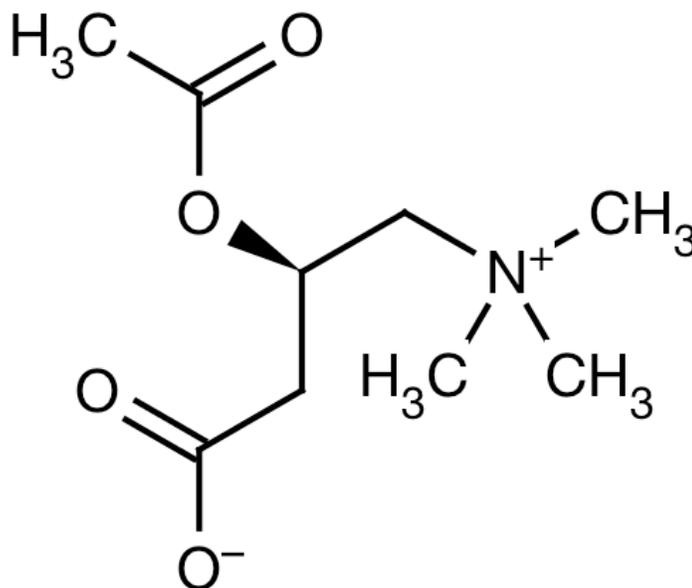


CINAPS Compound Dossier

Acetyl-L-carnitine



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Revised

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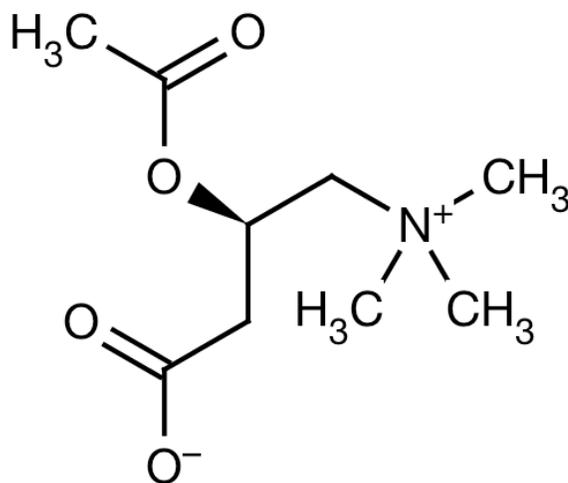
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I. Compound Information

Common name

Acetyl-L-carnitine

Structure



PubChem ID

18230

MF

C₉H₁₇NO₄

FW

203.24

CASRN

14992-62-2

Polar surface area

66.43

logP

-3.71

IUPAC name

(3R)-3-Acetyloxy-4-trimethylazaniumylbutanoate

Other names

Alcar; Nicetile sup®; Branigen sup®; Zibren sup®; Ceredor®; Normobren®

Drug class

Vitamin B Complex, Nootropic Agent

Notes

Acetyl-L-carnitine facilitates the transport of acetyl COA into mitochondria during the oxidation of fatty acids.

Development status

II. Rationale

Ila. Scientific Rationale / Mechanism

Since elevated free radical generation and other mitochondrial dysfunction are involved in neurodegenerative pathology, substances that support mitochondrial function and block free radical reactions from propagating represent reasonable candidates for chemopreventative or therapeutic treatment of these disorders. Acetyl L-carnitine and its non-acetylated derivative, L-carnitine, are both integral components of mitochondrial function. These substances facilitate the transport of long chain fatty acids into the mitochondria to generate the oxidative phosphorylation substrates NADH and FADH₂, and the removal of short chain and medium chain fatty acids that accumulate during normal and abnormal metabolism. Experimental evidence suggests that acetyl-L-carnitine boosts mitochondrial ATP production and also helps protect mitochondria against oxidative attack (**Kidd, 2005**). The improvement of mitochondrial respiration allows neurons to produce the ATP necessary to maintain the normal membrane potential and delays mitochondrial depolarization in response to a variety of stressors including oxidative damage (**Beal, 2003**). However, acetyl-L-carnitine has been shown to possess neuroprotective potential through a variety of other effects including increasing PKC activity and preventing lipid peroxidation. Recent studies have also shown that acetyl-L-carnitine reduces beta-amyloid toxicity in primary cortical neuronal cultures by upregulating vitagenes and increasing both heat shock protein HO-1, Hsp60 and Hsp70 expression (**Calabrese, 2008**). The upregulation of heat shock proteins is associated with high expression of the redox-sensitive transcription factor Nrf2, raising the possibility that acetylcarnitine, by promoting acetylation of DNA binding proteins, can induce post-translational modifications of critical target proteins endowed with DNA competence and transactivating activity (**Calabrese, 2005**). Furthermore, acetyl-L-carnitine appears to help maintain NMDA-sensitive glutamate receptors in neuronal membrane and increase the production of neurotrophins, two effects promoting synaptic plasticity.

Both L-carnitine and acetyl-L-carnitine have been shown to possess significant neuroprotective properties in *in vitro* and *in vivo* studies, including human clinical trials (as described in greater detail below). Thus, the use of an L-carnitine or acetyl-L-carnitine supplement is considered a potential treatment agent for Parkinson's disease and other neurodegenerative diseases, particularly when combined with an antioxidant such as lipoic acid. Indeed, studies have demonstrated that 4-week pretreatment with lipoic and/or acetyl-L-carnitine effectively protected SK-N-MC human neuroblastoma cells against rotenone-induced mitochondrial dysfunction, oxidative damage, and accumulation of α -synuclein and ubiquitin. Most notably, it was found that when combined, these two agents worked at 100- to 1000-fold lower concentrations than they did individually (**Zhang, 2008**).

In mammals, the carnitine pool consists of nonesterified L-carnitine and many acylcarnitine esters. Of these esters, acetyl-L-carnitine is quantitatively and functionally the most significant. These carnitines are derived from essential amino acids and must be synthesized or used from nutritional intake. Most healthy children and adults do not need to consume carnitine from food or supplements, as the liver and kidneys produce sufficient amounts from the amino acids lysine and methionine to meet daily needs. However, carnitine and acetyl-L-carnitine are available over-the-counter in various formulations as dietary supplements, mostly advertised as an aid to weight loss, to improve exercise performance, and to enhance the sense of well-being. Other indications advertised on supplements include increased male fertility, anti-aging and cognitive enhancement. The only forms available in the United States are L-carnitine and acetyl-L-carnitine. Propionyl-L-carnitine is approved for use in Europe, but not in the United States. While L-carnitine has been reported to have better oral bioavailability, acetyl-L-carnitine is thought to penetrate the blood brain barrier better than L-carnitine and may be most therapeutically useful as an agent for elevating brain carnitine levels (**Beal, 2003**).

Prescription acetyl-L-carnitine products have been classified as carnitine acetyltransferase stimulants,

II. Rationale (cont.)

or secondary antioxidants. One acetyl-L-carnitine product (levacecarnine) was developed by Sigma-Tau and launched in Italy as Nicetile sup® for the treatment of senile dementia and Alzheimer's disease. The compound was licensed to GlaxoSmithKline (GSK) and Duncan, and was launched by these companies as Branigen sup® and Zibren sup®, respectively. Other trades names or common names used or in use today include ALCAR, Ceredor® and Normobren®.

IIb. Consistency

n/a

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

In rat studies the neurotoxin 1-methyl-4-phenylpyridinium (MPP+), injected intracerebroventricularly (ICV) at 62.5 micrograms of MPP+/rat, produced 50% mortality. In the remaining animals, the ICV administration of MPP+ produced a decrease in dopamine (DA) concentration in striatum (83%), hypophysis (95%) and median eminence (70%). However, olfactory bulb and substantia nigra were not affected. Decreases in catecholamine concentration, tyrosine hydroxylase activity, and other indications of neurotoxicity of the dopaminergic system were observed. Acetyl-L-carnitine (i.p. injected daily for 8 days with 100 mg/kg of acetyl-L-carnitine, starting 3 days before MPP+ treatment) significantly protected against mortality produced by the ICV injection of MPP+. Indeed, rats treated with acetyl-L-carnitine showed no mortality; however, the acetyl-L-carnitine treatment did not demonstrate a significant protective effect on the dopaminergic system as assessed by catecholamine concentration or tyrosine hydroxylase, neurofilament or glial fibrillary acid protein (**Steffen, 1995**).

Methamphetamine, like MPP+, is thought to kill nigrostriatal dopaminergic neurons by inhibiting mitochondrial complex I, with cell death being partially attributable to mitochondrial dysfunction and oxidative stress damage (**Virmani, 2004**). This toxicity has been shown to be attenuated in vivo in rats by administration of L-carnitine (**Virmani, 2003**), and acetyl-L-carnitine can attenuate the toxicity of MPP+ in PC12 cells (**Virmani, 2004**) and neuroblastomas (**Mazzio, 2003**).

Studies with the excitotoxin and free radical precursor, quinolinic acid, and the mitochondrial toxin, 3-nitropropionic acid (3-NP) reveal oxidative stress, lipid peroxidation, and mitochondrial dysfunction in synaptosomal fractions. At micromolar concentrations, L-carnitine reduced the three markers of oxidative stress stimulated by both toxins alone or in combination. L-carnitine also prevented the rotation behavior evoked by quinolinic acid and the hypokinetic pattern induced by 3-NP in rats. Morphological alterations produced by both toxins (increased striatal glial fibrillary acidic protein-immunoreactivity for quinolinic acid and enhanced neuronal damage in different brain regions for 3-NP) were reduced by L-carnitine. In addition, L-carnitine prevented the synergistic action of 3-NP and quinolinic acid to increase motor asymmetry and depleted striatal GABA levels (**Silva-Adaya, 2008**).

IIIb. Animal Models: Non-human primates

Acetyl-L-carnitine has been reported to protect against MPTP-induced toxicity in the nonhuman primate. Specifically, acetyl-L-carnitine pretreated monkeys did not show signs of parkinsonism or electroretinographic changes typical of dopaminergic deficiency when given MPTP. In addition, pilot neurochemical and morphological data confirmed a partial protection effect. After MPTP treatment, those animals having received acetyl-L-carnitine had homovanillic acid values about 30% of those of normals in the caudate nucleus, and about 60% in the substantia nigra, while levels in the "unprotected" animals were considerably lower: only 16% of normal in the caudate nucleus and 40% in substantia nigra. In addition, tyrosine hydroxylase-labelled neurons in the substantia nigra of two acetyl-L-carnitine monkeys examined were somewhat reduced in number compared to control animals, but their morphology was intact. In contrast, in MPTP-treated monkeys without ALC administration there was a profound cell loss of tyrosine hydroxylase-positive neurons and the remaining ones showed severe degenerative changes (**Bodis, 1991**).

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

In an early pilot study, two groups of 10 subjects with Parkinson's disease received doses of 1 or 2 g acetyl-L-carnitine per day for seven days. The effects of this drug on intermittent luminous stimulation and on nocturnal sleep patterns were studied. With either dose of acetyl-L-carnitine the predominant effects were an improvement of the H response, sleep stages and spindling activity (**Puca, 1990**).

The clinical tolerability has been well documented through clinical trial programs for other CNS indications such as Alzheimer's disease. In general, intravenous, intramuscular and oral acetyl-L-carnitine is safe and well tolerated. At oral doses at or above approximately 3 grams/day, carnitine and acetyl-carnitine supplements may cause nausea, vomiting, abdominal cramps, diarrhea, and a "fishy" body odor. Acetyl-L-carnitine has been reported to increase agitation in some Alzheimer's disease patients and to increase seizure frequency and/or severity in some individuals with seizure disorder (**Hendler, 2001**). Only the L-isomer of carnitine is biologically active, and the D-isomer may actually compete with L-carnitine for absorption and transport, thereby increasing the risk of L-carnitine deficiency (**Seim, 2001**). Supplements containing a mixture of the D- and L-isomers (D,L-carnitine) have been associated with muscle weakness in patients with kidney disease. Controlled studies examining the safety of L-carnitine supplementation in pregnant and breastfeeding women are lacking (**Hendler, 2001**).

IVb. Epidemiological evidence

n/a

V. Relevance to other neurodegenerative diseases

Acetyl-L-carnitine, when administered at supraphysiologic concentrations, is neuroprotective in several animal models of global and focal cerebral ischemia. Three primary mechanisms of action support beneficial changes in neurochemical outcome measures performed with these in vivo models and with in vitro models of acute neuronal cell death. The metabolic hypothesis for acetyl-L-carnitine activity is based on the switch in oxidative metabolism from pyruvate to the acetyl component of acetyl-L-carnitine, leading to the reduction in postischemic brain lactate levels and elevation of ATP. The antioxidant mechanism involves the reduction of oxidative stress in both brain tissue and cerebrospinal fluid. In addition, experiments performed with primary cultures of rat cortical neurons indicate that the presence of acetyl-L-carnitine significantly inhibits both acute and delayed cell death following exposure to N-methyl-d-aspartic acid (NMDA), an excitotoxic glutamate antagonist. This third mechanism of inhibiting excitotoxicity could be extremely important in both acute brain injury and chronic neurodegenerative disorders. Finally, several other mechanisms of action appear possible, including a neurotrophic effect of acetyl-L-carnitine and inhibition of mitochondrial permeability transition. All of these mechanisms may play a role in, and are compatible with the concept that several brain injury pathways must be inhibited to optimize, therapeutic efficacy (**Zanelli, 2005**).

In clinical trials, acetyl-L-carnitine has on occasion been proven to have modest beneficial effects for Alzheimer's disease. A number of double-blind trials have been conducted, and a 2003 meta-analysis of 15 trials concluded acetyl-L-carnitine was beneficial for mild Alzheimer's disease, according to clinical and psychometric tests and clinicians' global assessments. Effective and well-tolerated oral intakes ranged from 1.5-3.0 g daily. One double-blind trial of acetyl-L-carnitine versus placebo for Alzheimer's disease included noninvasive bioenergetic monitoring using magnetic resonance spectroscopy. At the onset of the trial, magnetic resonance imaging detected probable abnormal cell membrane breakdown and abnormally low reserves of high-energy phosphate. After six months, the acetyl-L-carnitine group was significantly improved over the placebo group, with slowed progression of the disease and improvement of the metabolic measures as determined by magnetic resonance imaging. The researchers suggested acetyl-L-carnitine was facilitating neuronal membrane renewal and, through that process, restoring energy stores in the cortex (**Kidd, 2005**). In 2006, studies in rat cortical neurons treated with amyloid-beta peptide (A1-42) revealed that acetyl-L-carnitine exerts neuroprotective effects against A1-42 toxicity and oxidative stress in part by up-regulating the levels of glutathione and heat shock proteins (**Hafiz, 2006**). This evidence supports the pharmacological potential of acetyl-L-carnitine in the management of oxidative stress and neurotoxicity.

Evidence from randomized and controlled clinical trials suggests that acetyl-L-carnitine is also an effective agent for treatment of patients affected by peripheral neuropathies of different origin, including neuropathic pain associated with HIV (antiretroviral toxic neuropathy) or diabetes mellitus, and those caused by chemotherapeutic agents. Indeed, in both experimental and human diabetic neuropathy, peripheral nerve levels of carnitine and acetyl-L-carnitine are depleted. Multiple mechanisms are proposed to explain the protective effect of acetyl-L-carnitine against nerve damage and pain. One mechanism gaining favor is that acetyl-L-carnitine-induced alteration of mitochondrial energy substrates has an affect on nerve myoinositol utilization which translates into activation of protein kinase C and normalization of neural Na⁺/K⁺-ATPase. The correction of imbalances in redox-coupling and restoration of protein kinase C-mediated effects on NO-synthase also contributes to increased endoneurial blood flow (**Sima, 2007**). In the case of peripheral nerve injury due to trauma, similar mechanisms enable acetyl-L-carnitine to more rapidly normalize sensory neuronal function, a prerequisite for axonal regeneration, which in turn allows innervation density, and thereby quality of sensation, to return to normal (**Wilson, 2007**).

V. Relevance to other neurodegenerative diseases (cont.)

Recent studies suggest that nitric oxide (NO) and its reactive derivative peroxynitrite are implicated in the pathogenesis of multiple sclerosis (MS). Patients dying with MS demonstrate increased astrocytic inducible nitric oxide synthase (iNOS) activity, and increased levels of iNOS mRNA. Inducible nitric oxide synthase is upregulated in the CNS of animal models of MS (experimental allergic encephalomyelitis). In untreated MS patients, Western blot analysis showed increased nitrosative stress associated with a significant decrease of reduced glutathione (GSH) in MS patients. Increased levels of oxidized glutathione (GSSG) and nitrosothiols were also observed. Interestingly, daily oral treatment of MS patients with acetyl-L-carnitine (2 g/day) for 6 months resulted in decreased cerebral-spinal fluid levels of NO reactive metabolites and protein nitration, as well as increased content of GSH and GSH/GSSG ratio (**Calabrese, 2003**).

VI. Pharmacokinetics

Via. General ADME

Estimated human dietary intake of L-carnitine falls within the range of 1 to 15 $\mu\text{M}/\text{kg}$ body weight/day, whereas the rate of biosynthesis is about 1–2 $\mu\text{M}/\text{kg}$ body weight/day. After oral ingestion, dietary L-carnitine has a bioavailability of 54–86%; whereas, the bioavailability of bolus exogenous L-carnitine is 5–18%. This difference is due to swamping of absorption (GI) and renal reabsorption processes at high doses levels. Normal plasma concentration of L-carnitine in healthy adults with a mixed diet is 40–50 μM . When administered at doses 30–100 mg/kg p.o. in humans, L-carnitine peak plasma concentrations were 27–91 μM after 3 h, and returned to baseline within 24 h. Renal clearance is about 1-3 mL/min, suggesting an extensive rate of tubular reabsorption. The swamping of absorption and reabsorption processes by exogenous doses of acetyl-L-carnitine is also evident in the 100+ fold difference in volume of distribution and the 3-12 h half-life of i.v. L-carnitine, yet an estimated total body turnover time of 66 days (Calabrese, 2008). L-Carnitine is metabolized by the intestine to c-butyrobetaine and trimethylamine, the former excreted in feces and the latter in urine.

L-carnitine undergoes acetylation in rodent and human intestine, forming the biologically active and more mobile acetyl-L-carnitine. In Alzheimer's disease patients, supplementation with acetyl-L-carnitine (2 g/day) for 55 days, increased plasma concentrations of acetyl-L-carnitine from 7.2 to 10.3 μM (Calabrese, 2008).

Vib. CNS Penetration

It is believed that acetyl-L-carnitine is able to more readily cross the blood–brain barrier than L-carnitine. Alzheimer's disease patients treated with acetyl-L-carnitine i.v. or p.o. for 10–60 days have an increased concentration of acetyl-L-carnitine in the cerebrospinal fluid to 3.55 nM/mL from the basal level of 0.93 nM/mL (Calabrese, 2008).

Vic. Calculated $\log([\text{brain}]/[\text{blood}])$ (Clark Model): -1.41

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

No significant side-effects were observed during short-term (40 day) clinical studies on senile human subjects receiving a daily dose of 3 grams of acetyl-L-carnitine (**Bonavita, 1986**).

Acetyl-L-carnitine use should be avoided in patients with hypothyroidism. L-carnitine inhibits the activity of thyroid hormone (**Benvenega, 2004**). Theoretically this might also occur with acetyl-L-carnitine.

VIIb. Drug Interaction Potential

When used as a supplement, there are known interactions of acetyl-L-carnitine and L-carnitine with certain drugs, for example, pivalate-conjugated antibiotics (**Stanley, 2004**).

Taking L-carnitine 1 gram/day seems to significantly increase the anticoagulant effects of acenocoumarol. Acenocoumarol is an oral anticoagulant similar to warfarin, but shorter-acting (**Martinez, 1993**). While this interaction has only been reported with L-carnitine, it theoretically could occur with acetyl-L-carnitine. It is also possible that acetyl-L-carnitine or L-carnitine supplements could alter the anticoagulant activity of warfarin (coumadin).

Some drugs appear to alter acetyl-L-carnitine and L-carnitine levels. These include the pivalate-conjugated compounds that increase L-carnitine excretion; compounds that increase renal clearance or decrease renal reabsorption such as cisplatin®, valproic acid or ifosfamide® (**Natural Medicines Comprehensive Database, 2008**).

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