Courtesy of Donald Yance

Carnitine Monograph

Introduction and overview

Carnitine is essential in the transport of long chain fatty acids into the mitochondrial matrix and plays a key role in the oxidation of lipids. This means that carnitine improves fatty acid utilization and energy production.

Several studies have demonstrated that carnitine improves angina and ischemic heart disease. Carnitine also lowers triglyceride and cholesterol levels while increasing HDL levels. [1, 2]

Carnitine significantly reverses age-associated mitochondrial decay. It increases cellular respiration, membrane potential and cardiolipin levels. Carnitine has been shown to improve energy production within brain cells and is considered a neuroprotective agent because of its antioxidant action and membrane stabilizing effects.

Acetyl-L-carnitine (ALC) is an ester of the trimethylated amino acid, L-carnitine, and is synthesized in the human brain, liver, and kidney by the enzyme ALC-transferase. Studies have shown ALC may be of benefit in treating Alzheimer's dementia, depression in the elderly, HIV infection, peripheral neuropathies, ischemia and reperfusion of the brain, and cognitive impairment associated with various conditions.

Beneficial effects of Carnitine:

- Restores mitochondrial function and membrane fluidity- a specific heart tonic - improves cardiomyopathy, angina and ischemic heart disease.
- Age-retarding effects
- Improves exercise ability following a heart attack.
- Improves fatty acid utilization – important for exercise performance
- Restores the key enzyme, *Cytochrome c oxidase*, for energy reproduction.
- Enhances energy through the transportation of fatty acids converting into energy, via *beta oxidation*.
- Neuroprotective
- Improves Cerbro- and Cardiovascular blood flow
- Improves memory
- Reduces the effects of aging, including a reduction in age spots (lipofuscin)
- Alleviates depression, particularly in the elderly
- Improves endurance exercise by enhancing fatty acid utilization in skeletal muscle during exercise
- Significantly lowers plasma lipoprotein(a) levels in hypercholesterolemic individuals; also increase HDL cholesterol. [Elevated lipoprotein (a) levels contribute to the occurrence and severity of early-onset coronary disease and add to the already enhanced risk in patients with familial hypercholesterolaemia.]
- Hyperthyroidism
- Liver protective/regenerative
- Diabetic neuropathy
- GI and liver protection induced from alcohol
- Chemotherapy – a protective role (heart, kidney, nerve, brain)
- May be useful in weight management
- Immune system health: T-cells

Research studies

Cardiovascular Health

Over the years, an abundance of research has supported the use of L-carnitine for cardiovascular and neurological health, as well as many other areas. In 1982, one of the very first studies observed a significant increase in high-density lipoprotein ("good") cholesterol levels in two subjects given one gram per day of L-carnitine for 10 to 15 weeks. [3]

In 1992, an Italian study was conducted with 160 people, ages 39 to 86, all of whom had recently been diagnosed with severe heart concerns. The researchers administered L-carnitine to 81 of the participants; 79 served as controls, receiving no supplements. "For the whole period," reported the researchers, "[the L-carnitine group] showed, in comparison to the controls, an improvement in heart function." [4]

Japanese scientists conducting their own experiments with L-carnitine learned that in both laboratory animals and in humans, low levels of L-carnitine in heart muscles resulted in significant heart damage. In a separate study, the researchers found that supplementation with 900 milligrams of L-carnitine over 12 weeks dramatically improved the exercise tolerance of 12 people with heart problems. [5]

A double-blind study, 56 individuals with significant heart challenges received either L-carnitine or a placebo. Researchers noted an improvement in the occurrence of irregular heartbeats in those who took L-carnitine. What's more, individuals in this study who took the carnitine felt less discomfort and experienced fewer heart emergencies. [6]

Antiarrhythmic

Thresholds for electrically induced atrial fibrillation were measured in response to IV carnitine. Mean arterial pressure, heart rate, and mean aortic flow rate were also monitored. Carnitine 100 mg/kg resulted in an increase in mean aortic blood flow. The antiarrhythmic effect was much less than with 5 mg/kg quinidine, but after atropinization, 100 mg/kg carnitine was similar in antiarrhythmic effect to quinidine and did not result in the blood pressure depression seen with quinidine. [7]

Lowers plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus

A previous study has demonstrated that L-carnitine reduces plasma lipoprotein(a) (Lp[a]) levels in patients with hypercholesterolemia. OBJECTIVE: To test a tolerable Lp(a)-reducing agent in diabetic patients, we assessed the effect of a dietary supplementation of L-carnitine on plasma lipid levels, particularly Lp(a), of patients with type 2 diabetes mellitus (DM) and hypercholesterolemia. METHODS: In this 6-month, randomized, double-masked, placebo-controlled clinical trial, patients were enrolled, assessed, and followed up at the Diabetic and Metabolic Diseases Center of the Department of Internal Medicine and Therapeutics at the University of Pavia, Pavia, Italy. All study patients had newly diagnosed type 2 DM that was managed through dietary restriction alone throughout the study, as well as hypercholesterolemia. Patients were randomized to 1 of 2 groups. One group received L-carnitine, one 1-g tablet BID. The other group received a corresponding placebo. We assessed body mass index, fasting plasma glucose, postprandial plasma glucose, glycosylated hemoglobin, fasting plasma insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein (apo) A-I, apo B, and Lp(a) at baseline and at 1, 3, and 6 months of treatment. RESULTS: This study included 94 patients. The treatment group included 24 men and 22 women (mean [SD] age, 52 [6] years). The placebo group included 23 men and 25 women (mean [SD] age, 50 [7] years). The baseline characteristics of the groups did not differ significantly. The mean (SD) body weight, height, and body mass index were 78.2 (5.8) kg, 1.70 (0.04) m, and 27.3 (2.5) kg/m(2), respectively, in the L-carnitine group and 77.6 (6.4) kg, 1.71 (0.05) m, and 26.8 (2.2) kg/m(2), respectively, in the placebo group. In the treatment group, Lp(a) was significantly reduced at 3 and 6 months compared with baseline ($P < 0.05$) and $P < 0.01$, respectively). We observed a significant improvement after 6 months ($P < 0.05$) in the Lp(a) value in patients taking L-carnitine compared with those taking placebo. Between-group differences in other variables did not reach a level of significance at months 3 and 6. No drug-related adverse events were reported or observed. CONCLUSION: *In this preliminary study, after 3 and 6 months, L-carnitine significantly lowered the plasma Lp(a) level compared with placebo in selected hypercholesterolemic patients with newly diagnosed type 2 DM*. [8]

Myocardial infarction

Administration of L-carnitine in patients with anterior acute myocardial infarction (AMI) prevents left ventricular remodeling. Current study was aimed to assess the effect of L-carnitine administration on mortality and heart failure in patients with anterior AMI. Methods: CEDIM 2 trial was a randomized, double-blind, multicenter, placebo-controlled trial planned to enroll 4,000 patients with acute anterior AMI. The trial was interrupted after the enrolment of 2,330 patients because of the lower than expected enrolment rate. The primary end point was a composite of death and heart failure at 6 months; 5-day mortality was the secondary end point. Results: During the 6-month follow-up, the primary end-point was not significantly different between the L-carnitine and placebo group (9.2 vs. 10.5%, $p = 0.27$). A reduction in mortality was seen in the L-carnitine arm on day 5 (secondary end-point) from randomization (HR = 0.61, 95% CI 0.37-0.98, $p = 0.041$). Conclusions: In CEDIM 2 trial L-carnitine therapy led to a reduction in early mortality (secondary end-point) without affecting the risk of death and heart failure at 6 months in patients with anterior AMI, leading to a non-significant finding with respect to the primary end-point. [29]

Skeletal and cardiac myopathy

Carnitine plays an essential role in the transfer of long-chain fatty acids across the inner mitochondrial membrane. This transfer requires enzymes and transporters that accumulate carnitine within the cell

(OCTN2 carnitine transporter), conjugate it with long chain fatty acids (carnitine palmitoyl transferase 1, CPT1), transfer the acylcarnitine across the inner plasma membrane (carnitine-acylcarnitine translocase, CACT), and conjugate the fatty acid back to Coenzyme A for subsequent beta oxidation (carnitine palmitoyl transferase 2, CPT2). Deficiency of the OCTN2 carnitine transporter causes primary carnitine deficiency, characterized by increased losses of carnitine in the urine and decreased carnitine accumulation in tissues. **Patients can present with hypoketotic hypoglycemia and hepatic encephalopathy, or with skeletal and cardiac myopathy. This disease responds to carnitine supplementation**. Defects in the liver isoform of CPT1 present with recurrent attacks of fasting hypoketotic hypoglycemia. The heart and the muscle, which express a genetically distinct form of CPT1, are usually unaffected. These patients can have elevated levels of plasma carnitine. CACT deficiency presents in most cases in the neonatal period with hypoglycemia, hyperammonemia, and cardiomyopathy with arrhythmia leading to cardiac arrest. Plasma carnitine levels are extremely low. Deficiency of CPT2 present more frequently in adults with rhabdomyolysis triggered by prolonged exercise. More severe variants of CPT2 deficiency present in the neonatal period similarly to CACT deficiency associated or not with multiple congenital anomalies. Treatment for deficiency of CPT1, CPT2, and CACT consists in a low-fat diet supplemented with medium chain triglycerides that can be metabolized by mitochondria independently from carnitine, carnitine supplements, and avoidance of fasting and sustained exercise. [30]

Ameliorating Hypertension and Insulin Resistance in Subjects at Increased Cardiovascular Risk

Carnitine as, Acetyl-L-carnitine, acutely ameliorated insulin sensitivity in type 2 diabetics with insulin resistance. In this sequential off-on-off pilot study, we prospectively evaluated the effects of 24-week oral acetyl-L-carnitine (1 g twice daily) therapy on the glucose disposal rate (GDR), assessed by hyperinsulinemic euglycemic clamps, and components of the metabolic syndrome in nondiabetic subjects at increased cardiovascular risk a priori segregated into 2 groups with GDR 7.9 (n=16) or >7.9 (n=16) mg/kg per minute, respectively. Baseline GDR and systolic blood pressure were negatively correlated (n=32; P=0.001; r=–0.545), and patients with GDR 7.9 mg/kg per minute had higher systolic/diastolic blood pressure than those with higher GDR. Acetyl-L-carnitine increased GDR from 4.89±1.47 to 6.72±3.12 mg/kg per minute (P=0.003, Bonferroni-adjusted) and improved glucose tolerance in patients with GDR 7.9 mg/kg per minute, whereas it had no effects in those with higher GDRs. Changes in GDR were significantly different between groups (P=0.017, ANCOVA). Systolic blood pressure decreased from 144.0±13.6 to 135.1±8.4 mm Hg and from 130.8±12.4 to 123.8±10.8 mm Hg in the lower and higher GDR groups, respectively (P<0.05 for both; P<0.001 overall) and progressively recovered toward baseline over 8 weeks posttreatment. Total and high molecular weight adiponectin levels followed specular trends. Diastolic blood pressure significantly decreased only in those with higher GDRs. Treatment was well tolerated in all of the patients. Acetyl-L-carnitine safely ameliorated arterial hypertension, insulin resistance, impaired glucose tolerance, and hypoadiponectinemia in subjects at increased cardiovascular risk. Whether these effects may translate into long-term cardioprotection is worth investigating.[39]

Significantly Improves Patient Outcomes Following Heart Attack

In a recent systemic review of 13 controlled trials in 3,629 patients, involving 250 deaths, 220 cases of new heart failure, and 38 recurrent heart attacks, Carnitnine supplementation impressively and significantly improved cardiac health in patients after a heart attack. Based on analysis of these trials L-carnitine supplementation was associated with a significant reduction (27%) in death from all causes and a highly significant reduction (65%) in ventricular arrhythmias and anginal attacks (40%) following a heart attack, compared with placebo or control.[43]

Exercise Performance: Improves the utilization of long-chain fatty acids during exercise

Long-chain fatty acids (LCFA) are important sources of energy in contracting skeletal muscle: during the course of endurance exercise the contribution of LCFA in energy metabolism increases whereas when the intensity of exercise increases, the energy need is covered more and more by carbohydrates. Although this has been known for nearly 100 years, the mechanisms controlling fatty acid uptake and oxidation during various exercise modes are still not completely elucidated. Besides passive diffusion, data suggest that both membrane-associated and cytosolic fatty acid binding proteins are involved in the uptake of LCFA into skeletal muscle. However, data from human studies suggest that the regulation of fatty acid utilization in skeletal muscle during exercise lies mainly within the entrance into the mitochondria or metabolism within the mitochondria. Although possible compartmentalization within the cell makes definitive conclusions difficult, available evidence suggests that changes in malonyl CoA concentration in muscle do not play a major regulatory role in controlling LCFA oxidation during exercise in man. *In contrast, it is suggested that the availability of free carnitine may play a major regulatory role in oxidation*

of LCFA during exercise. [9]

Neuroprotective 1: Improves mitochondrial function

The neuroprotective action of l-carnitine (LC) in the rat model of 3-nitropropionic acid (3-NPA)-induced mitochondrial dysfunction was examined. 3-NPA is known to produce decreases in neuronal ATP levels via inhibition of the succinate dehydrogenase (SDH) at complex II of the mitochondrial electron transport chain. SDH is involved in reactions of the Krebs cycle and oxidative phosphorylation, and its inhibition leads to both necrosis and apoptosis. LC enhances mitochondrial metabolism and, together with its acetylated form, acetyl-l-carnitine (ALC), via the LC-ALC-mediated transfer of acetyl groups, plays an important modulatory role in neurotransmitter signal transduction pathways and gene expression in neuronal cells. In the study described here, adult male Sprague-Dawley rats were injected with 3-NPA alone or treated with LC prior to 3-NPA administration. Pretreatment with LC totally prevented the 3-NPA-induced decrease in brain temperature measured using temperature probes implanted intracranially. *It appears that the protective effects of LC against 3-NPA-induced neurotoxicity are achieved via compensatory enhancement of several pathways of mitochondrial energy metabolism*. The results of this and previous studies conducted by our division in the 3-NPA model of mitochondrial dysfunction demonstrate that 3-NPA may be employed in vivo to evaluate enhancers of mitochondrial function that might exert neuroprotective effects. [10]

Neuroprotective 2: Reduces Brain Injury after Hypoxia-Ischemia

Perinatal hypoxia-ischemia remains a significant cause of neonatal mortality and neurodevelopmental disability. *Numerous lines of evidence indicate that cerebral ischemic insults disrupt normal respiratory activity in mitochondria*. Carnitine (3-hydroxy-4-N-trimethylammonium-butyrate) has an essential role in fatty acid transport in the mitochondrion and in modulating potentially toxic acyl-CoA levels in the mitochondrial matrix. There are no naturally occurring esterases available to reduce the accumulation of acyl-CoA but this process can be overcome by exogenous carnitine. We used a newborn rat model of perinatal hypoxia-ischemia to test the hypothesis that treatment with L-carnitine would reduce the neuropathologic injury resulting from hypoxia-ischemia in the developing brain. We found that treatment with L-carnitine during hypoxia-ischemia reduces neurologic injury in the immature rat after both a 7- and 28-d recovery period. We saw no neuroprotective effect when L-carnitine was administered after hypoxia-ischemia. Treatment with D-carnitine resulted in an increase in mortality during hypoxia-ischemia. *Carnitine is easy to administer, has low toxicity, and is routinely used in neonates as well as children with epilepsy, cardiomyopathy, and inborn errors of metabolism. L-Carnitine merits further investigation as a treatment modality for the asphyxiated newborn or as prophylaxis for the at-risk fetus or newborn*. [11]

Neuroprotective 3

Some of the damage to the CNS that is observed following amphetamine and methamphetamine (METH) administration is known to be linked to increased formation of free radicals. This increase could be, in part, related to mitochondrial dysfunction and/or cause damage to the mitochondria, thereby leading to a failure of cellular energy metabolism and an increase in secondary excitotoxicity. The actual neuronal damage that occurs with METH-induced toxicity seems to affect dopaminergic cells in particular. METH-induced toxicity is related to an increase in the generation of both reactive oxygen (hydroxyl, superoxide, peroxide) and nitrogen (nitric oxide) species. Peroxynitrite (ONOO(-)), which is a reaction product of either superoxide or nitric oxide, is the most damaging radical. It can be reduced by antioxidants such as selenium, melatonin, and the selective nNOS inhibitor, 7-nitroindazole. METH-induced toxicity has been previously shown to increase production of the peroxynitrite stress marker, 3-nitrotyrosine (3-NT), in vitro, in cultured PC12 cells, and also in vivo, in the striatum of adult male mice. Pre- and post-treatment of mice with l-carnitine (LC) significantly attenuated the production of 3-NT in the striatum after METH exposure. *LC is a mitochondriotropic compound in that it carries long-chain fatty acyl groups into mitochondria for beta-oxidation. It was shown also to play a protective role against various mitochondrial toxins, such as 3-nitropropionic acid. The protective effects of LC against METH-induced toxicity could be related to its prevention of possible metabolic compromise produced by METH and the resulting energy deficits. In particular, LC may be maintaining the mitochondrial permeability transition (MPT) and modulating the activation of the mitochondrial permeability transition pores (mPTP), especially the cyclosporin-dependent mPTP. The possible neuroprotective mechanism of LC against METH-toxicity and the role of the mitochondrial respiratory chain and the generation of free radicals and their subsequent action on the MPT and mPTP are also being examined using an in vitro model of NGF-differentiated pheochromocytoma cells (PC12).* In preliminary experiments, the pretreatment of PC12 cells with LC (5 mM), added 10 min before METH (500 micro M), indicated that LC enhances METH-induced DA

depletion. The role of LC in attenuating METH-evoked toxicity is still under investigation and promises to reveal information regarding the underlying mechanisms and role of mitochondria in the triggering of cell death. [12]

Neuroprotective 4

A plant and fungal toxin, 3-NPA, acts as an inhibitor of mitochondrial function via irreversible inactivation of the mitochondrial inner membrane enzyme, succinate dehydrogenase (SDH). Inhibition of SDH disturbs electron transport and leads to cellular energy deficits and neuronal injury. We have shown that pretreatment with l-carnitine, while not significantly attenuating SDH inhibition, prevented hypothermia and oxidative stress-associated increased activity of free radical-scavenging enzymes. Here, a neurohistological method was applied to examine the effect of carnitine pretreatment against 3-NPA-induced neurotoxicity. Twenty adult male Sprague-Dawley rats were randomly divided into two groups (n = 10/group). Rats in the first group were injected twice with 3-NPA at 30mg/kg s.c., 2 days apart, and the second group of animals received l-carnitine pretreatment at 100mg/kg 30-40min before 3-NPA administration. Rats in both groups were perfused 7 days later and their brains harvested. Degenerating neurons were identified and localized via the fluorescent marker Fluoro-Jade B. In the three animals that survived 3-NPA dosing, one exhibited no pathology, one exhibited moderate unilateral damage to the striatum, and the third exhibited extensive bilateral neuronal degeneration in multiple forebrain regions. In the seven surviving animals that received l-carnitine prior to 3-NPA insult, six exhibited no lesions, while one exhibited a modest unilateral lesion in the striatum. It appears that l-carnitine is protective against 3-NPA-induced toxicity, as reflected by both reduced mortality and significantly reduced neuronal degeneration. [13]

Neuroprotective 5

The present study investigates the effects of Acetyl-L-carnitine (ALCAR) against the toxicity of 1-methyl-4-phenylpyridinium (MPP(+)), the neurotoxic metabolite of MPTP, in murine brain neuroblastoma cells. MPP(+), a potent mitochondrial toxin, induced a dose-dependent reduction in mitochondrial oxygen consumption and cell viability, corresponding to an accelerated rate of cellular glucose utilization. Treatment with ALCAR, but not L-carnitine, prevented MPP(+) toxicity and partially restored intracellular ATP concentrations, but did not reverse the MPP(+)-induced loss of mitochondrial oxygen consumption. These data indicate that protective effects are independent of oxidative phosphorylation. ALCAR had a substantial glucose sparing effect in both controls and MPP(+)-treated groups, demonstrating a potential role in enhancing glucose utilization through glycolysis. Antagonizing the entry of fatty acids into the mitochondria, with either insulin or malonyl CoA, did not interfere with ALCAR protection against MPP(+). On the contrary, insulin potentiated the protective effects of ALCAR. In conclusion, these data indicate that ALCAR protects against MPP(+) toxicity, independent of mitochondrial oxidative capacity or beta-oxidation of fatty acids. In contrast, the protective effects of ALCAR appear to involve potentiation of energy derived from glucose through anaerobic glycolysis. [14]

Neuroprotective VI L-carnitine protects brain DNA from age-related damage

Dr P. A. R. Juliet of Nagoya University in Japan and colleagues gave 4 month old and 24 month old rats 300 milligrams acetyl-L-carnitine per kilogram body weight for 7, 14 and 21 days following which their brain cortex, hippocampus, striatum, hypothalamus and cerebellum were examined for antioxidant enzyme activity, nucleic acid (DNA and RNA) levels, and DNA damage.

Carnitine levels were lower in all brain regions examined in the 24 month old rats than in the 4 month old animals, although longer supplementation with L-carnitine was reflected in increased brain levels of the amino acid in the older animals, which was not observed in the younger rats. Older rats also had lower brain levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, as well as lower DNA and RNA levels in the cortex, hippocampus and striatum, however in older rats who received L-carnitine, the researchers found enhanced levels of antioxidants and nucleic acids that increased with duration of the treatment, which again, were not found to be effected by carnitine in the younger rats.

When DNA damage was assessed, it was found to be higher in the older rat brains than in the younger rats, particularly in the cortex, hippocampus and striatum, areas in which L-carnitine appeared to provide the greatest protective benefit. L-carnitine provides its neuroprotective effect by promoting energy production, activating a DNA repairing enzyme and enhancing antioxidant status.[15]

Significantly improves early stages of Alzheimer's disease and vascular dementia

Efficacy, safety and tolerability of acetyl-L-carnitine (ALC) were studied during the double-blind placebo-controlled 12-week trial in patients with mild (initial) dementia caused by the Alzheimer's disease (AD) and

vascular dementia (VD). ALC was administered in doses from 2250 to 3000 mg per day. Patient's state was assessed with some scales (MMSE, CGI etc) and a battery of neuropsychological tests. The treatment effect of ALC was 2,8 times higher than in placebo-treated patients. The clinical improvement by CGI scores was significantly better in AD patients compared to VD and did not depend on the severity of baseline cognitive deficit. The drug was well-tolerated. ALC can be recommended in the abovementioned doses for treatment of early stages of AD and VD.[40]

Improvements in mood, energy and overall Q-o-L

In a recent randomized, double-blind, placebo-controlled study ALC (2 grams daily) treatment was associated with significant improvement in patient energy levels, general functioning and well-being. The improvement of quality of life is associated with reduction of anxiety and depression.[41]

Protective role against alcohol-induced gastric lesions

We have investigated in the current study the possible protective effects of two carnitine esters known to have powerful anti-oxidant potential namely, propionyl L-carnitine (PLC) and acetyl L-carnitine (AC) against alcohol-induced gastric lesions in rats. Both drugs were administered as a single oral dose of 200mgkg(-1) body weight 1h before alcohol intake. Both carnitine esters could protect the gastric mucosa against the injurious effect of absolute alcohol and promote ulcer healing as evidenced from the ulcer index (UI) values. Propionyl L-carnitine prevented alcohol-induced increase in thiobarbituric acid-reactive substances (TBARS), an index of lipid peroxidation. The propionyl carnitine ester also increased the gastric content of reduced glutathione (GSH), besides it increased the enzymatic activities of gastric superoxide dismutase (SOD) and glutathione-S-transferase (GST). Likewise, AC did protect against the ulcerating effect of alcohol and mitigate most of the biochemical adverse effects induced by alcohol in gastric mucosa, but to a lesser extent than PLC. Neither PLC nor AC did affect catalase activity in gastric tissue. *Based on these observations, one could conclude that carnitine esters, particularly PLC could partly protect gastric mucosa from alcohol-induced acute mucosal injury, and these gastroprotective effects might be probably induced, at least partly, through anti-oxidant mechanisms*. [16]

Improves Exercise Capacity in Post-MI Heart Failure

Exercise capacity in patients with several types of cardiovascular disease can be improved with dietary carnitine, or carnitine derivatives. Mechanisms underlying this improvement remain largely unknown in part due to a lack of animal models of cardiac pathology in which carnitine derivatives improve exercise tolerance. Our goal was to evaluate the ability of propionyl-L-carnitine (PLC) to improve exercise tolerance in a rat model of exercise intolerance. Fischer 344 rats were followed after either a moderate size MI (n = 22) or sham MI surgery (n = 14). Starting 10 days post-surgery 10 of the MI and 7 of the sham rats received 100 mg/kg/day PLC in drinking water, which increased plasma and LV total l-carnitine concentrations 15-23% ($p < 0.05$). Rats were followed longitudinally until a statistically significant decrease in exercise capacity occurred in one of the groups, at which time all rats were sacrificed for study of the isolated perfused hearts. At 12-weeks post-MI exercise capacity had decreased 16 +/- 7% ($p < 0.05$) in the MI group, but remained within 3% of baseline in the MI group that received PLC and the sham groups. Both MI groups exhibited the same degree of LV dilation, decrease in fractional shortening, and blunting of the response to isoproterenol. We conclude that supplemental dietary PLC attenuates the exercise intolerance that occurs secondary to post-MI heart failure in rats, but that this beneficial effect is not attributable to altered LV remodeling, an improved response to beta-adrenergic stimulation, or increased skeletal muscle citrate synthase activity. [17]

Alleviates alcohol-induced liver damage: role of tumor necrosis factor-alpha.

Excessive alcohol intake induces hepatic fatty infiltration, which has been suggested to sensitize the liver to further damage. To test this hypothesis, L-carnitine, a constitutional lipotropic compound, was administered to rats chronically treated with ethanol by liquid diet feeding for 10 weeks. RESULTS*: Ethanol administration caused marked steatosis, mild inflammation and elevated plasma alanine aminotransferase and tumor necrosis factor alpha (TNF-alpha) concentrations. Dietary supplementation with L-carnitine significantly reduced all these parameters as well as the hepatic concentration of thiobarbituric acid reactive substances, an indicator of lipid peroxidation products. Pretreatment with L-carnitine also significantly blunted ethanol-induced stimulation of TNF-alpha release by isolated Kupffer cells.* This study provides direct support for the notion that steatosis sensitizes the liver to further damage and suggests an involvement of TNF-alpha in this process. [18]

Diabetic Neuropathy

Alterations in cyclooxygenase (COX) pathway activity have been implicated in the pathogenesis of

experimental diabetic neuropathy (EDN). These studies explore the relationships between COX-mediated and acetyl-L-carnitine (ALC)-sensitive defects that contribute to functional, metabolic, and vascular abnormalities of EDN. The effects of nonselective COX inhibition with flurbiprofen were contrasted with selective COX-2 inhibition with meloxicam, administered alone and in combination with ALC in nondiabetic (ND) and streptozotocin-induced diabetic (STZ-D) rats. Flurbiprofen treatment of ND rats replicated many of the biochemical and physiological abnormalities of EDN, i.e., reduced motor nerve conduction velocity (MNCV), total and endoneurial nerve blood flow (NBF), Na,K-ATPase activity, and myo-inositol (MI) and taurine content. In STZ-D rats, however, flurbiprofen paradoxically prevented endoneurial NBF deficits but not MNCV slowing. Coadministration of 50 mg x kg(-1) x day(-1) ALC prevented reductions in MNCV, Na,K-ATPase activity, and endoneurial NBF in flurbiprofen-treated ND and STZ-D rats. In contrast, selective COX-2 inhibition with meloxicam was without effect on MNCV, NBF, or MI content in ND rats and prevented MNCV slowing and NBF deficits in STZ-D rats. Western blot analysis showed unchanged sciatic nerve COX-1 protein but increased COX-2 protein abundance in STZ-D versus ND rats. These results imply 1) a tonic role of the COX-1 pathway in the regulation of nerve osmolytes and Na,K-ATPase activity and the maintenance of NBF in ND animals and 2) activation of the COX-2 pathway as an important mediator of NBF and MNCV deficits in EDN. [19]

Diabetic neuropathy: A long-term, randomized, double-blind, placebo-controlled study

To assess the efficacy and tolerability of acetyl-L-carnitine (levacecarnine; LAC) versus placebo in the treatment of diabetic neuropathy, mainly by evaluating the effects of treatment on electrophysiological parameters and pain symptoms. DESIGN: This was a multicentre (n = 20), randomized, double-blind, placebo-controlled, parallel-group study. PATIENTS: 333 patients meeting clinical and/or neurophysiological criteria for diabetic neuropathy were enrolled. INTERVENTIONS: Patients were randomised to treatment with LAC or placebo. LAC (or placebo) was started intramuscularly at a dosage of 1000 mg/day for 10 days and continued orally at a dosage of 2000 mg/day for the remainder of the study (355 days). MAIN OUTCOME PARAMETERS AND RESULTS: The main efficacy parameter was the effect of treatment on 6- and 12-month changes from baseline in nerve conduction velocity (NCV) and amplitude in the sensory (ulnar, sural and median) and motor (median, ulnar and peroneal) nerves. The effect of treatment on pain was also evaluated by means of a visual analogue scale (VAS). Among the 294 patients with impaired electrophysiological parameters at baseline, those treated with LAC showed a statistically significant improvement in mean NCV and amplitude compared with placebo ($p < 0.01$). The greatest changes in NCV (at 12 months) were observed in the sensory sural nerve (7 m/sec in the LAC group vs +1.0 m/sec in the placebo group), sensory ulnar nerve (+2.9 vs +0.1 m/sec, respectively) and motor peroneal nerve (+2.7 vs -0.2 m/sec), whereas the greatest changes in amplitude were recorded in the motor peroneal nerve (+2.2 vs +0.1 mV). After 12 months of treatment, mean VAS scores for pain were significantly reduced from baseline by 39% in LAC-treated patients ($p < 0.0$ vs baseline) compared with 8% in placebo recipients. LAC was well tolerated over the study period. CONCLUSIONS: LAC was effective and well tolerated in improving neurophysiological parameters and in reducing pain over a 1-year period. LAC is, therefore, a promising treatment option in patients with diabetic neuropathy. [20]

Mitochondrial enhancement- Improves cognitive impairment in Alzheimer's

Oxidative mitochondrial decay is a major contributor to aging. Some of this decay can be reversed in old rats by feeding them normal mitochondrial metabolites, acetylcarnitine (ALC) and lipoic acid (LA), at high levels. Feeding the substrate ALC with LA, a mitochondrial antioxidant, restores the velocity of the reaction (K(m)) for ALC transferase and mitochondrial function. The principle appears to be that, with age, increased oxidative damage to protein causes a deformation of structure of key enzymes with a consequent lessening of affinity (K(m)) for the enzyme substrate. The effect of age on the enzyme-binding affinity can be mimicked by reacting it with malondialdehyde (a lipid peroxidation product that increases with age). In old rats (vs. young rats), mitochondrial membrane potential, cardiolipin level, respiratory control ratio, and cellular O(2) uptake are lower; oxidants/O(2), neuron RNA oxidation, and mutagenic aldehydes from lipid peroxidation are higher. Ambulatory activity and cognition decline with age. Feeding old rats ALC with LA for a few weeks restores mitochondrial function; lowers oxidants, neuron RNA oxidation, and mutagenic aldehydes; and increases rat ambulatory activity and cognition (as assayed with the Skinner box and Morris water maze). A recent meta-analysis of 21 double-blind clinical trials of ALC in the treatment of mild cognitive impairment and mild Alzheimer's disease showed significant efficacy vs. placebo. A meta-analysis of 4 clinical trials of LA for treatment of neuropathic deficits in diabetes showed significant efficacy vs. placebo. [21]

Hyperthyroidism

Old studies in animals and unblinded studies in a few hyperthyroid patients suggested that L -carnitine is a periferal antagonist of thyroid hormone action at least in some tissues. This conclusion was substantiated by our recent observation that carnitine inhibits thyroid hormone entry into the nucleus of hepatocytes, neurons, and fibroblasts. In the randomized, double-blind, placebo-controlled 6-month trial reported here, we assessed whether 2 or 4 g/d oral L-carnitine were able to both reverse and prevent/minimize nine hyperthyroidism- related symptoms. We also evaluated changes on nine thyroid hormone-sensitive biochemical parameters and on vertebral and hip mineral density (bone mineral density). Fifty women under a fixed TSH-suppressive dose of L -T(4) for all 6 months were randomly allocated to five groups of 10 subjects each. Group 0 associated placebo for 6 months; groups A2 and A4 started associating placebo (first bimester), substituted placebo with 2 or 4 g/d carnitine (second bimester), and then returned to the association with placebo. Groups B2 and B4 started associating 2 and 4 g/d carnitine for the first two bimesters, and then substituted carnitine with placebo (third bimester). Symptoms and biochemical parameters worsened in group 0. In group A, symptoms and biochemical parameters worsened during the first bimester, returned to baseline or increased minimally during the second bimester (except osteocalcin and urinary OH-proline), and worsened again in the third bimester. In group B, symptoms and biochemical parameters (except osteocalcin and urinary OH-proline) did not worsen or even improved over the first 4 months; they tended to worsen in the third bimester. In both the A and B groups, the two doses of carnitine were similarly effective. At the end of the trial, bone mineral density tended to increase in groups B and A (B > A). In conclusion, L-carnitine is effective in both reversing and preventing symptoms of hyperthyroidism and has a beneficial effect on bone mineralization. Because hyperthyroidism depletes the body deposits of carnitine and since carnitine has no toxicity, teratogenicity, contraindications and interactions with drugs, carnitine can be of clinical use. [22]

Male Reproductive Health

Improves sperm motility in men with fertility problems

The researchers chose 60 infertile men between the ages of 20 and 40 to take a combination of L-carnitine and L-acetyl-carnitine or a placebo for six months. Two months after the patients had completed their course of supplements, the men who had taken L-carnitine and L-acetyl-carnitine had increased sperm concentration and movement. The most significant improvements in sperm motility, both forward and total, were observed in men who had the lowest levels of moving sperm when the study began. The researchers noted that four spontaneous pregnancies were achieved during the study by men who had taken the combination therapy. *Combined treatment with L-carnitine was effective in increasing sperm motility, especially in groups with lower baseline levels (of moving sperm),* they concluded. [23]

Peyronie's disease

In the first study, the reduction in pain was the same in both subgroups. Propionyl-l-carnitine plus verapamil significantly reduced penile curvature, plaque size, cavernosal artery end-diastolic velocity, the need for surgery and disease progression, and increased the International Index of Erectile Function score and resistivity index of the cavernosal arteries. Tamoxifen plus verapamil had none of these effects. No drug combination affected the peak systolic velocity. Patients receiving verapamil had no side effects but those taking tamoxifen did. In the second study propionyl-l-carnitine and verapamil modified the disease patterns as in the first and no patient had side-effects. CONCLUSION: The combination of propionyl-l-carnitine and verapamil can be considered the therapy of choice for advanced and resistant Peyronie's disease. [24]

48 patients with Peyronie's disease (15 acute and 33 initial chronic), were randomized equally into two groups. The first group used tamoxifen 20 mg twice daily for 3 months and the second acetyl-L-carnitine 1 g twice daily for 3 months. The disease and stages were diagnosed and identified using a history, objective examination, pharmacologically induced erection, autophotography during erection, and basic and dynamic colour Doppler ultrasonography. Penile curvature, plaque size, pain and disease progression were assessed. The differences between the groups or between the variables before and after therapy were compared using analysis of variance or the chi-squared test. RESULTS: Acetyl-L-carnitine was significantly more effective than tamoxifen in reducing pain and in inhibiting disease progression. Acetyl-L-carnitine reduced penile curvature significantly, while tamoxifen did not; both drugs significantly reduced plaque size. Tamoxifen induced significantly more side-effects than acetyl-L-carnitine. CONCLUSIONS: These results suggest that acetyl-L-carnitine is significantly more effective and safe than tamoxifen in the therapy of acute and early chronic Peyronie's disease. [25]

L-carnitine linked to better mental and physical function in the very old

Supplements of L-carnitine improved total muscle mass and boosted cognitive performance among a group

of centenarians. Sixty-six subjects over 100 years of age took part in the study, which also reported reductions in fat mass and fatigue during the placebo-controlled, randomized, double-blind, 2-phase study. "Among all the substances whose concentration decreases with age, L-carnitine diminution is fundamentally important, given its function in the production of energy," explained the authors. The researchers recruited 66 men and women with an average age of 101 to take part in the study. The subjects, showing signs of fatigue after only slight physical activity, were randomly assigned to receive either the daily L-carnitine supplement (two grams) or placebo for six months. At the end of the study, the researchers report that the supplementation with L-carnitine was associated with significant reductions in fat mass, compared to placebo. Indeed, the active supplement group lost 1.6 kg of fat mass, while the placebo group gained 0.6 kg. Total muscle mass in the L-carnitine-supplemented group increased by three kilograms more than the placebo group, report the researchers. Moreover, measurements of fatigue, obtained from a six-minute walking corridor test, decreased after L-carnitine supplementation. Cognitive performance, measured using the 30-point Mini-Mental State Examination (MMSE), showed increases of 4.1 points for the L-carnitine group, compared to only 0.6 points on average for the placebo group. Reductions in mental fatigue were also associated with L-carnitine supplementation. The researchers noted several limitations with their study including using subjects who displayed signs of mild cognitive deficit, having bad eyesight, hearing or who were illiterate. They also note that the subjects were assisted by someone at all times.

Chemotherapy: Protective Effects

Protects heart against adriamycin toxcitiy

Evidence suggest L-carnitine administration, like CO Q 10, can prevent the cardiac toxicity, caused by the chemotherapeutic drug adriamycin. [26]

Kidney protective against cisplatin

This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is an additional risk factor and/or a mechanism in cisplatin-induced nephrotoxicity and to gain insights into the possibility of a mechanism-based protection by L-carnitine against this toxicity. Methods: 60 male Sprague-Dawley rats were divided into six groups of 10 animals each and received one of the following treatments: The first three groups were injected intraperitoneally with normal saline, L-carnitine (500 mg/kg), and D-carnitine (750 mg/kg), respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, L-carnitine and D-carnitine, respectively, for 5 successive days before and after a single dose of cisplatin (7 mg/kg). Six days after cisplatin treatment, the animals were sacrificed, and serum as well as kidneys were isolated and analyzed. Results: A single dose of cisplatin resulted in a significant increase in blood urea nitrogen (BUN), serum creatinine, malondialdehyde (MDA) and nitric oxide (NO) and a significant decrease in total carnitine, reduced glutathione (GSH) and adenosine triphosphate (ATP) content in kidney tissues. Interestingly, L-carnitine supplementation attenuated cisplatin-induced nephrotoxicity manifested by normalizing the increase of serum creatinine, BUN, MDA and NO and the decrease in total carnitine, GSH and ATP content in kidney tissues. In the carnitine-depleted rat model, cisplatin induced a progressive increase in serum creatinine and BUN as well as a progressive reduction in total carnitine and ATP content in kidney tissue. Histopathological examination of kidney tissues confirmed the biochemical data, i.e. L-carnitine supplementation protected against cisplatin-induced kidney damage, whereas D-carnitine aggravated cisplatin-induced renal injury. Conclusion: Data from this study suggest that: (1) oxidative stress plays an important role in cisplatin-induced kidney damage; (2) carnitine deficiency should be viewed as an additional risk factor and/or a mechanism in cisplatin-induced renal dysfunction, and (3) L-carnitine supplementation attenuates cisplatin-induced renal dysfunction. [27]

Chemotherapy-Neuroprotective: cisplatin and taxol

Antineoplastic drugs belonging to platinum or taxane families are severely neurotoxic, inducing the onset of disabling peripheral neuropathies with different clinical signs. Acetyl-L-carnitine (ALC) is a natural occurring compound with a neuroprotective activity in several experimental paradigms. In this study we have tested the hypothesis that ALC may have a protective role on cisplatin and paclitaxel-induced neuropathy. EXPERIMENTAL DESIGN: Sensory nerve conduction velocity (SNCV) was measured in rats before, at end, and after an additional follow-up period from treatments with cisplatin, paclitaxel, or with the respective combination with ALC. In addition, serum from treated animals was collected to measure the levels of circulating NGF, and left sciatic nerves were processed for light and electron microscope observations. ALC interference on cisplatin and paclitaxel antitumor activity and

protective mechanisms were investigated using several in vitro and in vivo models. RESULTS: ALC cotreatment was able to significantly reduce the neurotoxicity of both cisplatin and paclitaxel in rat models, and this effect was correlated with a modulation of the plasma levels of NGF in the cisplatin-treated animals. Moreover, experiments in different tumor systems indicated the lack of interference of ALC in the antitumor effects of cisplatin and paclitaxel. The transcriptional profile of gene expression in PC12 cells indicated that ALC, in the presence of NGF, was able to positively modulate NGFI-A expression, a gene relevant in the rescue from tissue-specific toxicity. Finally, the transcriptionally ALC-mediated effects were correlated to increase histone acetylation. In conclusion, our results indicate that ALC is a specific protective agent for chemotherapy-induced neuropathy after cisplatin or paclitaxel treatment without showing any interference with the antitumor activity of the drugs. [28]

Carnitine prevents cisplatin induced cardiotoxicity

This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is a risk factor during development of cisplatin (CDDP)-induced cardiomyopathy and if so, whether carnitine supplementation by propionyl-L-carnitine (PLC) could offer protection against this toxicity. To achieve the ultimate goal of this study, a total of 60 adult male Wistar albino rats were divided into six groups. The first three groups were injected intraperitoneally with normal saline, PLC (500 mg kg(-1)), and d-carnitine (500 mg kg(-1)) respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, PLC and D-carnitine, respectively, for 5 successive days before and after a single dose of CDDP (7 mg kg(-1)). On day 6 after CDDP treatment, animals were sacrificed, serum as well as hearts were isolated and analyzed. CDDP resulted in a significant increase in serum creatine phosphokinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH), thiobarbituric acid reactive substances (TBARS) and total nitrate/nitrite (NO(x)) and a significant decrease in reduced glutathione (GSH), total carnitine, and adenosine triphosphate (ATP) content in cardiac tissues. In the carnitine-depleted rat model, CDDP induced dramatic increase in serum cardiomyopathy enzymatic indices, CK-MB and LDH, as well as progressive reduction in total carnitine and ATP content in cardiac tissue. Interestingly, PLC supplementation resulted in a complete reversal of the increase in cardiac enzymes, TBARS and NO(x), and the decrease in total carnitine, GSH and ATP, induced by CDDP, to the control values. Moreover, histopathological examination of cardiac tissues confirmed the biochemical data, where PLC prevents CDDP-induced cardiac degenerative changes while d-carnitine aggravated CDDP-induced cardiac tissue damage. In conclusion, data from this study suggest for the first time that carnitine deficiency and oxidative stress are risk factors and should be viewed as mechanisms during development of CDDP-related cardiomyopathy and that carnitine supplementation, using PLC, prevents the progression of CDDP-induced cardiotoxicity. [34]

Carnitine and cisplatin: prevents liver toxicity

This study investigates whether or not carnitine deficiency is a risk factor and could contribute to cisplatin-induced liver toxicity. A total of 60 adult male Wistar albino rats were divided into six groups. The first three groups were injected intraperitoneally with normal saline, propionyl-l-carnitine (500 mg/kg), and d-carnitine (500 mg/kg), respectively, for 10 successive days. The fourth, fifth and sixth groups were injected intraperitoneally with the same doses of normal saline, propionyl-l-carnitine and d-carnitine, respectively, for 5 successive days before and after a single dose of cisplatin (7 mg/kg). Administration of the standard nephrotoxic dose of cisplatin did not produce any changes in serum alanine transaminase and gamma-glutamyl transferase and no morphological changes in liver tissues. However, it did produce a significant increase in thiobarbituric acid reactive substances and total nitrate/nitrite and a significant decrease in reduced glutathione content in liver tissues. On the other hand, combined treatment with cisplatin and d-carnitine induced a dramatic increase in serum alanine transaminase and gamma-glutamyl transferase, as well as progressive reduction in total carnitine and ATP content in liver tissue. Moreover, histopathological examination of liver tissues confirmed the biochemical data, where cisplatin and d-carnitine combination showed signs of liver injury manifested as focal necro-inflammatory changes and portal inflammation. Interestingly, in carnitine supplemented rats using propionyl-l-carnitine, cisplatin did not produce any biochemical and histopathological changes in liver tissues. In conclusion, data from this study suggest for the first time that (1) carnitine deficiency is a risk factor and could precipitate cisplatin-induced hepatotoxicity, (2) oxidative stress is not the main cause of cisplatin-related hepatotoxicity and (3) propionyl-l-carnitine prevents the development of cisplatin-induced liver injury. [35]

L-carnitine and cancer cachexia

Cancer cachexia (CC), a progressive loss of body mass, leads to malnutrition and deficiencies of essential substances including polyunsaturated fatty acids (PUFAs) and L-carnitine (LC). The availability of these 2 compounds determines the rate of eicosanoid synthesis, which modulates inflammatory processes and hemostasis. We compared the effects of administration of emulsions containing long chain triglycerides (LCTs) relative to a 50:50 mix of medium chain triglycerides (MCTs) with LCTs on hemostasis and inflammatory reactions in patients with CC. The study was conducted on 50 patients with CC (23 women, 27 men) aged 66 ± 11 years with a mean loss in body weight of 21 ± 9% in the previous 6 months. Twenty patients received MCTs/LCTs while 30 received LCTs. Total parenteral nutrition (TPN) was administered using the 'all in one' method (25 kcal/kg/day, protein 1.2 g/kg/day). Selected parameters of coagulation and inflammatory state were evaluated on days 1, 5, 7 and 11 of TPN. Initial concentrations of D-dimers, fibrinogen, plasminogen activator inhibitor type 1 (PAI-1), fibronectin, CRP and IL-6 significantly exceeded the upper limit of the reference values. After 10 days of TPN, we detected significant differences in inflammatory state and hemostasis. Immunological state and hemostasis varied depending on the type of fat emulsion administered. The most likely reasons are the 2-fold higher concentrations of PUFAs in LCTs relative to MCTs/LCTs and a deficiency of LC in skeletal muscles. Both of these factors may contribute to the observed increase in the rate of eicosanoid synthesis.[42]

Carnitine improves symptoms associated with male aging.
To compare testosterone undecanoate versus propionyl-L-carnitine plus acetyl-L-carnitine and placebo in the treatment of male aging symptoms. METHODS: A total of 120 patients were randomized into three groups. The mean patient age was 66 years (range 60 to 74). Group 1 was given testosterone undecanoate 160 mg/day, the second group was given propionyl-L-carnitine 2 g/day plus acetyl-L-carnitine 2 g/day. The third group was given a placebo (starch). Drugs and placebo were given for 6 months. The assessed variables were total prostate-specific antigen, prostate volume, peak systolic velocity, end-diastolic velocity, resistive index of cavernosal penile arteries, nocturnal penile tumescence, total and free testosterone, prolactin, luteinizing hormone, International Index of Erectile Function score, Depression Melancholia Scale score, fatigue scale score, and incidence of side effects. The assessment was performed at intervals before, during, and after therapy. RESULTS: Testosterone and carnitines significantly improved the peak systolic velocity, end-diastolic velocity, resistive index, nocturnal penile tumescence, International Index of Erectile Function score, Depression Melancholia Scale score, and fatigue scale score. Carnitines proved significantly more active than testosterone in improving nocturnal penile tumescence and International Index of Erectile Function score. Testosterone significantly increased the prostate volume and free and total testosterone levels and significantly lowered serum luteinizing hormone; carnitines did not. No drug significantly modified prostate-specific antigen or prolactin. Carnitines and testosterone proved effective for as long as they were administered, with suspension provoking a reversal to baseline values. Only the group 1 prostate volume proved significantly greater than baseline 6 months after testosterone suspension. Placebo administration proved ineffective. Negligible side effects emerged. CONCLUSIONS: Testosterone and, especially, carnitines proved to be active drugs for the therapy of symptoms associated with male aging. [31]

L-carnitine supplementation significantly ($p < 0.05$) increased IGFBP-3 concentrations prior to and at 30, 120, and 180 minutes after acute exercise.
The purpose of this investigation was to examine the influence of L-carnitine L-tartrate (LCLT) supplementation using a balanced, cross-over, placebo-controlled research design on the anabolic hormone response (i.e., testosterone [T], insulin-like growth factor-I, insulin-like growth factor-binding protein-3 [IGFBP-3], and immunofunctional and immunoreactive growth hormone [GHif and GHir]) to acute resistance exercise. Ten healthy, recreationally weight-trained men (mean +/- SD age 23.7 +/- 2.3 years, weight 78.7 +/- 8.5 kg, and height 179.2 +/- 4.6 cm) volunteered and were matched, and after 3 weeks of supplementation (2 g LCLT per day), fasting morning blood samples were obtained on six consecutive days (D1-D6). Subjects performed a squat protocol (5 sets of 15-20 repetitions) on D2. During the squat protocol, blood samples were obtained before exercise and 0, 15, 30, 120, and 180 minutes post-exercise. After a 1-week washout period, subjects consumed the other supplement for a 3-week period, and the same experimental protocol was repeated using the exact same procedures. Expected exercise-induced increases in all of the hormones were observed for GHir, GHif, IGFBP-3, and T. Over the recovery period, LCLT reduced the amount of exercise-induced muscle tissue damage, which was assessed via magnetic resonance imaging scans of the thigh. LCLT supplementation significantly ($p < 0.05$) increased IGFBP-3 concentrations prior to and at 30, 120, and 180 minutes after acute exercise. No other direct effects of

LCLT supplementation were observed on the absolute concentrations of the hormones examined, but with more undamaged tissue, a greater number of intact receptors would be available for hormonal interactions. These data support the use of LCLT as a recovery supplement for hypoxic exercise and lend further insights into the hormonal mechanisms that may help to mediate quicker recovery. [32]

Carnitine and Lipoic acid prevent free radical damage to heart mitochondria from aging

Oxidative modification alters the function of proteins and is thought to play an important role in the decline of cellular function during aging process. In the present study, we have evaluated the levels of oxidant production, protein oxidation, reduced and oxidized glutathione in young, middle aged and aged rats. The animals were divided into six groups, each group consisting of six animals each. Groups I and II were young rats, Groups III and IV were middle-aged rats and Groups V and VI were aged rats. Groups II, IV and VI were treated with carnitine (300 mg/kg bw) and Dl-alpha-Lipoic acid (100 mg/kg bw) for 28 days. Statistical significance was carried out using ANOVA. There was a significant reduction in the levels of reduced glutathione and Redox ratio ($P<0.05$) in aged rats whereas elevation in the levels of oxidant production, protein carbonyls, advanced oxidation protein products and oxidized glutathione were observed. Co-supplementation of carnitine and lipoic acid improved these levels to near normalcy. Thus we conclude that the utilization of carnitine and lipoic acid will lead to an improvement in the quality of living during the later stages of life by preventing free radical induced damage to the proteins. [33]

Protect DNA damage, improves immune status enhances T-cells

In aged animals, administration of L: -carnitine for 21 days significantly decreased the levels of lipid peroxides and improved the activities of antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase. L: -Carnitine enhanced T-cell proliferative responses as evaluated by T-cell proliferation assay using [(3)H] thymidine incorporation and also significantly reduced DNA damage, apoptosis and TNF-alpha level in lymphocytes of aged animals. Our results suggest that L: -carnitine may have a vital role in improving functions in the cells of the immune system particularly the lymphocytes possibly through its antioxidant action. [37]

Improves insulin resistance and Type II diabetes

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. [38]

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