

Carnitine and sports medicine: Use or abuse?

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The appeal of carnitine supplementation to improve exercise performance in healthy subjects

- Carnitine has important roles in muscle bioenergetics
- Muscle carnitine deficiency associated with profound impairment of muscle function
- Carnitine is a natural compound
- Oral carnitine in doses of several grams not toxic
- Muscle carnitine content decreases under various conditions

Thus, more carnitine must be better!

Despite appeal of rationale, no consensus on benefit

Trial data reviewed in several recent publications – examples from conclusions:

“In conclusion, carnitine is an essential element in the oxidative pathway and its absence causes serious muscle disorders but supplementation has no major effect on muscle function”

Le Borgne and Demarquoy, Science & Sports 18:125-133, 2003

“In the aggregate,...these studies suggest that carnitine supplementation does not improve maximal oxygen uptake or metabolic status during exercise in healthy humans.”

Brass, Am J Clin Nutr 72(Suppl):618S-623S, 2000

While benefit not clearly demonstrated, data to date can not be interpreted as excluding any benefit either

Hypothesis - Carnitine supplementation improves exercise performance in healthy subjects: Key questions

1. Can carnitine supplementation increase skeletal muscle carnitine content in healthy subjects?
2. How much carnitine is required to support optimal skeletal muscle metabolism?
3. Does carnitine supplementation alter energy homeostasis during exercise in healthy subjects?
4. How can changes in performance be assessed in healthy subjects?

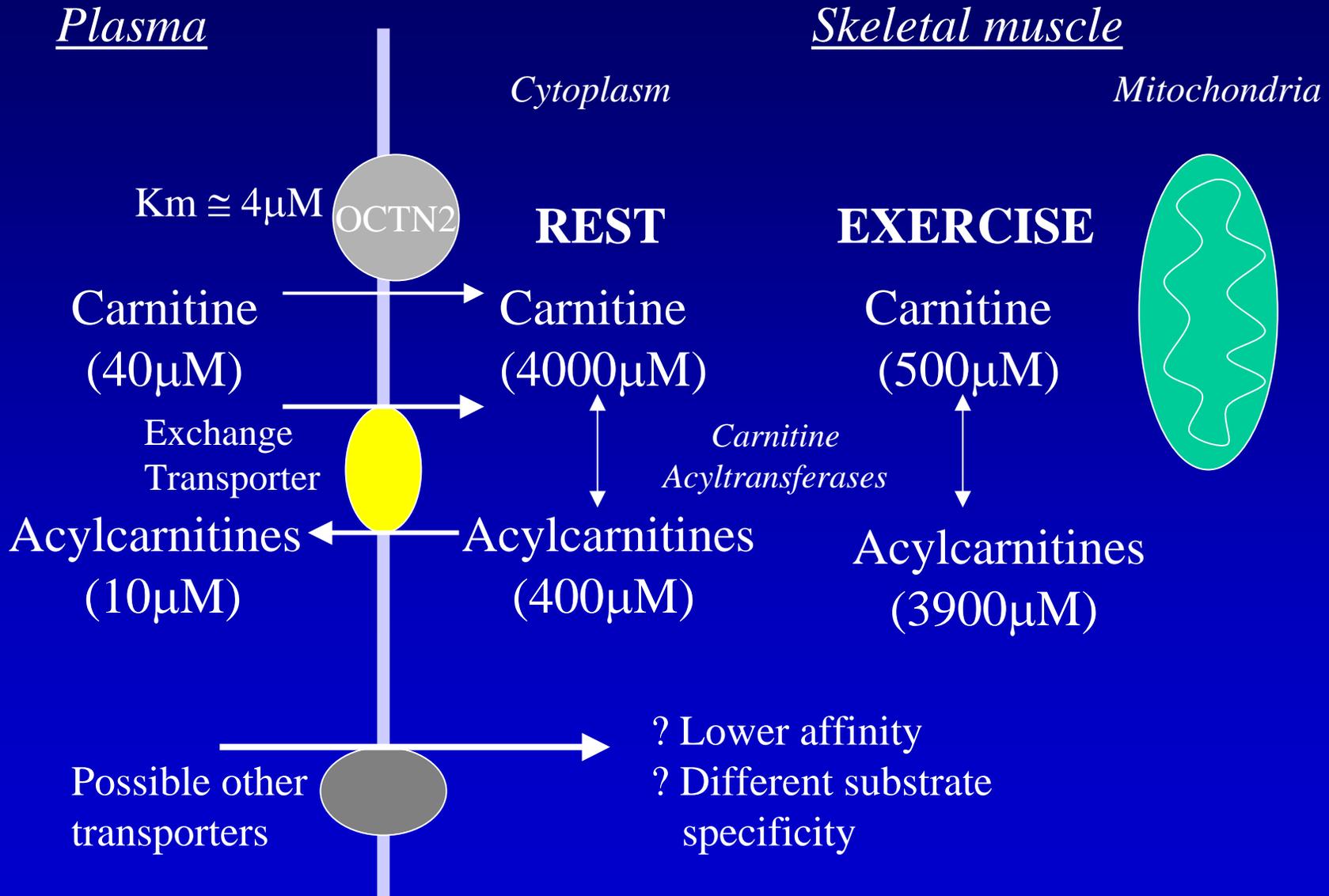
**Can carnitine supplementation
increase skeletal muscle
carnitine content in healthy
subjects?**

What happens when 1 gram of carnitine is administered to a healthy subject?

| | <u>Intravenous</u> | <u>Oral</u> |
|--|--------------------|------------------|
| Reaches systemic circulation | 1 g | 0.15 g |
| Peak plasma [] | 800 μM | 70 μM |
| Initial Vd | | 20 L |
| Removal from central Vd | | Hours |
| Amount recovered in urine over first 24 hours | 0.8 g | 0.09g |

Compare with total body carnitine pool of 20 g

Skeletal muscle carnitine transport



Does carnitine supplementation increase muscle carnitine content in healthy subjects?

MODEL

RESULT

Rat/human – single IV dose: No or little increase in muscle carnitine

Rat chronic oral (10-50d): Muscle carnitine increased 30-70%

Human 4-6 g/d oral x 7-14d: No change in muscle carnitine content
(*Vukovich et al Med Sci Sports Exerc 26:1122, 1994; Barnett et al Int J Sport Nutr 4:280, 1994*)

Humans during training 2g orally x 4-24 weeks: Placebo group decr 10%, carnitine treated increase 10% muscle carnitine
(*Arenas et al Muscle & Nerve 14:598, 1991; Arenas et al FEBS Lett 341:91, 1994*)

Does carnitine supplementation increase muscle carnitine content in healthy subjects?

Thus, IF oral carnitine supplementation increases muscle carnitine content it requires long term therapy and the increase is likely small

How much carnitine is required
to support optimal skeletal
muscle metabolism?

Carnitine requirements for fatty acid oxidation in muscle

- Carnitine palmitoylcarnitine I (muscle form) with K_m for carnitine of 400 – 1000 μM
 - Implies that enzyme saturated with respect to carnitine under normal conditions (more won't make reaction go faster)
 - However, carnitine may be compartmentalized within myocyte
 - Carnitine concentrations fall dramatically during high-intensity exercise (while rates of fatty acid oxidation decrease)
 - CPT I – independent actions of carnitine may have regulatory relevance

Models of muscle carnitine deficiency: Human primary carnitine deficiency

- Primary carnitine deficiency with profound muscle weakness
- Carnitine supplementation dramatically improves function without normalizing muscle carnitine content
 - Carnitine therapy increases muscle carnitine content to between 3 and 50% of normal values

Can functional improvement in disease state be equated with maximizing performance in a healthy individual?

Models of muscle carnitine deficiency: Human pivalate prodrug exposure

- Prodrugs generate pivalate (trimethylacetic acid) after ingestion
- Pivalate metabolized to pivaloyl-CoA, and then to pivaloylcarnitine
- Increased obligatory urinary carnitine losses as pivaloylcarnitine result in total body carnitine deficiency with long term therapy
 - Pivalate prodrug treatment reducing muscle carnitine content by 10 – 60% without reported effects on muscle function
 - Pivalate prodrug treatment reducing muscle content by 90% associated with a variety of symptoms consistent with muscle functional impairment

**Suggests small changes in muscle carnitine content
without consequences**

Thus,

- No data define relationship between muscle carnitine content and muscle metabolism or function
- Clinical and animal data suggest that muscle function sensitive to carnitine content when content <25-50% of normal, but insensitive to changes in muscle carnitine content around the normal value
- Studies in models discussed have not been designed to detect subtle functional changes as muscle carnitine content changes

Does carnitine supplementation
alter energy homeostasis during
exercise in healthy subjects?

Approaches for assessing energy homeostasis

- Labeled substrate fluxes (radio- or stable isotope)
- Whole body respiratory quotient (VCO_2/VO_2)
- VO_2 per work performed
- VO_{2max}
- Lactate accumulation
- Muscle glycogen utilization
- Muscle content of intermediates
- Plasma glucose/fatty acid concentrations
- Expression muscle enzymes

Note: Any changes may not reflect effects of carnitine inside muscle

Carnitine supplementation alters energy homeostasis during exercise

Gorostiaga et al Int J Sports Med 10:169-174, 1989

10 endurance trained subjects (mean VO₂max 62 ml/kg/min)

Double blind, crossover design, placebo vs. 2g/d carnitine x 28d

Exercise at 66% VO₂max x 45 min baseline and after each Rx period

| | <u>Placebo</u> | <u>Carnitine</u> |
|---------------------------------|----------------|------------------|
| RQ at minutes 28-37 of exercise | 0.98 | 0.96 (p<0.04) |
| Blood lactate at 45 min | 3.05 mM | 2.95 (p>0.1) |
| Blood glucose at 40 min | 4.35 mM | 4.63 mM (p>0.1) |
| Blood glycerol at 40 min | 0.198 mM | 0.238 mM (p>0.1) |
| Blood free fatty acids at rest | 0.143 mM | 0.284 mM (p>0.1) |

Siliprandi et al Biochim Biophys Acta 1034: 17-21, 1990

10 subjects 2 g carnitine vs. placebo 1 hr before max exercise

| | | |
|--------------------------------|-------|-----------------|
| Blood lactate at peak exercise | 14 mM | 12 mM (p<0.001) |
|--------------------------------|-------|-----------------|

Carnitine supplementation does not alter energy homeostasis during exercise

Soop et al J Appl Physiol 64:2394-2399, 1988

- 7 subjects studied at baseline and after 5 d of 5g carnitine/day and 1g day of study
- 120 minutes at 50% VO_2max
- Catheter into femoral artery and vein to allow A-v difference to be calc
- $[^{14}\text{C}]$ -oleic acid used to assess fatty acid oxidation

| <u>Parameter at 120 min exercise</u> | <u>Control</u> | <u>Carnitine</u> |
|---|-----------------|------------------|
| Plasma lactate | 1.26 mM | 1.06 mM |
| Lactate A-v difference (mmol/min) | 0.25 \pm 0.16 | -0.05 \pm 0.07 |
| Glucose A-v difference (mmol/min) | 2.82 \pm 0.39 | 2.58 \pm 0.23 |
| Oleic acid turnover ($\mu\text{mole}/\text{min}$) | 1100 \pm 100 | 990 \pm 110 |

Only statistically significant effect of carnitine was to decrease resting glucose (4.52 vs. 4.31 mM)

How can changes in performance
be assessed in healthy
subjects?

Approaches to assessing physical performance in clinical research

- Maximal aerobic capacity ($\text{VO}_{2\text{max}}$)
- Lactate (anaerobic) threshold
- Ability to sustain a submaximal workload (endurance)
- Perception of exertion/fatigue
- Ambulatory activity/function
- Six-minute walk
- Strength
- Response to training
- Performance at athletic task (i.e. running time)

Challenge in measuring athletic performance

- Blinding
- Test-retest consistency
- How big an effect on performance matters?

Atlanta 1996 Olympics men's 1500 m run:

Gold – 3:35.78

Bronze – 3:36.72 (-0.44%)

Sydney 2000 men's 100 m freestyle

Gold – 48.30 sec

8th – 49.44 sec (-2.3%)

Sydney men's marathon

Gold – 2:10:11

10th – 2:14:50 (-3.3%)

So, where are we?

- Rationale for carnitine supplementation seems reasonable, but...
- Scientific underpinnings for the rationale weak
 - Pharmacokinetics do not favor systemic delivery
 - Transport systems do not favor increase in muscle carnitine content
 - Unclear if supra-physiologic carnitine content affects muscle metabolism/function
- Understanding system predicts factors relevant to clinical carnitine supplementation (e.g. long duration of therapy)

So, where are we?

- Clinical research on metabolism and function during exercise challenging
- Evidence to date does not support the hypothesis that carnitine supplementation improves physical performance in healthy subjects, but

The absence of evidence is not evidence of absence

Where do we need to go?

- Research into biochemical, pharmacological and physiologic determinants of the response to carnitine supplementation
- Well designed, adequately powered clinical trials of carnitine supplementation that incorporate both robust clinical performance endpoints and data relevant to mechanistic interpretation

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