L-carnitine has been suggested in human immunodeficiency virus–infected humans treated with nucleoside analogues, and, as a dietary supplement, it may improve symptoms of fatigue in humans.

Despite its use in clinical studies, little is known about the metabolic disposition of acetyl-L-carnitine. Bioavailability of oral acetyl-L-carnitine has not been studied in normal humans. In older humans (70–86 years) with senile dementia (probable Alzheimer’s disease), oral administration of acetyl-L-carnitine·HCl at 2 g/day divided into three doses for 50 days raised the plasma concentration of acetyl-L-carnitine from 7.2 to 10.3 µmol/L. Nonesterified L-carnitine concentration in plasma was unchanged and total L-carnitine (nonesterified carnitine plus all acylcarnitine esters) rose modestly from 50.7 to 55.5 µmol/L.

Acetyl-L-carnitine·HCl administered intravenously as a bolus (500 mg) to normal adult humans was mostly excreted in urine, as nonesterified L-carnitine and acetyl-L-carnitine, during the first 24 h after dosing. Area-under-the-curve (AUC) measurements for plasma L-carnitine and acetyl-L-carnitine returned to baseline between 24 and 48 h after administration of the bolus. Clearance of transformation (conversion of acetyl-L-carnitine to L-carnitine; CL_{A,B}) was calculated for the period of 0 to 24 h after dose administration. CL_{A,B} was 14.1 L/h and 9.04 L/h for females and males, respectively. Average renal clearance of acetyl-L-carnitine over the same time period
was much slower, 1.32 L/h and 0.93 L/h for females and males, respectively. These results suggest that a large proportion of the acetyl moiety of the exogenously administered acetyl-L-carnitine is either rapidly utilized or stored (in a form other than acetyl-L-carnitine).

UNRESOLVED QUESTIONS AND OPPORTUNITIES FOR FURTHER RESEARCH

Does the therapeutic effect of L-carnitine require that target tissue concentration be increased, or only that an exchange between intra- and extracellular compartments occur prior to irreversible elimination via the kidneys? Extracellular non-esterified carnitine may exchange with intracellular acylcarnitine esters, thus removing those esters from the intracellular environment. This process could modulate the rate of fatty acid- and/or glucose-derived carbon flow through the citric acid cycle and electrons through the electron transport chain, and thus reduce the potential for oxidative damage due to inefficient electron flow. Exchange may occur with very low concentrations of toxic acylcarnitine esters, thereby increasing cellular longevity and metabolic health. Acylcarnitine ester concentrations in the circulation and acylcarnitine ester excretion rapidly increase following an oral or intravenous administration of L-carnitine supplement, but the quantitative and functional significance of this exchange has not been evaluated.

Do changes in intracellular L-carnitine concentration or changes in intracellular concentrations of specific acylcarnitine esters directly or indirectly trigger changes in metabolic activity? Modest increases in tissue carnitine concentration may occur with repeated-dose L-carnitine supplementation. L-Carnitine or its esters may regulate expression of specific genes. Modest changes in the concentrations of these metabolites may subtly alter expression of these genes, leading to changes in enzyme concentrations that shift metabolic activity of affected cells. Alternatively, or in addition, L-carnitine and/or its esters may protect specific proteins from oxidative damage, by binding to specific, vulnerable sites. Modest increases in the concentrations of these compounds would favor increased binding, and thus increased protection. Liu and colleagues have demonstrated this effect on carnitine acetyltransferase in vitro. L-Carnitine and/or its esters may also affect, in a concentration-dependent manner, the phosphorylation state of key enzymes in metabolism whose activity is regulated by this reversible covalent modification. Dietary supplementation of endurance athletes with L-carnitine at 2 g b.i.d. for 4 weeks resulted in substantial increases in activities of skeletal muscle pyruvate dehydrogenase and the respiratory chain enzymes, NADH-cytochrome c reductase, succinate-cytochrome c reductase, and cytochrome c oxidase (Table 3). The mechanism or mechanisms underlying these changes have not been established.

Acetyl-L-carnitine given as an oral supplement or as a therapeutic agent to rats and to humans has been shown to provide some health-related benefits. Information available from a very few pharmacokinetic studies indicates that much of the acetyl-L-carnitine that is absorbed is rapidly cleaved, presumably by trans-acetylation or by hydrolysis. The question arises: Do the benefits of oral acetyl-L-carnitine, either as a supplement or as a therapeutic agent, stem from intact acetyl-L-carnitine directed to target tissues, from the acetyl unit as acetate or some other activated form, or from
l-carnitine derived from the parent molecule? Thus far, in vivo pharmacokinetic studies to determine the metabolic fate of acetyl-L-carnitine and its two component parts have been inadequate to answer this question.

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REFERENCES


