HHS Public Access

Author manuscript

Diabetes Metab Res Rev. Author manuscript; available in PMC 2017 November 29.

Published in final edited form as:

Diabetes Metab Res Rev. 2009 September ; 25(Suppl 1): S45–S49. doi:10.1002/dmrr.987.

Carnitine and type 2 diabetes

Randall L. Mynatt*

Pennington Biomedical Research Center, Baton Rouge, LA, USA

Summary

Studies in humans and animals demonstrate that *"lipid over supply"* causes or worsens insulin resistance via multiple mechanisms involving the accumulation of intracellular lipids in multiple tissues. In particular, the accumulation of fatty acyl CoA derivatives/metabolites in muscle inhibits both insulin signaling and glucose oxidation. Therefore agents that ameliorate the accumulation of fatty acyl CoA derivatives and/or their metabolites would be beneficial in the treatment or prevention of insulin resistance and T2D.

Hyperinsulemic/euglycemic clamp studies in humans and carnitine supplementation studies in rodents provide "proof-of-concept" that carnitine is effective at improving insulin-stimulated glucose utilization and in reversing abnormalities of fuel metabolism associated with T2D.

Carefully controlled clinical trials are warranted to determine the efficacy dietary carnitine supplementation as an adjunctive treatment for type 2 diabetes.

Keywords

carnitine; diabetes; insulin resistance; acetyl-CoA

Introduction

Considerable evidence supports the idea that the over supply of dietary fat exceeds the storage capacity of adipose tissue and leads to the ectopic accumulation of lipids resulting in a 'metabolic stress' in skeletal muscle, liver and possibly other tissues leading to insulin resistance [1–4]. However, despite intense investigation, the precise signalling events leading to fatty acid induced-insulin resistance are equivocal. One prevailing theory is that lipid over supply leads to the accumulation of diacylglycerol and fatty acyl-CoA, which are directly linked to defects in insulin signalling. Both long-chain fatty acyl CoAs and diacylglycerol activate protein kinase C theta [5], which increases serine phosphorylation with subsequent inhibition of IRS-1 tyrosine phosphorylation [6,7]. Another hypothesis is that long-chain acyl-CoA are also precursors for ceramide. Ceramide activates a protein phosphatase that dephosphorylates Akt/PKB resulting in inhibition of GLUT4 translocation and glycogen synthesis [8,9], and it has been reported that inhibition of ceramide synthesis ameliorates

*Correspondence to: Randall L. Mynatt, Pennington, Biomedical Research Center, Baton, Rouge, LA 70808, USA. mynattrl@pbrc.edu.

Conflict of interest

The author has declared that there are no conflicts of interest.

insulin resistance [10]. Recent work suggests that the lipid over supply leads to the accumulation of incompletely metabolized fatty acids in the mitochondria causing 'mitochondrial stress' leading to insulin resistance [11–13]. Despite the lack of a consensus mechanism, it is clear that fatty acid over supply leads to ectopic accumulation of several lipid metabolites that are detrimental to insulin signalling. Logically, treatments, such as carnitine, that can reduce the lipid metabolites should improve insulin sensitivity. Carnitine is a conditionally essential nutrient that enables mitochondrial import and export of acyl-CoAs. Carnitine is essential for fatty acid transport into the mitochondria (Figure 1). A second and potentially critical role of carnitine is to increase acyl and acetyl group efflux out of the mitochondria and into the plasma (as acyl-carnitines and acetyl-carnitine) reducing the accumulation of the intermediate products of beta-oxidation. The carnitine hypothesis (Figure 2) states that carnitine will reduce lipid metabolites within skeletal muscle via increased oxidation and increased export and that this reduction in lipotoxicity will lead to an increase in insulin signalling and improve mitochondrial capacity.

Previous studies

Hyperinsulinaemic–euglycaemic clamp studies provide some of the most convincing evidence on the effects of L-carnitine on glucose disposal [14–20]. Ferrannini *et al.* reported that during a hyperinsulinaemic–euglycaemic clamp in healthy volunteers, intravenous LC infusion caused a significant 17% increase of whole body glucose utilization. The enhancement of total glucose metabolism was quantitatively accounted for by a 50% increase in non-oxidative glucose disposal [16]. Again in healthy volunteers, Stephens *et al.* [19,20] reported a 30% increase of glycogen and a 40% decrease of lactate contents in the muscle biopsies of LC-infused group at the end of a clamp study and calculate whole body muscle glycogen content to be 250 g greater in the LC group. This study, along with Ferrannini *et al.*, suggests that an increase in muscle LC concentration may divert muscle glucose uptake towards glycogen storage in healthy subjects. There is also *in vitro* evidence indicating that increased fatty acid oxidation benefits glucose uptake and storage [21,22]. Over expression of carnitine palmitoyltransferase I in L6 myotubes increases oxidation of the long-chain fatty acids and increases insulin stimulation of glucose incorporation into glycogen by 60%.

In another clamp study, Mingrone *et al.* [18] reported whole body glucose uptake and glucose storage were higher with LC administration in both healthy controls and type 2 diabetic subjects, but glucose oxidation was increased only in the type 2 diabetes (T2D) group. Plasma lactate levels were also decreased in the T2D group with carnitine infusion. Likewise, Capaldo *et al.* [14] found a 16% increase in glucose disposal with carnitine infusion in diabetic subjects. In a study by De Gaetano *et al.* [15], healthy human volunteers were subjected to an intravenous glucose tolerance test, together with indirect calorimetry after a bolus of glucose plus LC or a bolus of glucose plus saline. Calorimetry showed a significant increase in respiratory quotient, resulting from a significant increase in carbohydrate oxidation rate during carnitine administration. There is one recent study, from Gonzales-Ortiz *et al.* [23], reporting no significant effects on supplemental carnitine on glucose disposal. However, the study consisted of three male and three female diabetic subjects/group and was woefully underpowered, and there appears to be either procedural

problems with the clamp itself or experimental design because there is a 30% increase in the M-value for the control group during the 4-week trial.

As far as we know, there are three human studies with carnitine as a dietary supplement in relation to glycaemic control. One study from China [24] and one from Italy [25] found that carnitine lowered circulating lipids but did not improve fasting glucose levels. Another study conducted in Iran [26] reported that dietary carnitine lowered fasting glucose levels, but increased triglycerides.

Dietary L-carnitine supplementation on studies in mice

Dietary carnitine supplementation attenuates the development of insulin resistance in mice fed high-fat diets without changing food intake or body weight. C57BL/6J mice were fed a high-fat (45% of energy from fat, 20% from protein, 35% from carbohydrate) diet ±0.5% L-Carnitine for 8–12 weeks. Carnitine supplementation increased the ability of insulin to lower blood glucose in the carnitine-supplemented mice compared to mice fed the non-supplemented diet (Figure 3).

The effects of carnitine supplementation on body weight and food intake were also measured in C57BL/6J mice fed the high-fat diet ±0.5% L-Carnitine. L-Carnitine supplementation did not alter food intake or bodyweight (data not shown), which is consistent with our food intake data in a transgenic model (BAP-agouti) for obesity and T2D [27]. These mouse data are also consistent with data showing no effect of dietary carnitine supplementation on food intake in rats [28,29].

In another study, obese/diabetic mice were fed a semi-purified diet ±0.5% L-carnitine for 4 weeks, and indirect calorimetry was used to determine the effects of carnitine supplementation on substrate utilization and energy expenditure. Basal carbohydrate oxidation was higher in the carnitine-supplemented group [average daily respiratory exchange ratio (RER) was 0.886 ± 0.01 in the control group and 0.914 ± 0.01 in the carnitine-supplemented group $p < 0.01$] (Figure 4). Immediately upon insulin administration, the RER rose quickly to values near 1.0 in the carnitine-supplemented group, but remained below 0.9 in the non-supplemented group. However, during the later post-insulin phase, RER dropped to simililarly low levels in both groups, suggesting increased fat oxidation due to rebound hypoglycermia. Twenty-four-hour total energy expenditure tended to be higher in the carnitine-supplemented mice, although the difference between groups did not reach statistical significance. Physical activity was unchanged in the carnitine-supplemented group compared to controls. Taken together, these data clearly show that supplemental carnitine improves insulin-stimulated glucose utilization in obese/diabetic mice and abnormalities of fuel metabolism typical of type 2 diabetes.

Dietary carnitine supplementation increases tissue export and urinary excretion of acyl-carnitines. Using a metabolomic approach, we measured acyl-carnitine species in skeletal muscle, liver, white adipose tissue, plasma and urine. There are modest increases in most acyl-carnitines in tissues [27], but carnitine supplementation has the greatest impact on circulating and urinary levels of acyl carnitines. Short-chain acyl carnitines (C6 or less) were

the most abundant acyl-carnitines constituting 99% of the total acyl-carnitines in skeletal muscle, 95% in plasma, 96% in white fat, and 93% in liver [27]. Acetyl-carnitine derives from acetyl-CoA and is the most abundant species in tissues, blood and urine. The effects of carnitine supplementation on the tissue export of acetyl-carnitine were striking (Figure 5), causing a doubling of circulating acetyl-carnitine. In terms of mass, the doubling in circulating levels of acetyl-carnitine is higher than the rest of the other acyl-carnitine species combined. To determine the fate of the elevated circulating acyl-carnitines, acyl-carnitines were also measured in the urine. Similar to plasma, the short-chain acyl carnitines were more abundant than the medium and long-chain acyl carnitines in the urine. Carnitine supplementation increased acetyl-carnitine excretion by 75-fold (Figure 5). We estimated the circulating pool of acetyl-carnitine, by assuming that there is 6 mL blood/100 g bodyweight (2.5 mL/40g mouse). We did not measure acyl-carnitines in whole blood, but mouse blood is about 50% plasma or 1.25 mL/40g mouse. Plasma concentrations of acetyl-carnitine are about 50 μM in carnitine-supplemented mice, yielding a plasma pool of acetyl-carnitine of about 10 mg. Therefore about half of the plasma pool of acetyl-carnitine is excreted daily. The increased levels of circulating acyl-carnitines combined with the increased excretion of acyl-carnitines support the hypothesis that there is tissue export of acyl moieties, especially short-chain acyl-carnitines, into circulation and partial excretion in the urine.

Summary and future directions

Based on studies that have elegantly evaluated the role of both insulin secretion and insulin resistance, it is now well established that T2D is a progressive disease. The current non-pharmacological management for patients with T2D utilizes medical nutrition therapy and enhanced physical activity as cornerstones of treatment. When that approach fails to achieve normoglycaemia, pharmacological means represent the traditional approach for clinical medicine. However, because of the widespread use of dietary supplements by the general public, supplementation with the use of agents that may effectively increase insulin sensitivity (such as carnitine), represent a very attractive and novel approach for adjunctive therapy of diabetes. Based on our pre-clinical results, we hypothesize that carnitine supplementation in humans will reduce lipotoxic metabolites improving both mitochondrial function and insulin signalling. Extrapolating from our pre-clinical dosing to the clinical setting, we propose a dose of 3 g/day costing approximately ¢50 (US). The results from the carefully controlled experiments will aid in understanding the mechanisms by which lipid oversupply leads to insulin resistance in skeletal muscle and how L-carnitine supplementation remodels fatty acid metabolism, insulin action and mitochondrial function. In light of the beneficial effects of exercise on insulin resistance, future studies should also examine the possible synergistic effects of L-carnitine and exercise.

Acknowledgments

This work was partially supported by a CNRU Center Grant # 1P30 DK072476 entitled ‘Nutritional Programming: Environmental and Molecular Interactions’ sponsored by NIDDK.

References

1. Boden G, Shulman GI. Free fatty acids in obesity and type 2 diabetes: defining their role in the development of insulin resistance and beta-cell dysfunction. Eur J Clin Invest. 2002; 32(Suppl 3): 14–23. [PubMed: 12028371]
2. McGarry JD. Banting lecture 2001: dysregulation of fatty acid metabolism in the etiology of type 2 diabetes. Diabetes. 2002; 51:7–18. [PubMed: 11756317]
3. Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest. 2000; 106:171–176. [PubMed: 10903330]
4. Unger RH. Lipotoxic diseases. Annu Rev Med. 2002; 53:319–336. [PubMed: 11818477]
5. Kelley DE, Mandarino LJ. Fuel selection in human skeletal muscle in insulin resistance: a reexamination. Diabetes. 2000; 49:677–683. [PubMed: 10905472]
6. De Fea K, Roth RA. Protein kinase C modulation of insulin receptor substrate-1 tyrosine phosphorylation requires serine 612. Biochemistry. 1997; 36:12939–12947. [PubMed: 9335553]
7. Ravichandran LV, Esposito DL, Chen J, Quon MJ. Protein kinase C-zeta phosphorylates insulin receptor substrate-1 and impairs its ability to activate phosphatidylinositol 3-kinase in response to insulin. J Biol Chem. 2001; 276:3543–3549. [PubMed: 11063744]
8. Chavez JA, Knotts TA, Wang LP, Li G, Dobrowsky RT. A role for ceramide, but not diacylglycerol, in the antagonism of insulin signal transduction by saturated fatty acids. J Biol Chem. 2003; 278:10297–10303. [PubMed: 12525490]
9. Long SD, Pekala PH. Lipid mediators of insulin resistance: ceramide signalling down-regulates GLUT4 gene transcription in 3T3-L1 adipocytes. Biochem J. 1996; 319:179–184. [PubMed: 8870666]
10. Holland WL, Brozinick JJ, Wang LP, Hawkins ED, Sargent KM, et al. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. Cell Metab. 2007; 5:167–179. [PubMed: 17339025]
11. Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, et al. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. Cell Metab. 2008; 7:45–56. [PubMed: 18177724]
12. Muoio DM, Koves TR. Skeletal muscle adaptation to fatty acid depends on coordinated actions of the PPARs and PGC1 alpha: implications for metabolic disease. Appl Physiol Nutr Metab. 2007; 32:874–883. [PubMed: 18059612]
13. Muoio DM, Koves TR. Lipid-induced metabolic dysfunction in skeletal muscle. Novartis Found Symp. 2007; 286:24–38. discussion 38–46, 162–3, 196–203. [PubMed: 18269172]
14. Capaldo B, Napoli R, Di Bonito P, Albano G, Sacca L. Carnitine improves peripheral glucose disposal in non-insulin-dependent diabetic patients. Diabetes Res Clin Pract. 1991; 14:191–195. [PubMed: 1778112]
15. De Gaetano A, Mingrone G, Castagneto M, Calvani M. Carnitine increases glucose disposal in humans. J Am Coll Nutr. 1999; 18:289–295. [PubMed: 12038470]
16. Ferrannini E, Buzzigoli G, Bevilacqua S, Boni C, Del Chiaro D, Oleggini M, et al. Interaction of carnitine with insulin-stimulated glucose metabolism in humans. Am J Physiol. 1988; 255:E946–E952. [PubMed: 3059823]
17. Giancaterini A, De Gaetano A, Mingrone G, Gniuli D, Liverani E, Capristo E, et al. Acetyl-L-carnitine infusion increases glucose disposal in type 2 diabetic patients. Metabolism. 2000; 49:704–708. [PubMed: 10877193]
18. Mingrone G, Greco AV, Capristo E, Benedetti G, Giancaterini A, De Gaetano A, et al. L-carnitine improves glucose disposal in type 2 diabetic patients. J Am Coll Nutr. 1999; 18:77–82. [PubMed: 10067662]
19. Stephens FB, Constantin-Teodosiu D, Greenhaff PL. New insights concerning the role of carnitine in the regulation of fuel metabolism in skeletal muscle. J Physiol. 2007; 581:431–444. [PubMed: 17331998]
20. Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. An acute increase in skeletal muscle carnitine content alters fuel metabolism in resting human skeletal muscle. J Clin Endocrinol Metab. 2006; 91:5013–5018. [PubMed: 16984983]

21. Perdomo G, Commerford SR, Richard AM, Adams SH, Corkey BE, O'Doherty RM, et al. Increased beta-oxidation in muscle cells enhances insulin-stimulated glucose metabolism and protects against fatty acid-induced insulin resistance despite intramyocellular lipid accumulation. J Biol Chem. 2004; 279:27177–27186. [PubMed: 15105415]
22. Sebastian D, Herrero L, Serra D, Asins G, Hegardt FG. CPT I overexpression protects L6E9 muscle cells from fatty acid-induced insulin resistance. Am J Physiol Endocrinol Metab. 2007; 292:E677–E686. [PubMed: 17062841]
23. Gonzalez-Ortiz M, Hernandez-Gonzalez SO, Hernandez-Salazar E, Martinez-Abundis E. Effect of oral L-carnitine administration on insulin sensitivity and lipid profile in type 2 diabetes mellitus patients. Ann Nutr Metab. 2008; 52:335–358. [PubMed: 18714152]
24. Liang Y. The effects of oral L-carnitine treatment on blood lipid metabolism and the body fat content in the diabetic patient. Asia Pac J Clin Nutr. 1998; 7:192–195. [PubMed: 24393648]
25. Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R, et al. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. Clin Ther. 2003; 25:1429–1439. [PubMed: 12867219]
26. Rahbar AR, Shakerhosseini R, Saadat N, Taleban F, Pordal A, Gollestan B, et al. Effect of L-carnitine on plasma glycemic and lipidemic profile in patients with type II diabetes mellitus. Eur J Clin Nutr. 2005; 59:592–596. [PubMed: 15741989]
27. Power RA, Hulver MW, Zhang JY, Dubois J, Marchand RM, Ilkayeva O, et al. Carnitine revisited: potential use as adjunctive treatment in diabetes. Diabetologia. 2007; 50:824–832. [PubMed: 17310372]
28. Rhew TH, Sachan DS. Dose-dependent lipotropic effect of carnitine in chronic alcoholic rats. J Nutr. 1986; 116:2263–2269. [PubMed: 3794832]
29. Sachan DS, Dodson WL. Effects of L-carnitine on carbon tetrachloride-induced changes in serum and liver lipids and acylcarnitines. J Environ Pathol Toxicol Oncol. 1992; 11:125–129. [PubMed: 1625182]
30. Arduini A, Bonomini M, Savica V, Amato A, Zammit V. Carnitine in metabolic disease: potential for pharmacological intervention. Pharmacol Ther. 2008; 120:149–56. [PubMed: 18793670]

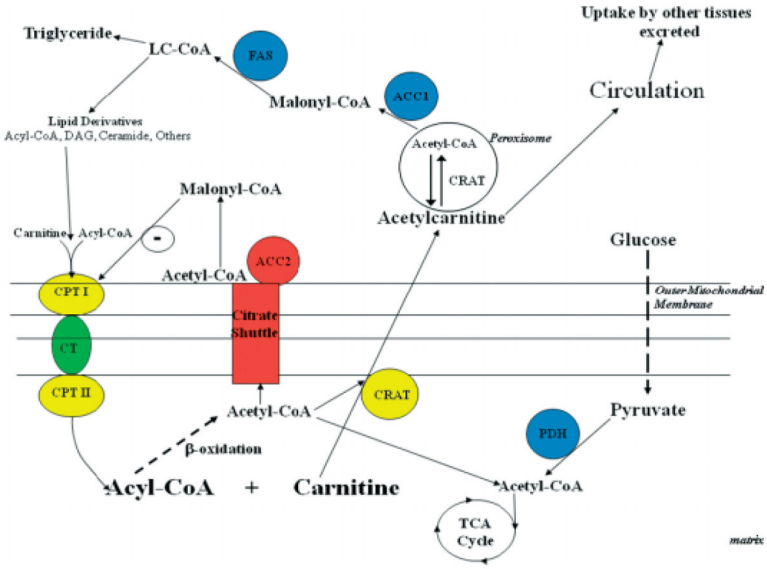

Figure 1.

Fatty acid oxidation/synthesis cycle. Long-chain fatty acids are first activated in the cytosol to long-chain acyl-CoA (LC-CoA). Carnitine palmitoyltransferase I (CPT-I) is located in the outer mitochondrial membrane and cataylzes the formation of acyl-carnitines from carnitine and LC-CoA. The acyl-carnitines are transported across the inner mitochondrial membrane. Once in the matrix, carnitine palmitoyltransferase II (CPT-II) hydrolyses the acyl-carnitine to free carnitine and LC-CoA, for beta-oxidation. Acetyl-CoA either enters the TCA cycle or is transported out of the mitochondria as citrate or serves as a substrate for carnitine acetyl transferase (CRAT). The acetyl-carnitine exits the mitochondria and is either hydrolyzed in peroxisomes or enters the circulation

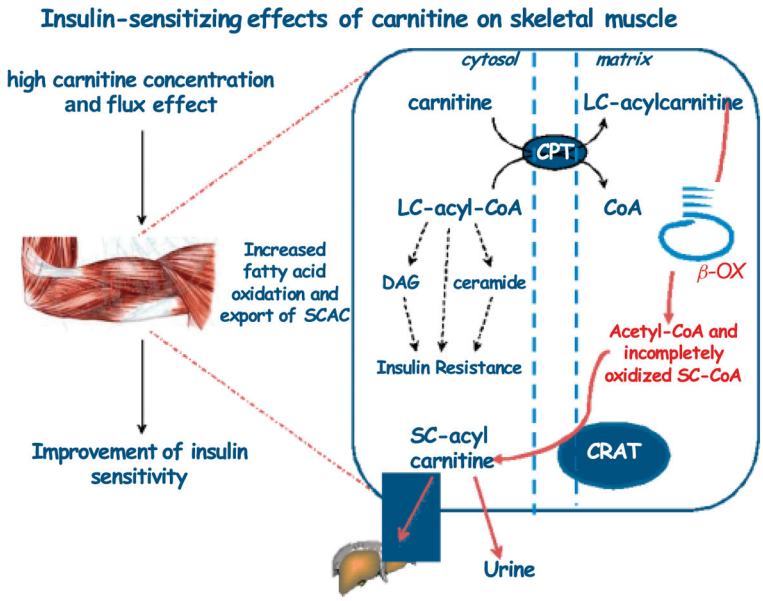

Figure 2.

The carnitine hypothesis states that carnitine will increase the flux of acyl-CoA transport into the mitochondria and export of incompletely oxidized fatty acids and acetyl CoA (SCAC), and relieve a lipotoxic ‘brake’ on both insulin signalling and mitochondrial function. Adapted from Adruini *et al* [30]

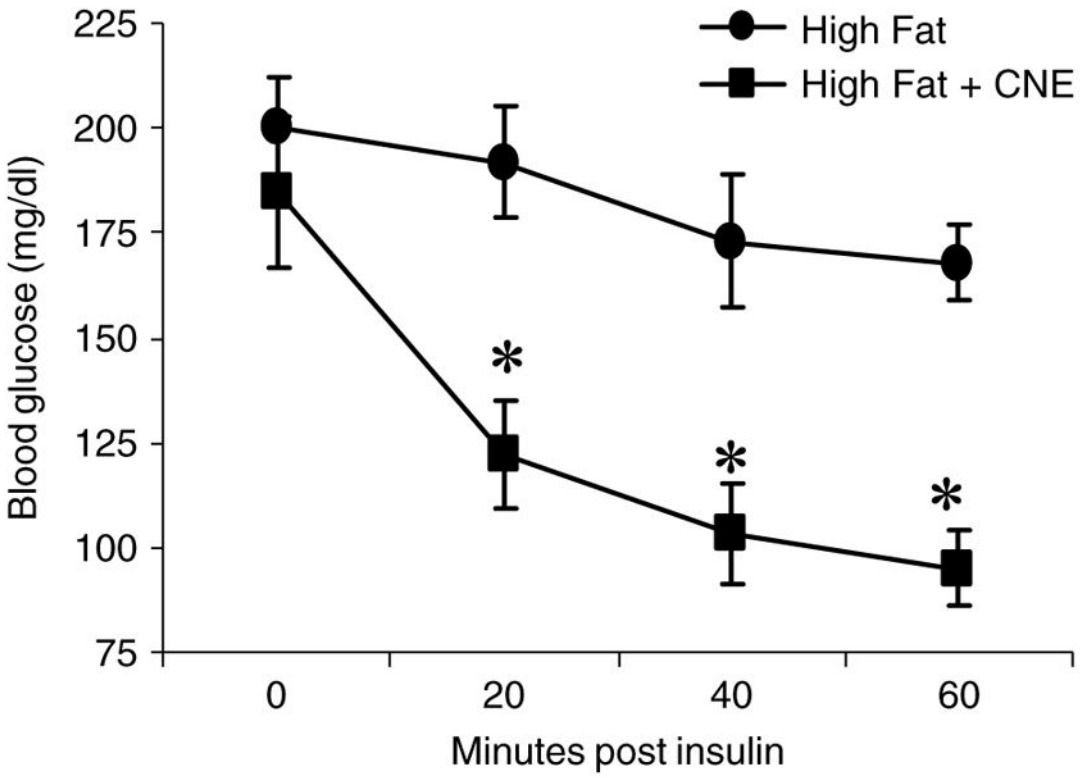

Figure 3.

Effects of dietary carnitine supplementation on insulin action in mice fed high-fat diets. C57Bl/6 male mice were fed a high fat diet ±0.5% L-carnitine. Blood glucose concentrations were measured following an i.p. insulin dose of 0.1 U/kg body weight. Values are mean ± SEM, $n = 31$ control group, $n = 36$ carnitine group. *Indicates significantly different from non-supplemented mice, $p < 0.01$

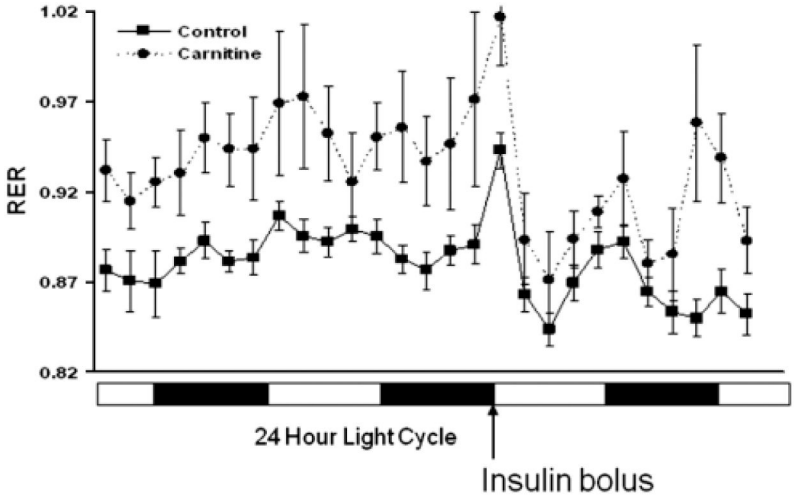

Figure 4.

Effects of carnitine supplementation on substrate utilization. Transgenic, (beta-actin promoter-agouti) obese/diabetic mice were fed a semi-purified ±0.5% L-carnitine for 4 weeks. The mice were then placed in the Oxymax CLAMS system for a 3-day acclimation period before measurements began. After 2 days of measurements, the mice were given an intraperitoneal bolus of insulin (1U/mouse) at 7 a.m. for the final day of data collection. Values are reported as mean ± SEM, $n = 7$ control group and $n = 8$ carnitine group

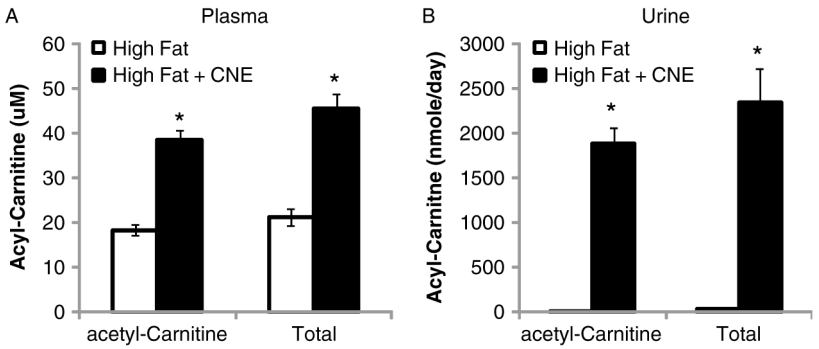

Figure 5.

Acyl-carnitine export and excretion. Acyl-carnitines were measured in C57BL/6J mice fed a high-fat diet ±0.5% L-carnitine for 12 weeks. Data are means ± SEM. $n = 7$ per group. Indicates significantly different from high fat fed mice, $p < 0.05$