A threshold exists for the stimulatory effect of insulin on plasma L-carnitine clearance in humans

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Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. A threshold exists for the stimulatory effect of insulin on plasma L-carnitine clearance in humans. Am J Physiol Endocrinol Metab 292:E637–E641, 2007. First published October 17, 2006; doi:10.1152/ajpendo.00508.2006.—Maintaining hyperinsulinemia (~160 μU/ml) during steady-state hypercarnitinenemia (~550 μmol/l) increases skeletal muscle total carnitine (TC) content by ~15% within 5 h. The aim of the present study was to further examine the relationship between serum insulin concentration and skeletal muscle carnitine accumulation by attempting to identify the serum insulin concentration at which this stimulatory effect of insulin on carnitine retention becomes apparent. On four randomized experimental visits, eight healthy men (body mass index 23.8 ± 0.9 kg/m²) underwent a 6-h euglycemic insulin clamp of 5, 30, 55, or 105 mU·m⁻²·min⁻¹ accompanied by a 5-h iv infusion of L-carnitine (15 mg/kg bolus followed by 10 mg·kg⁻¹·h⁻¹). The clamps produced steady-state serum insulin concentrations of 10.1 ± 0.5, 4.88 ± 1.0, 88.9 ± 2.8, and 173.9 ± 6.5 mU/ml, respectively. During L-carnitine infusion, plasma TC concentration remained above 450 μmol/l during all four visits. However, there was a significant treatment effect of insulin (P < 0.001), such that by the end of infusion the plasma TC concentration in the 55- and 105-mU clamps was lower than that seen in the 5- (P < 0.05 and P < 0.01, respectively) and 30-mU (P < 0.01) clamps. The findings demonstrate that only high circulating serum insulin concentrations (≥90 μU/ml) are capable of stimulating skeletal muscle carnitine accumulation. This is of relevance to athletes, and the treatment of obesity and type 2 diabetes, where increasing skeletal muscle carnitine content may be used as tool to modify skeletal muscle energy metabolism.

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MORE THAN 95% OF THE BODY’S TOTAL CARNITINE (TC) L-3-HYDROXY-4-N,N,N-TRIMETHYLAMINOBUTYRIC ACID) STORE EXISTS WITHIN SKELETAL MUSCLE TISSUE AS EITHER FREE OR ACYL CARNITINE (6), WHERE, AS A SUBSTRATE FOR CARNITINE PALMITOYLTRANSFERASE I (CPT I), IT PLAYS AN ESSENTIAL ROLE IN THE TRANSLATION OF LONG-CHAIN FATTY ACYL GROUPS INTO THE MITOCHONDRIAL MATRIX FOR SUBSEQUENT β-OXIDATION (14, 15). ANOTHER METABOLIC ROLE OF CARNITINE IN SKELETAL MUSCLE IS TO REGULATE THE MITOCHONDRIAL ACETYL-COA/COASH RATIO, IN A REACTION CATALYZED BY CARNITINE ACYLTRANSFERASE TO FORM ACETYL-CARNITINE, BY BUFFERING EXCESS ACETYL-COA PRODUCTION WHEN ITS RATE OF FORMATION FROM PYRUVATE OXIDATION OUTWEIGHS THE DEMANDS OF THE TCA CYCLE, I.E., DURING HIGH-INTENSITY EXERCISE (1, 9, 11, 18). HOWEVER, THIS ACETYLATION DEPLETES THE SKELETAL MUSCLE FREE CARNITINE POOL, AND IT HAS BEEN HYPOTHEZISED THAT THE RESULTING REDUCTION IN THE AVAILABILITY OF FREE CARNITINE TO CPT I MIGHT BE LIMITING TO FAT OXIDATION IN HUMAN SKELETAL MUSCLE DURING EXERCISE. FOR EXAMPLE, PREVIOUS RESEARCH (31) HAS DEMONSTRATED THAT A 30% DECREASE IN THE RATE OF FAT OXIDATION DURING HIGH-INTENSITY EXERCISE >70% VO2 MAX, MEASURED USING A [U-13C]PALMITATE TRACER, WAS PARALLELED BY A 65% DECREASE IN SKELETAL MUSCLE FREE CARNITINE CONTENT. IN ADDITION, DECREASED FAT OXIDATION RATES DURING MODERATE-INTENSITY EXERCISE HAVE BEEN REPORTED WHEN FREE CARNITINE AVAILABILITY WAS REDUCED BY 46% AS A RESULT OF A DIETARY-INDUCED INCREASE IN GLYCOLYTIC FLUX (25). IN LINE WITH THIS HYPOTHESIS, IT HAS BEEN PROPOSED THAT INCREASING SKELETAL MUSCLE TC CONTENT VIA EXOGENOUS L-CARNITINE ADMINISTRATION MIGHT ALLEVIATE THE DECLINE IN FAT OXIDATION RATES ROUTINELY OBSERVED DURING THESE CONDITIONS OF HIGH GLYCOLYTIC FLUX (28). FURTHERMORE, IT IS POSSIBLE THAT SUCH AN INCREASE IN MUSCLE CARNITINE CONTENT COULD POSITIVELY IMPACT UPON FAT OXIDATION RATES DURING EXERCISE IN METABOLIC DISEASES SUCH AS OBESITY AND TYPE 2 DIABETES. BOTH CONDITIONS ARE ASSOCIATED WITH AN IMPAIRED ABILITY OF SKELETAL MUSCLE TO OXIDIZE FATTY ACIDS DURING EXERCISE, OCCURRING PERHAPS AS A RESULT OF HIGH GLYCOLYTIC FLUX (2, 3, 20) AND, CONSEQUENTLY, REDUCED MUSCLE FREE CARNITINE AVAILABILITY LIMITING LONG-CHAIN FATTY ACYL GROUP TRANSLOCATION.

The majority of the pertinent studies in humans to date, however, have failed to increase skeletal muscle carnitine content via oral or intravenous L-carnitine administration per se (7, 28, 32). For example, neither feeding 2 g/day L-carnitine for 3 mo (32) nor intravenously infusing L-carnitine for 5 h in the fasted state (28) had an effect on muscle TC content. The most likely reason for these findings is the fact that the Km for carnitine of the sarcolemmal carnitine transporter OCTN2 in vitro is 4.3 μmol/l (30), which would suggest that, in the basal state, where plasma TC concentration is ~50 μmol/l (28, 32), skeletal muscle carnitine uptake is saturated. Thus simply increasing plasma L-carnitine availability will not increase skeletal muscle carnitine accumulation, and therefore, investigation into alternative strategies to increase muscle carnitine content is warranted.

Recent research by ourselves (28, 29) has demonstrated that maintaining hyperinsulinemia (~160 μU/ml) in the presence of a supraphysiological plasma carnitine concentration of ~550 μmol/l for 5 h increased skeletal muscle TC content by ~15% in healthy human volunteers. This finding was in concordance with the hypothesis that insulin would augment Na⁺-dependent skeletal muscle carnitine transport via OCTN2, secondary...
to its action of increasing sarcolemmal Na\(^+\)-K\(^+\) ATPase pump activity and, therefore, intracellular Na\(^+\) flux. Furthermore, the increase in skeletal muscle carnitine content was associated with a large reduction in glycolytic flux and carbohydrate oxidation [decreased muscle pyruvate dehydrogenase complex (PDC) activity and lactate content and increased muscle glycogen accumulation] despite conditions of identical carbohydrate administration, suggesting a carnitine-mediated increase in fat oxidation (29). However, the serum insulin concentration used to achieve this increase in muscle carnitine content, and its associated metabolic effects, was close to the upper physiological limit and would be difficult to achieve by dietary means alone. If L-carnitine is to be used as a tool to modify skeletal muscle energy metabolism, it would be pertinent to identify the relationship between serum insulin concentration and muscle carnitine accumulation in humans.

When L-carnitine is administered intravenously (15 mg/kg bolus followed by 10 mg·kg\(^{-1}\)·h\(^{-1}\)), an increase in skeletal muscle TC content occurs during hyperinsulinemia and is paralleled by a decrease in plasma TC concentration, demonstrating that a relationship exists between plasma carnitine clearance and muscle carnitine accumulation during hyperinsulinemia (28). With this in mind, the aim of the present study was to further examine the relationship between serum insulin concentration and muscle carnitine accumulation by attempting to identify the serum insulin concentration at which a decrease in plasma carnitine concentration becomes apparent during intravenous L-carnitine infusion.

**METHODS**

**Subjects.** Eight healthy, moderately-trained, nonvegetarian men (age 20.3 ± 0.4 yr, body mass 76.2 ± 2.7 kg, and body mass index 23.8 ± 0.9 kg/m\(^2\)) participated in the present study, which was approved by the University of Nottingham Medical School Ethics Committee, in accordance with the Declaration of Helsinki. Before taking part in the study, all subjects underwent routine medical screening and completed a general health questionnaire. All gave their consent to take part in the study and were aware that they were free to withdraw from the experiment at any point.

**Study protocol.** Subjects reported to the laboratory with a voided bladder following an overnight fast on four occasions, separated by at least a 2-wk “washout” period, having collected urine for the previous 24 h. On arrival, subjects were asked to rest in a supine position on a bed while a cannula was inserted retrogradely into a superficial vein on the dorsal surface of the nondominant hand. This hand was kept in a hand-warming unit (air temperature 55°C) to arterialize the venous sampling of blood glucose concentration (YSI 2300 STATplus; Yellow Springs Instruments, Yellow Springs, OH). In addition, 5 ml of arterialized-venous blood were obtained every hour (and at 80 min) for 6 h. Two milliliters of this blood were collected into lithium heparin containers, and, after centrifugation, the plasma was removed and immediately frozen in liquid nitrogen. These samples were then stored at −80°C and analyzed at a later date for TC concentrations using a radioenzymatic assay described by Cederblad et al. (8). The remaining blood was allowed to clot, and, after centrifugation, the serum was stored frozen at −80°C. Insulin concentration was measured in these samples at a later date with a radioimmunoassay kit (Coat-a-Count Insulin; Euro-Diagnostic Products). The volume of each 24-h urine collection was recorded, and a 5-ml aliquot was removed and stored at −80°C to be analyzed at a later date for TC concentration using the radioenzymatic method of Cederblad et al. (8).

**Statistical analysis.** A two-way ANOVA (time and treatment effects, GraphPad Prism version 3; GraphPad Software) was performed to detect differences in plasma TC and serum insulin concentration. If significance was achieved, a repeated-measures one-way ANOVA with Tukey’s post hoc test (GraphPad Prism version 3) was used to locate differences between treatments at each time point. A repeated-measures one-way ANOVA (GraphPad Prism version 3) was also used to compare 24-h urinary TC excretion between treatments. Area under the serum insulin concentration × time curve was calculated using the least squares method (GraphPad Prism version 3). Statistical significance was declared at \(P < 0.05\), and all the values are means ± SE.

**RESULTS**

**Serum insulin.** Following the 60-min equilibration period, the four insulin infusion rates of 5, 30, 55, and 105 mU·m\(^{-2}\)·min\(^{-1}\) produced steady-state serum insulin concentrations of 10.1 ± 0.5, 48.8 ± 1.0, 88.9 ± 2.8, and 173.9 ± 6.5 mU/l, respectively (Fig. 1). This equated to area under the serum insulin concentration × time curve values of 3.6 ± 0.3, 16.7 ± 1.7 (\(P < 0.05\) vs. 5 mU·m\(^{-2}\)·min\(^{-1}\) clamp), 29.5 ± 2.3 (\(P < 0.05\) vs. 30 mU·m\(^{-2}\)·min\(^{-1}\) clamp), and 69.0 ± 6.2 (\(P < 0.001\) vs. 55 mU·m\(^{-2}\)·min\(^{-1}\) clamp) U·l\(^{-1}\)·min\(^{-1}\), respectively. The total volumes of 20% glucose solution infused to maintain these circulating insulin concentrations were 208 ± 54, 1,088 ± 80, 1,503 ± 125, and 1,419 ± 70 ml, respectively.

**Plasma carnitine.** The plasma TC concentration over 5 h of L-carnitine infusion during each of the four insulin clamps is illustrated in Fig. 1. From similar basal plasma TC concentrations of 50.4 ± 2.4, 46.0 ± 3.2, 44.4 ± 2.7, and 50.8 ± 1.7 μmol/l, the bolus 15 mg/kg L-carnitine infusion (indicated by the arrow) produced mean peak plasma TC concentrations \((t = 80)\) of 541.3 ± 18.0, 550.8 ± 18.4, 548.2 ± 37.4, and 514.7 ± 18.9 μmol/l during insulin infusions at 5, 30, 55, and 105 mU·m\(^{-2}\)·min\(^{-1}\), respectively. Although plasma TC concentration remained elevated above 450 μmol/l throughout all four clamps, plasma TC concentration during the 55 and 105...
mU·m⁻²·min⁻¹ clamps appeared to diverge from the 5 and 30 mU·m⁻²·min⁻¹ clamps from 3 h onward (treatment effect, \( P < 0.001 \)), such that plasma TC concentration during the 105 mU·m⁻²·min⁻¹ clamp was lower than the 30 mU·m⁻²·min⁻¹ clamp at 5 (\( P < 0.05 \)) and 6 h (\( P < 0.01 \)) and lower than the 5 mU·m⁻²·min⁻¹ clamp at 6 h (\( P < 0.01 \)). Similarly, plasma TC concentration during the 55 mU·m⁻²·min⁻¹ clamp was lower than during the 5 (\( P < 0.05 \)) and 30 mU·m⁻²·min⁻¹ clamp (\( P < 0.01 \)) clamps at 6 h.

Urinary carnitine. Urinary TC excretion [concentration (mg/l) \( \times \) urinary volume (liters)] was similar for the 24 h before each visit (62.1 ± 13.8, 63.8 ± 9.8, 67.3 ± 16.9, and 57.4 ± 6.6 mg for the insulin infusions rates of 5, 30, 55, and 105 mU·m⁻²·min⁻¹, respectively) and for the 24 h following each L-carnitine infusion (3.45 ± 0.26, 3.31 ± 0.24, 3.57 ± 0.22, and 3.30 ± 0.24 g for the insulin infusions rates of 5, 30, 55, and 105 mU·m⁻²·min⁻¹, respectively).

**DISCUSSION**

A decrease in steady-state plasma TC concentration was observed when intravenous L-carnitine administration was accompanied by hyperinsulinemia (\(~160 \text{ mU/l}\)) and was matched by a \(~15\%\) increase in muscle TC content (28). The aim of the present study was to further examine the relationship between serum insulin concentration and muscle carnitine accumulation by attempting to identify the serum insulin concentration at which a decrease in plasma TC concentration becomes apparent during intravenous L-carnitine infusion. In this respect, the main finding from the present study was that steady-state plasma TC concentration was significantly lower when L-carnitine was administered intravenously in the presence of high (\(~90 \text{ mU/l}\)) and very high (\(~170 \text{ mU/l}\)) serum insulin concentrations compared with when serum insulin concentration was maintained at \(~10 \text{ mU/l}\) (fasted) or \(~50 \text{ mU/l}\) during insulin clamp conditions. Collectively, these observations indicated that insulin will not stimulate muscle carnitine retention unless a serum insulin concentration \(~90 \text{ mU/l}\) is achieved during hypercarnitinnemia. Our findings are in concordance with the hypothesis that insulin can augment \(\text{Na}^+\)-dependent skeletal muscle carnitine transport in humans, secondary to its action of increasing sarcoplemmal \(\text{Na}^+\)-\(\text{K}^+\)-ATPase pump activity (28, 29), but show that it will require a relatively high serum insulin concentration to achieve this effect.

Following the initial L-carnitine bolus, plasma TC concentration peaked at \(~550 \text{ mU/l}\), which is in agreement with previous studies (5, 13, 17, 26, 28) that have administered similar intravenous doses, and was maintained >450 mU/l for the duration of each euglycemic insulin clamp (Fig. 2). The intravenous L-carnitine infusion rate during each clamp was \(~80 \text{ mU/min}\). If we assume that the plasma TC concentration during the 55 and 105 mU·m⁻²·min⁻¹ insulin clamps was at a steady state throughout the rate of elimination (i.e., \(~80 \text{ mU/ml}\) min). The total TC clearance from plasma over the infusion periods can therefore be calculated as the rate of elimination divided by the steady-state plasma concentration (\(~485 \text{ mU/ml}\) during both visits), equating to 165 ml/min. The renal clearance during L-carnitine infusion reported in other studies (5, 17, 26, 28) is \(~100 \text{ ml/min}\), equating to a 65 ml/min difference between plasma and renal TC clearance. Since the rate of tissue uptake equals the plasma concentration \(\times\) plasma clearance, it can be calculated that plasma TC was transported into skeletal muscle at a rate of \(~32 \text{ ml/min}\) during the 55 and 105 mU·m⁻²·min⁻¹ insulin clamp visits, which over the 5-h L-carnitine infusion period equates to \(~2 \text{ g}\) (although this does not take into account the initial 15 mg/kg bolus). Therefore, if we assume that all of the difference between plasma TC clearance and renal TC clearance is due to an insulin-mediated transport of carnitine into skeletal muscle, then we can speculate from the above calculations that skeletal muscle TC content would have been increased by \(~10\%\) (assuming a

**Fig. 2.** Plasma total carnitine (TC) concentration during 6-h intravenous insulin infusion rates of 5, 30, 55, and 105 mU·m⁻²·min⁻¹ combined with a 5-h intravenous L-carnitine infusion. **\( P < 0.05\), plasma TC concentration during the 105 mU·m⁻²·min⁻¹ insulin infusion significantly lower than during the 30 mU·m⁻²·min⁻¹ insulin infusions at 5 h, and plasma TC concentration during the 55 mU·m⁻²·min⁻¹ insulin infusion significantly lower than during the 5 and 30 mU·m⁻²·min⁻¹ insulin infusions at 6 h. **\( P < 0.01\), plasma TC concentration during the 105 mU·m⁻²·min⁻¹ insulin infusion significantly lower than during the 5 and 30 mU·m⁻²·min⁻¹ insulin infusions at 6 h. The arrow indicates the commencement of the L-carnitine infusion. Values are means ± SE (\( n = 8 \)).
whole body skeletal muscle carnitine content of 20 g (6, 23),
which is in agreement with the increase in muscle carnitine
content we have observed in two studies following 5 h of
hypercarnitinemia in the presence of a 105 mU·m⁻²·min⁻¹
clamp (28, 29). Furthermore, the present findings suggest that
a steady-state serum insulin concentration of ~90 mU/l
(achieved during the 55 mU·m⁻²·min⁻¹ clamp) is sufficient to
stimulate muscle carnitine transport to a similar degree as that
at higher insulin concentrations (28, 29), which could be
important, because a circulating insulin concentration of
around this magnitude is more practical to achieve in the
everyday setting.

Carnitine is a substrate for CPT I and, therefore, plays an
essential role in the translocation of long-chain fatty acids into
the mitochondrial matrix for subsequent β-oxidation (14, 15).
Another metabolic role of carnitine in skeletal muscle is to
regulate the mitochondrial acetyl-CoA/CoASH ratio. In a re-
action catalyzed by carnitine acetyltransferase to form acetyl-
carnitine, carnitine buffers excess acetyl-CoA production when
its rate of condensation with oxaloacetate is less than its rate of
formation by pyruvate, i.e., during high-intensity exercise (1, 9,
11, 18). However, this acetylation depletes the free carnitine
pool, and it has been hypothesized that the resulting reduction in
the availability of free carnitine to CPT I might be limiting to
long-chain fatty acid oxidation in human skeletal muscle
during exercise. Indeed, research has demonstrated that, as
exercise intensity increases to >70% VO₂max, muscle free

carnitine content falls to ~30% (5.6 mmol/kg dm) of the TC
store and is paralleled by a 35% decrease in the rate of fat
oxidation (measured using a [U-¹³C]palmitate tracer (31)).
On the basis of this evidence, it was hypothesized that muscle free
carnitine availability becomes limiting to fat oxidation at a
concentration of ~5 mmol/kg dm (or ~1.52 mM intracellular
water). This seems plausible given that the reported Kᵣ of CPT
I for free carnitine in human skeletal muscle is 0.48 mM (21).

Furthermore, the catalytic site of CPT I for carnitine is located
within the contact sites of the outer and inner mitochondrial
membranes (33), which will limit its exposure to the predom-
nantly cytosolic store of free carnitine. Consequently, the 10% in-
crease in muscle carnitine content predicted in the present
study during a steady-state serum insulin concentration of ≥90
mU/l might alleviate the decline in fat oxidation observed
during exercise with high glycolytic flux (25) or at high

tensities (31), which could be of major relevance to exercise
performance due to the sparing of muscle glycogen. In line
with this theory, increasing skeletal muscle carnitine content
has been reported to delay fatigue development by 25% in rat
soleus muscle strips in vitro (4). Furthermore, our most recent
research (29) has demonstrated that a 15% increase in skeletal
muscle carnitine content, achieved during conditions identical
to the 105 mU·m⁻²·min⁻¹ insulin clamp of the present study,
resulted in an inhibition of muscle PDC activity, a decrease in
muscle lactate content, and, following an overnight fast, an
increase in muscle glycogen and long-chain acyl-CoA content
compared with control (saline infusion during euglycaemic
hyperinsulinemia) despite identical carbohydrate administra-
dition during both visits. Due to carnitine’s role in long-chain
fatty acyl group translocation into the mitochondrial matrix, we
believe it is entirely plausible that the apparent reduction in
glycolytic flux and carbohydrate oxidation (decreased PDC
activity and lactate content and increased glycogen accumula-
tion) could have been caused by a carnitine-mediated increase
in skeletal muscle long-chain fatty acid oxidation. It is not
unreasonable to predict, therefore, that increasing muscle TC
content would indeed alleviate the decline in skeletal muscle
fat oxidation seen during incremental exercise in healthy indi-
viduals. In addition, any mechanism that increases fat oxida-
tion is also relevant to metabolic diseases such as obesity and
type 2 diabetes, where an impairment of fat oxidation has been
reported during exercise, occurring perhaps as a result of high
glycolytic flux (2, 3, 10, 19, 20).

There were no differences in 24-h urinary carnitine excretion
across the visits, suggesting that the reduction in plasma TC
clearance during the 55 and 105 mU·m⁻²·min⁻¹ insulin
clamps was not due to increased urinary carnitine clearance. In
healthy humans, >90% of free carnitine filtered at the kidney
is reabsorbed when plasma free carnitine concentration is in its
normal range (23, 24). However, when plasma carnitine con-
centration exceeds this range (>70 μmol/l), the excess carni-
tine is rapidly eliminated and the renal clearance of carnitine
is similar to the values obtained for creatinine clearance (i.e.,
approximating the glomerular filtration rate), suggesting that
carnitine is readily filtered through the glomeruli and that the
high capacity for tubular reabsorption proposed for free carni-
tine is saturated. For example, following intravenous adminis-
tration of l-carnitine, 42% of a 2.3-g dose is retrieved in the
urine after 2 h, and 70 and 82% of a 2- and 6-g dose, respec-
tively, is retrieved after 24 h (5, 17, 26), which is in
agreement with the 70% mean recovery in this study following
an ~5-g dose. A urine collection was not obtained for the 5 h
of each l-carnitine infusion during the present study, so it is
difficult to calculate renal carnitine clearance during this time.

However, because plasma TC concentration was maintained
considerably higher (>450 μmol/l) than the normal range for
the duration of each insulin clamp, we can predict that plasma
carnitine filtration was at a maximum during all clamps and
that, assuming carnitine reabsorption was saturated, we would
not expect to see any differences between clamps in the 5-h
urinary TC recovery. Indeed, in our previous study there was
no difference in urinary TC clearance, compared with control,
when l-carnitine was infused for 5 h in the presence of
hyperinsulinemic clamp (28).

During each insulin clamp, a 20% glucose solution was
infused to maintain a fasting blood glucose concentration of
4.5 mmol/l. Therefore, because 1,503 ± 125 and 1,419 ± 70
ml of glucose was infused during the 55 and 105
mU·m⁻²·min⁻¹ insulin clamps, respectively, with 208 ± 54 ml
infused during the 5 mU·m⁻²·min⁻¹ insulin
clump, it could be suggested that the lower plasma TC con-
centration was due to a dilution effect. However, this would
seem unlikely since, for example, there was a fivefold differ-
ence in the volume of glucose infused between the 5 and 30
mU·m⁻²·min⁻¹ insulin clamps (208 ± 54 vs. 1,088 ± 80 ml,
respectively), with no difference in plasma TC concentra-
tion (Fig. 2).

In conclusion, the present study demonstrates that insulin
can stimulate plasma carnitine clearance, most likely into
skeletal muscle, based on the findings of our previous studies
(28, 29), but only when present at a physiologically high
concentration. This could be of significant relevance to ath-
letes, and in the treatment of obesity and type 2 diabetes, if
l-carnitine is to be used as a tool to modify skeletal muscle energy metabolism.

REFERENCES