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

Charles J. Rebouche, Ph.D.
Carrier-mediated and Passive

Carnitine + Acetyl-CoA

↓↓

Acetylcarnitine + CoA

Passive Paracellular

Passive Transcellular
Absorption of Dietary L-Carnitine

Metabolism of L-Carnitine in the Large Intestine

L-Carnitine

\[ \text{Crotonobetaine} \]

\[ \text{γ-Butyrobetaine} \]

\[ \text{Trimethylamine} \]

\[ \text{Trimethylamine Oxide} \]

Liver

Feces

Urine
Carnitine Kinetics in Humans

Data from: Rebouche & Engel (1984) J Clin Invest 73, 857-867
A Kinetic Model for Carnitine Metabolism in Humans

Endogenous synthesis

\[ Q_c \] 3.1 mmol

Absorbed from diet

\[ Q_a \] 0.81 mmol

\[ K_{ca} = 0.30 \]
\[ K_{ac} = 0.087 \]

\[ K_{ab} = 0.005 \]
\[ K_{ba} = 0.52 \]

\[ Q_b \] 84 mmol

\[ K_{oa} = 0.071 \]

Urinary Excretion

Data from: Rebouche & Engel (1984) J Clin Invest 73, 857-867
Renal Carnitine Excretion

Diet Supplement

Diet -> Small Intestine -> Large Intestine

Extracellular Fluid

Liver

Other Tissues

Kidney

Synthesis

Urinary Excretion

Fecal Excretion

Microbial Degradation

Reabsorption
## Bioavailability of Oral Carnitine Supplements

<table>
<thead>
<tr>
<th>Dose</th>
<th>Bioavailability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
<td>0.16</td>
<td>Harper et al., 1988</td>
</tr>
<tr>
<td>6 g*</td>
<td>0.05</td>
<td>Harper et al., 1988</td>
</tr>
<tr>
<td>30 and 100 mg/kg</td>
<td>0.16, 0.14</td>
<td>Rizza et al., 1992</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>0.18</td>
<td>Segre et al., 1988</td>
</tr>
<tr>
<td>2 g every 12 h</td>
<td>0.14 - 0.16</td>
<td>Sahajwalla et al., 1995</td>
</tr>
<tr>
<td>600 mg, 3 times/day</td>
<td>0.17</td>
<td>Rebouche, 1991</td>
</tr>
</tbody>
</table>
# Kinetic Parameters for Oral Carnitine Supplements

<table>
<thead>
<tr>
<th>Dose</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g</td>
<td>4.9</td>
<td>6.5</td>
<td>Harper et al., 1988</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>5.2</td>
<td>1.9</td>
<td>Segre et al., 1988</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>3.7</td>
<td></td>
<td>Segre et al., 1988</td>
</tr>
<tr>
<td>30 mg/kg</td>
<td>3.0</td>
<td>3.0</td>
<td>Rizza et al., 1992</td>
</tr>
<tr>
<td>100 mg/kg</td>
<td>3.5</td>
<td>4.1</td>
<td>Rizza et al., 1992</td>
</tr>
<tr>
<td>2 g</td>
<td>3.1–3.4</td>
<td></td>
<td>Sahajwalla et al., 1995</td>
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<tr>
<td>600 mg</td>
<td>4.0</td>
<td></td>
<td>Rebouche, 1991</td>
</tr>
</tbody>
</table>
Serum Response to Multiple Oral Dosing

- Open circles - 8 am sample
- Filled circles - 6 pm sample
- Blue circles - carnitine supplement
- Red circles - no supplement
Carnitine Supplement in Rats

Carnitine Supplement and Acylcarnitine Ester Appearance

- Serum acylcarnitine ester concentrations
  - no supplement: 7.27 µmol/L
  - supplement: 13.9 µmol/L

- Acylcarnitine ester excretion
  - no supplement: 3.27 µmol/kg/day
  - supplement: 6.06 µmol/kg/day

- Ratio, non-esterified carnitine/total carnitine in urine
  - no supplement: 0.58
  - supplement: 0.62
Acetyl-L-carnitine IV Pharmacokinetics

Plasma Concentration (µmol/L)

Acetyl-L-carnitine HCl 500 mg i.v. in healthy volunteers

Time (h)

Acetyl-L-carnitine and L-Carnitine Clearance and Interconversions

<table>
<thead>
<tr>
<th></th>
<th>Renal Clearance</th>
<th>“Clearances of Transformation”</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>$CL_{ALC-LC}$</td>
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<tr>
<td><strong>Sex</strong></td>
<td><strong>Basal</strong></td>
<td>$0-12$</td>
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<tr>
<td>$CL_{ALC}$</td>
<td>$F$</td>
<td>0.57</td>
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<tr>
<td></td>
<td>$M$</td>
<td>0.35</td>
</tr>
<tr>
<td>$CL_{LC}$</td>
<td>$F$</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>$M$</td>
<td>0.24</td>
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Future Research Directions

• Do benefits of oral L-carnitine supplements accrue from increase of intracellular carnitine concentrations, or from increased IC/EC carnitine-acylcarnitine exchange?

• Acetyl-L-carnitine supplements: Where do the acetyl and carnitine moieties go, and how much goes intact (as acetyl-L-carnitine)?
Summary and Highlights

- Dietary carnitine is absorbed by active transport and diffusion processes, whereas supplements are absorbed primarily by diffusion. Intracellular acetylation plays a role in the absorption process.
- Renal excretion/reabsorption provides driving force for homeostatic regulation of carnitine metabolism.
- Rapid carnitine-carnitine and carnitine-acylcarnitine ester exchange occurs between tissues and extracellular compartment.
- Repeated dosing L-carnitine supplements are capable of maintaining increased circulating and probably tissue carnitine concentrations.
- Acetyl-L-carnitine supplements are rapidly deacetylated.