

Acetyl-L-Carnitine Overview

Carnitine is an amino acid that is synthesized in the liver and kidneys from lysine and methionine. Its major biochemical function is to facilitate the transport and metabolism of long-chain fatty acids into the mitochondria for beta-oxidation and energy generation.

There is extensive research on carnitine, as seen in the following research overview. The focus is on athletic performance and enhanced endurance; increased fat metabolism; lowering of cholesterol and triglyceride levels; and heart protection. Because carnitine facilitates fatty acid transport into the mitochondria for oxidation, researchers initially theorized that it is possible that elevated carnitine levels would permit a greater/faster transport of fat leading to increased fat oxidation, which may impact weight loss and/or endurance performance. When the body relies on fat for energy this could result in sparing of muscle glycogen and a subsequent enhancement of exercise performance. Researchers also theorized that supplemental carnitine could help to reduce lactic acid accumulation in muscles by buffering pyruvate and, therefore, enhance endurance.

Exercise and endurance studies are ongoing and researchers express difficulty in measuring results. However, unequivocal results in kidney dialysis patients show that low carnitine levels in the dialysate can lead to elevated levels of blood lipids. Similarly, studies of heart disease patients have shown that carnitine supplements (2g/ day over 6 months) can reduce cholesterol and triglyceride levels. In one important study among patients who suffered a heart attack, carnitine supplements (2-3 g/day over 4-8 weeks) resulted in a reduction in the amount of damage to the heart muscle and an increase in heart muscle viability. In angina sufferers, carnitine reduces the incidence of angina and cardiac arrhythmias as well as reduces the need for anti-angina and anti-arrhythmic medications. In addition, carnitine (2g/ day for 6 months) can also increase exercise tolerance in patients with angina – meaning that they can exercise longer and at a higher level before experiencing chest pain.

Dietary Sources: meat and dairy products.

Daily Reference Intake: There is no DRI or RDA for carnitine.

Side Effects: Carnitine supplementation has an excellent safety record. Doses of 2-6 grams per day over a period of 6 months have been studied with no observed adverse side effects. The D-Carnitine, inactive form is not recommended.

(Source: www.supplementwatch.com)

Research Overview

Acetyl-L-carnitine research shows the following:

1. Treats age-related macular degeneration (HUMAN)
2. Reduces metabolic abnormalities induced by alcohol (ANIMAL)
3. Reverses biochemical and behavioral parameters of brain aging
4. Maintains myocardial function (ANIMAL)
5. Ameliorates oxidative damage, enzyme activity, substrate-binding affinity, and mitochondrial dysfunction (ANIMAL)
6. Improves metabolic function while decreasing oxidative stress (ANIMAL)
7. Normalizes age-dependent disturbances such as membrane lipid metabolism and/or composition (ANIMAL)
8. Reduces age-associated deterioration in auditory sensitivity and improves cochlear function (ANIMAL)
9. Reverses the age-related decrement in the mitochondrial pyruvate metabolism (ANIMAL)
10. Benefits various cognitive functions in the middle-aged and elderly and is a metabolic cofactor (REVIEW-HUMAN)
11. Has a beneficial effect on the neuromuscular junction and on muscle fiber structure in ageing or after nerve crushing (ANIMAL)
12. Reverses age-related decrement in mitochondrial carnitine-acylcarnitine exchange activity (ANIMAL)
13. Enhances spatial acquisition in of rats with age-related behavioral impairments in a novel environment (ANIMAL) Two Studies.
14. Has positive effects on the brain NMDA receptor system (ANIMAL)
15. Theoretically useful in Alzheimer's (REVIEW) (ANIMAL)
16. Preserves, at least partially, learning and memory from the natural decay occurring with age (ANIMAL)
17. Has a neurotrophic action on the peripheral nervous system with possible applications in age-related peripheral nerve changes (ANIMAL)
18. Has a positive effect on age-related changes in the dopaminergic system (ANIMAL)
19. Rescues aged neurons may be by increasing their responsiveness to neuronotrophic factors in the CNS (ANIMAL)
20. Shows improvements in spatial memory (ANIMAL)
21. Acetyl-L-carnitine is a precursor of acetylcholine.
22. Attenuates certain age-related cognitive deficits and may have a beneficial effect on longevity (ANIMAL)
23. Being investigated as a determinant of neuronal longevity

24. Reduces the age-dependent loss of glucocorticoid receptors in the hippocampus (ANIMAL)
25. Mainly affects the inner membrane protein composition of cerebellar mitochondria (ANIMAL)
26. Improves cognitive performance, ameliorates age-related deficits (ANIMAL)
27. May be the first agent suitable for clinical use in the prevention of neuronal death after peripheral nerve trauma (ANIMAL)
28. May assist treatment of peripheral neuropathy in patients on antiretroviral therapy
29. Positively affects spatial memory and nerve growth factor levels (ANIMAL)
30. Rescues neurons from beta 25-35-induced neurotoxicity (ANIMAL)
31. Exerts a neuroprotective effect and decreases stress exposure in the CNS (ANIMAL)
32. May have a role in counteracting degenerative disease
33. Restores choline acetyltransferase activity in the hippocampus (ANIMAL)
34. Considered useful as a therapeutic agent in neurodegenerative disorders (ANIMAL)
35. Significantly elevated beta-NGF (nerve growth factor) (ANIMAL)
36. Has neurotrophic properties (ANIMAL)
37. Restores choline acetyltransferase activity (ANIMAL)
38. Important in the development of therapeutic strategies to counteract degenerative diseases of the CNS
39. Abolished the age-associated reduction of a specific mRNA levels in the basal forebrain of old animals (ANIMAL)
40. Compared to Alzheimer's patients on placebo, acetyl-L-carnitine-treated patients showed significantly less deterioration in their Mini-Mental Status and Alzheimer's Disease Assessment Scale test scores. (HUMAN)
41. Has a neuroprotective effect
42. Suggests a neurotrophic property exerted on those central cholinergic pathways typically damaged by aging (ANIMAL)
43. Long-term treatment completely prevents the loss of choline acetyltransferase activity in the CNS of aged rats (ANIMAL)
44. Preserves and/or facilitates the functionality of carnitines, the concentrations of which are diminished in the brain of old animals (ANIMAL)
45. Stimulates nerve growth factor receptors (ANIMAL)
46. Doubled the number of aged neurons treated compared to controls (ANIMAL)
47. Rescues aged neurons by increasing their responsiveness to neuronotrophic factors in the CNS (ANIMAL)
48. Increases choline acetyltransferase activity and of nerve growth factor receptor expression in the striatum (ANIMAL)
49. Chronic treatment prevents some age-related impairments of CNS (ANIMAL)
50. Improves cognitive performance of aged rats, ameliorates these age-related deficits.
- 51.-62. Human Research on Down Syndrome, Alzheimer's, dementia. 11 Citations

Acetyl-L-Carnitine Abstracts (50)

Acetyl-L-Carnitine Citations (11)

Acetyl-L-Carnitine: 50 Research Abstracts

1_ *Ophthalmologica*. 2003 SepOct;217(5):3517.

Mitotropic compounds for the treatment of age-related macular degeneration. The metabolic approach and a pilot study.

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Recent histopathologic studies have shown that mitochondria and peroxisomes of the retinal pigment epithelium may play a central role in the pathophysiology of age-related macular degeneration (AMD). We supposed that compounds which improve mitochondrial functions (mitotropic compounds) may show beneficial effects in preventing AMD. Fourteen patients affected by early AMD were treated with a mixture containing Acetyl-L-Carnitine (ALC), polyunsaturated fatty acids (PUFAs), coenzyme Q10 (CoQ10) and vitamin E, while an equal number of age and sex-matched patients affected by early AMD were treated with vitamin E only. Recovery time after macular photostress, foveal sensitivity and mean defect in the visual field as well as blood lipid levels were recorded at the beginning and after 3, 6, 9, 12 and 24 months of follow-up. In the treated group, all the visual functions showed slight improvement which was evident after 3 months of treatment and remained nearly stationary by the end of 24 months. The same tests in the control group showed slow worsening. The divergence between treated and control groups became more marked with time, but the difference was not significant at any time of the follow-up. These findings suggest that the blend of ALC, PUFA, CoQ10 and vitamin E may improve retinal functions in early AMD. Copyright 2003 S. Karger AG, Basel

2_ *Int J Tissue React*. 2002;24(3):8996.

Long-term ethanol administration enhances age-dependent modulation of redox state in brain and peripheral organs of rat: protection by acetyl carnitine.

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Evidence is accumulating that intermediates of oxygen reduction may be associated with the development of alcoholic disease. Free radical-induced perturbation of the oxidant/antioxidant balance in the cell is widely recognized as the main causative factor of age-related disorders. In the present study we investigated the effects of 20 months of ethanol consumption on the antioxidant defense system in different rat organs compared with normal aging in the absence and presence of treatment with L-acetyl carnitine. We demonstrate that aged rats underwent significant perturbation of the antioxidant defense system, as indicated by depletion of reduced glutathione (GSH) content, increased oxidized GSH, free radical-induced luminescence associated with increased hydroxynonenal content and decreased GSH reductase activity. These modifications, observed particularly in brain and liver compared with other organs, were enhanced by long-term alcohol exposure and, interestingly, were significantly reduced with acetyl carnitine supplements. Our results indicate that decreased GSH reductase activity and thiol depletion are important factors in effecting a pathogenic role for oxidative stress in aging and in all situations in which age-correlated and oxidant-induced changes occur, such as in alcoholism. Administration of acetyl carnitine greatly reduces these metabolic abnormalities. Our findings support its pharmacological potential in the management of alcoholic disturbances.

3_ *Brain Res*. 2002 Dec 13;957(2):22330.

Reversal of biochemical and behavioral parameters of brain aging by melatonin and acetyl L-carnitine.

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The potential utility of dietary supplementation in order to prevent some of the oxidative and inflammatory changes occurring in the brain with age, has been studied. The cerebral cortex of 27-month-old male B6C3F1 mice had elevated levels of nitric oxide synthase 1 (EC 1.14.13.39) (nNOS) and peptide nitrotyrosine relative to cortices of younger (4-month-old) animals. After 25-month-old mice received basal diet together with 300 mg/l acetyl L-carnitine in the drinking water for 8 weeks, these levels were fully restored to those found in younger animals. A partial restoration was found when old animals received basal diet supplemented with 200 ppm melatonin in the diet. Levels of mRNA (messenger RNA) for nNOS were unchanged following these treatments implying translational regulation of nNOS activity. Behavioral indices indicative of exploratory behavior were also depressed in aged animals. Dietary supplementation with melatonin or acetyl L-carnitine partially reversed these changes. These findings suggest that dietary supplementation cannot merely arrest but indeed reverse some age-related increases in markers of oxidative and inflammatory events occurring with the cortex.

4_ *Ann N Y Acad Sci*. 2002 Apr;959:491507.

Mitochondrial decay in the aging rat heart: evidence for improvement by dietary supplementation with Acetyl-L-Carnitine and/or lipoic acid.

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Mitochondrial decay has been postulated to be a significant underlying part of the aging process. Decline in mitochondrial function may lead to cellular energy deficits, especially in times of greater energy demand, and compromise vital ATP-dependent cellular operations, including detoxification, repair systems, DNA replication, and osmotic balance. Mitochondrial decay may also lead to enhanced oxidant production and thus render the cell more prone to oxidative insult. In particular, the heart may be especially susceptible to mitochondrial dysfunction due to myocardial dependency on beta-oxidation of fatty acids for energy and the postmitotic nature of cardiac myocytes, which would allow for greater accumulation of mitochondrial mutations and deletions. Thus, maintenance of mitochondrial function may be important to maintain overall myocardial function. Herein, we review the major age-related changes that occur to mitochondria in the aging heart and the evidence that two such supplements, Acetyl-L-Carnitine (ALCAR) and (R)-alpha-lipoic acid, may improve myocardial bioenergetics and lower the increased oxidative stress associated with aging. We and others have shown that feeding old rats ALCAR reverses the age-related decline in carnitine levels and improves mitochondrial beta-oxidation in a number of tissues studied. However, ALCAR supplementation does not appear to reverse the age-related decline in cardiac antioxidant status and thus may not substantially alter indices of oxidative stress. Lipoic acid, a potent thiol antioxidant and mitochondrial metabolite, appears to increase low molecular weight antioxidant status and thereby decreases age-associated oxidative insult. Thus, ALCAR along with lipoic acid may be effective supplemental regimens to maintain myocardial function.

5_ Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):187681.

Age-associated mitochondrial oxidative decay: improvement of carnitine acetyltransferase substrate-binding affinity and activity in brain by feeding old rats acetyl-L-carnitine and/or R-alpha-lipoic acid.

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We test whether the dysfunction with age of carnitine acetyltransferase (CAT), a key mitochondrial enzyme for fuel utilization, is due to decreased binding affinity for substrate and whether this substrate, fed to old rats, restores CAT activity. The kinetics of CAT were analyzed by using the brains of young and old rats and of old rats supplemented for 7 weeks with the CAT substrate Acetyl-L-Carnitine (ALCAR) and/or the mitochondrial antioxidant precursor R-alpha-lipoic acid (LA). Old rats, compared with young rats, showed a decrease in CAT activity and in CAT-binding affinity for both substrates, ALCAR and CoA. Feeding ALCAR or ALCAR plus LA to old rats significantly restored CAT-binding affinity for ALCAR and CoA, and CAT activity. To explore the underlying mechanism, lipid peroxidation and total iron and copper levels were assayed; all increased in old rats. Feeding old rats LA or LA plus ALCAR inhibited lipid peroxidation but did not decrease iron and copper levels. Ex vivo oxidation of young rat brain with Fe(II) caused loss of CAT activity and binding affinity. In vitro oxidation of purified CAT with Fe(II) inactivated the enzyme but did not alter binding affinity. However, in vitro treatment of CAT with the lipid peroxidation products malondialdehyde or 4-hydroxynonenal caused a decrease in CAT-binding affinity and activity, thus mimicking age-related change. Preincubation of CAT with ALCAR or CoA prevented malondialdehyde-induced dysfunction. Thus, feeding old rats high levels of key mitochondrial metabolites can ameliorate oxidative damage, enzyme activity, substrate-binding affinity, and mitochondrial dysfunction.

6_ Proc Natl Acad Sci U S A. 2002 Feb 19;99(4):18705.

Feeding Acetyl-L-Carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress.

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Mitochondria-supported bioenergetics decline and oxidative stress increases during aging. To address whether the dietary addition of Acetyl-L-Carnitine [ALCAR, 1.5% (wt/vol) in the drinking water] and/or (R)-alpha-lipoic acid [LA, 0.5% (wt/wt) in the chow] improved these endpoints, young (24 mo) and old (2428 mo) F344 rats were supplemented for up to 1 mo before death and hepatocyte isolation. ALCAR+LA partially reversed the age-related decline in average mitochondrial membrane potential and significantly increased ($P = 0.02$) hepatocellular O_2 consumption, indicating that mitochondria-supported cellular metabolism was markedly improved by this feeding regimen. ALCAR+LA also increased ambulatory activity in both young and old rats; moreover, the improvement was significantly greater ($P = 0.03$) in old versus young animals and also greater when compared with old rats fed ALCAR or LA alone. To determine whether ALCAR+LA also affected indices of oxidative stress, ascorbic acid and markers of lipid peroxidation (malondialdehyde) were monitored. The hepatocellular ascorbate level markedly declined with age ($P = 0.003$) but was restored to the level seen in young rats when ALCAR+LA was given. The level of malondialdehyde, which was significantly higher ($P = 0.0001$) in old versus young rats, also declined after ALCAR+LA supplementation and was not significantly different from that of young unsupplemented rats. Feeding ALCAR in combination with LA increased metabolism and lowered oxidative stress more than either compound alone.

7_ Neurochem Res. 2000 Mar;25(3):3959.

Effect of long-term feeding with Acetyl-L-Carnitine on the age-related changes in rat brain lipid composition: a study by ^{31}P NMR spectroscopy.

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Changes in brain lipid composition have been determined in 24-month-old Fischer rats with respect to 6-month-old ones. The cerebral levels of sphingomyelin and cholesterol were found to be significantly increased in aged rats, whereas the amount of

phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, and phosphatidic acid appear to be unaffected by aging. Longterm feeding with Acetyl-L-Carnitine was able to reduce the agedependent increase of both sphingomyelin and cholesterol cerebral levels with no effect on the other measured phospholipids. These findings shown that changes in membrane lipid metabolism and/or composition represent one of the alterations occurring in rat brain with aging, and that longterm feeding with Acetyl-L-Carnitine can be useful in normalizing these agedependent disturbances.

8_ Am J Otol. 2000 Mar;21(2):1617.

Biologic activity of mitochondrial metabolites on aging and agerelated hearing loss.

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HYPOTHESIS: Compounds that upregulate mitochondrial function in an aging model will improve hearing and reduce some of the effects of aging. **BACKGROUND:** Reactive oxygen metabolites (ROM) are known products of oxidative metabolism and are continuously generated in vivo. More than 100 human clinical conditions have been associated with ROM, including atherosclerosis, arthritis, autoimmune diseases, cancers, heart disease, cerebrovascular accidents, and aging. The ROM are extremely reactive and cause extensive DNA, cellular, and tissue damage. Specific deletions within the mitochondrial DNA (mtDNA) occur with increasing frequency in age and presbycusis. These deletions are the result of chronic exposure to ROM. When enough mtDNA damage accrues, the cell becomes bioenergetically deficient. This mechanism is the basis of the mitochondrial clock theory of aging, also known as the membrane hypothesis of aging. Nutritional compounds have been identified that enhance mitochondrial function and reverse several agerelated processes. It is the purpose of this article to describe the effects of two mitochondrial metabolites, alphasialipoic acid and acetyl Lcarnitine, on the preservation of agerelated hearing loss. **METHODS:** Twentyone Fischer rats, aged 24 months, were divided into three groups: acetyl1carnitine, alphasialipoic acid, and control. The subjects were orally supplemented with either a placebo or one of the two nutritional compounds for 6 weeks. Auditory brainstem response testing was used to obtain baseline and posttreatment hearing thresholds. Cochlear, brain, and skeletal muscle tissues were obtained to assess for mtDNA mutations. **RESULTS:** The control group demonstrated an expected age-associated threshold deterioration of 3 to 7 dB in the 6week study. The treated subjects experienced a delay in progression of hearing loss. Acetyl1carnitine improved auditory thresholds during the same time period ($p < 0.05$). The mtDNA deletions associated with aging and presbycusis were reduced in the treated groups in comparison with controls. **CONCLUSIONS:** These results indicate that in the proposed decline in mitochondrial function with age, senescence may be delayed by treatment with mitochondrial metabolites. Acetyl1carnitine and alphasialipoic acid reduce age-associated deterioration in auditory sensitivity and improve cochlear function. This effect appears to be related to the mitochondrial metabolite ability to protect and repair ageinduced cochlear mtDNA damage, thereby upregulating mitochondrial function and improving energyproducing capabilities.

9_ FEBS Lett. 1999 Jul 9;454(3):2079.

The effect of aging and Acetyl-L-Carnitine on the pyruvate transport and oxidation in rat heart mitochondria.

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The effect of aging and acute treatment with Acetyl-L-Carnitine on the pyruvate transport and oxidation in rat heart mitochondria was studied. The activity of the pyruvate carrier as well as the rates of pyruvatesupported respiration were both depressed (around 40%) in heart mitochondria from aged rats, the major decrease occurring during the second year of life. Administration of Acetyl-L-Carnitine to aged rats almost completely restored the rates of these metabolic functions to the level of young control rats. This effect of Acetyl-L-Carnitine was not due to changes in the content of pyruvate carrier molecules. The heart mitochondrial content of cardiolipin, a key phospholipid necessary for mitochondrial substrate transport, was markedly reduced (approximately 40%) in aged rats. Treatment of aged rats with Acetyl-L-Carnitine reversed the age-associated decline in cardiolipin content. As the changes in cardiolipin content were correlated with changes in rates of pyruvate transport and oxidation, it is suggested that Acetyl-L-Carnitine reverses the agerelated decrement in the mitochondrial pyruvate metabolism by restoring the normal cardiolipin content.

10_ Altern Med Rev. 1999 Jun;4(3):14461.

A review of nutrients and botanicals in the integrative management of cognitive dysfunction.

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Dementias and other severe cognitive dysfunction states pose a daunting challenge to existing medical management strategies. An integrative, early intervention approach seems warranted. Whereas, allopathic treatment options are highly limited, nutritional and botanical therapies are available which have proven degrees of efficacy and generally favorable benefitorisk profiles. This review covers five such therapies: phosphatidylserine (PS), Acetyl-L-Carnitine (ALC), vinpocetine, Ginkgo biloba extract (GbE), and Bacopa monniera (Bacopa). PS is a phospholipid enriched in the brain, validated through doubleblind trials for improving memory, learning, concentration, word recall, and mood in middleaged and elderly subjects with dementia or agerelated cognitive decline. PS has an excellent benefitorisk profile. ALC is an energizer and metabolic cofactor which also benefits various cognitive functions in the middleaged and elderly, but with a slightly less favorable benefitorisk profile. Vinpocetine, found in the lesser periwinkle Vinca minor, is an excellent vasodilator and cerebral metabolic enhancer with proven benefits for vascularbased cognitive dysfunction. Two metaanalyses of GbE demonstrate the best preparations offer limited benefits for vascular insufficiencies and

even more limited benefits for Alzheimer's, while "commodity" GbE products offer little benefit, if any at all. GbE (and probably also vinpocetine) is incompatible with bloodthinning drugs. Bacopa is an Ayurvedic botanical with apparent antianxiety, antifatigue, and memorystrengthening effects. These five substances offer interesting contributions to a personalized approach for restoring cognitive function, perhaps eventually in conjunction with the judicious application of growth factors.

11_ Mech Ageing Dev. 1995 Nov 3;85(1):3753.

Age and traumadependent modifications of neuromuscular junction and skeletal muscle structure in the rat. Effects of longterm treatment with Acetyl-L-Carnitine.

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The influence of ageing and crushing of the sciatic nerve on the morphology of the neuromuscular junction (NMJ) and on the muscle fiber composition were studied in the rat soleus muscle using histochemical techniques associated with image analysis. The influence of a 6month treatment with Acetyl-L-Carnitine (ALCAR, 150 mg/kg/day) on the age and crushingdependent changes of the NMJ and on agerelated modifications of the muscle fiber composition was assessed as well. In control old and injured young rats a loss of complexity of the NMJ was observed. Treatment with ALCAR resulted in an increased endplate complexity both in old rats and in young rats injured by crushing, in comparison with respective controls. The structure of the rat soleus muscle changes with increasing age. Modification mainly consists in a type II fiber atrophy, and in the alteration of the peculiar mosaic organization of the soleus muscle fibers. In ALCARtreated old rats, the morphology of the soleus muscle fibers was similar to that observed in adult animals. These findings suggest that treatment with ALCAR has a beneficial effect on NMJ and on muscle fiber structure in ageing or after nerve crushing. The possible mechanism of action of this 'trophic' effect of ALCARtreatment is discussed.

12_ Mech Ageing Dev. 1995 Oct 13;84(2):10312.

Carnitineacylcarnitine translocase activity in cardiac mitochondria from aged rats: the effect of Acetyl-L-Carnitine.

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Agerelated changes in mitochondrial fatty acids metabolism may underlie the progressive decline in cardiac function. The effect of aging and acute treatment with Acetyl-L-Carnitine on fatty acids oxidation and on carnitineacylcarnitine translocase activity in rat heart mitochondria was studied. Rates of palmitoylcarnitine supported respiration as well as carnitinecarnitine and carnitinepalmitoylcarnitine exchange reactions were all depressed (approx. 35%) in heart mitochondria from aged rats. These effects were almost completely reversed following treatment of aged rats with Acetyl-L-Carnitine. Heart mitochondrial cardiolipin content was significantly reduced (approx. 38%) in aged rats. Treatment of aged rats with Acetyl-L-Carnitine restored the level of cardiolipin to that of young rats. It is suggested that Acetyl-L-Carnitine is able to reverse agerelated decrement in mitochondrial carnitineacylcarnitine exchange activity by restoring the normal cardiolipin content.

13_ J Gerontol A Biol Sci Med Sci. 1995 Jul;50(4):B23236.

Acetyl-L-Carnitine: chronic treatment improves spatial acquisition in a new environment in aged rats.

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Chronic Acetyl-L-Carnitine (ALCAR) treatment prevents some agerelated memory impairment. The present experiment examined the effects of aging and ALCAR in Fischer 344 rats on retention of spatial discrimination test in a familiar environment (FE), and on the acquisition of a spatial discrimination in a novel environment (NE). Rats 18 months or 3 months old were trained with a new procedure to assess spatial discrimination in the Morris water maze. Performance during acquisition in FE was used to assign each old rat to one of two classes: Good Performers (GP) and Poor Performers (PP) based on their swim time to reach the platform. The old rats displayed heterogeneous performance and a spatial discrimination deficit. Chronic ALCAR treatment enhanced spatial acquisition in the NE of rats with agerelated behavioral impairments and had a slight effect on retention of the spatial discrimination in the FE.

14_ Neurochem Res. 1994 Jul;19(7):7958.

Age-dependent loss of NMDA receptors in hippocampus, striatum, and frontal cortex of the rat: prevention by Acetyl-L-Carnitine.

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Acute i.p. administration of Acetyl-L-Carnitine (ALCAR), a component of several biological systems, has been found to modify spontaneous and evoked electrocortical activity in young rats, and, in the old rats, to improve learning ability and to increase the number of NMDA receptors in the whole brain. The present study was aimed at ascertaining the effect of chronic treatment with ALCAR added to drinking water on agerelated changes in the different brain areas of rats. In twentyfourmonthold rats, ALCAR treatment for six months significantly impeded the decline in the number of NMDA receptors within the hippocampus, the frontal cortex and the striatum compared to the adult animal. This finding thus confirms the previously reported positive effect of ALCAR

on the brain NMDA receptor system.

15_ Ann N Y Acad Sci. 1993 Sep 24;695:3246. Acetyl-L-Carnitine and Alzheimer's disease: pharmacological considerations beyond the cholinergic sphere. Carta A, Calvani M, Bravi D, Bhuachalla SN. SigmaTau Pharmaceuticals, Department of Scientific Affairs, Gaithersburg, Maryland 20878.

Since ALCAR and Lcarnitine are "shuttles" of long chain fatty acids between the cytosol and the mitochondria to undergo betaoxidation, they play an essential role in energy production and in clearing toxic accumulations of fatty acids in the mitochondria. ALCAR has been considered of potential use in senile dementia of the Alzheimer type (SDAT) because of its ability to serve as a precursor for acetylcholine. However, pharmacological studies with ALCAR in animals have demonstrated its facility to maximize energy production and promote cellular membrane stability, particularly its ability to restore membranal changes that are agerelated. Since recent investigations have implicated abnormal energy processing leading to cell death, and severitydependent membrane disruption in the pathology of Alzheimer's disease, we speculate that the beneficial effects associated with ALCAR administration in Alzheimer patients are due not only to its cholinergic properties, but also to its ability to support physiological cellular functioning at the mitochondrial level. This hypothetical mechanism of action is discussed with respect to compelling supportive animal studies and recent observations of significant decrease of carnitine acetyltransferase (the catalyst of Lcarnitine acylation to Acetyl-L-Carnitine) in autopsied Alzheimer brains.

16_ Physiol Behav. 1992 Jul;52(1):1857.

Active avoidance learning in old rats chronically treated with levocarnitine acetyl.
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The aging laboratory animal is recognized as a suitable experimental model for the investigation on drugs potentially able to retard the agedependent decline in cognitive functions. There is robust evidence that levocarnitine acetyl (ALCAR), the acetyl derivative of carnitine, when administered chronically, prevents some agerelated deficits of the central nervous system, mainly at the hippocampal level. On the basis of this evidence and because learning of active avoidance was demonstrated to become impaired with age, we decided to investigate the effect of ALCAR in rats. For statistical evaluation of results, the Cluster Analysis technique was chosen. This procedure pointed out the great heterogeneity of the old population and allowed the classification of the animals into homogeneous groups according to their response pattern. The effect of ALCAR was evident in the higher number of treated old animals yielding escape responses, indicating that ALCAR can preserve, at least partially, learning and memory from the natural decay occurring with age.

17_ Int J Clin Pharmacol Res. 1992;12(56):25362.

Morphological and electrophysiological changes of peripheral nervemuscle unit in the aged rat prevented by levocarnitine acetyl.
Scarfo C, Falcinelli M, Pacifici L, Bellucci A, Reda E, De Angelis C, Ramacci MT, Angelucci L.
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The effects of levocarnitine acetyl on structure and function of the sciatic nerve and neuromuscular junctions of the soleus and extensor digitorum longus muscles were studied in the aged rat. To that end, neuromuscular conduction velocity (NMCV) was measured in vivo and morphological and morphometric evaluations were performed. Treatment with levocarnitine acetyl, 150 mg/kg day for six months, restored NMCV values to the levels measured in the young rat; significantly reduced the number of degenerating elements; and increased the number of myelinated fibres having normal structural features. In the soleus and extensor digitorum longus muscles, levocarnitine acetyl increased the complexity of neuromuscular junctions. These experimental findings suggest a neurotrophic action of levocarnitine acetyl on the peripheral nervous system that might have therapeutical applications in agerelated peripheral nerve changes.

18_ J Neurosci Res. 1991 Nov;30(3):5559.

Effect of Acetyl-L-Carnitine on the dopaminergic system in aging brain.
Sershen H, Harsing LG Jr, BanaySchwartz M, Hashim A, Ramacci MT, Lajtha A. Center for Neurochemistry, Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York 10962.

We studied the effect of Acetyl-L-Carnitine (ALCAR) on dopamine release and the effect of longterm Acetyl-L-Carnitine treatment on agerelated changes in striatal dopamine receptors and brain amino acid levels. In striatal tissue that had been incubated with [3H]dopamine, Acetyl-L-Carnitine increased the release of [3H]dopamine evoked by electrical stimulation. In striatal tissue from aged mice administered Acetyl-L-Carnitine for 3 months, the release of [3H]dopamine evoked by electrical stimulation was higher than that of its aged control; the release after a second stimulation was similar in the two groups. There was a significant decline in the number of D1 striatal dopamine receptors with age. The Bmax was 51% lower in 1.5yearold mice than in 4monthold animals. Administration of Acetyl-L-Carnitine for 3 months diminished the reduction in the binding of [3H]SCH23390. [3H]Spiperone binding to D2 receptors was not decreased with age and was not affected by Acetyl-L-Carnitine treatment. Agerelated decreases in levels of several amino acids were observed in several brain regions. Acetyl-L-Carnitine lessened the reduction in the level of taurine only in the striatum. The findings confirm the multiple effects of Acetyl-L-Carnitine in brain, and suggest that its administration can have

a positive effect on age-related changes in the dopaminergic system.

19_ Brain Res Dev Brain Res. 1991 Apr 24;59(2):22130.

Acetyl-L-Carnitine enhances the response of PC12 cells to nerve growth factor.

Tagliavola G, Angelucci L, Ramacci MT, Werrbach-Perez K, Jackson GR, Perez-Polo JR.

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We have demonstrated that treatment of rat pheochromocytoma (PC12) cells with Acetyl-L-Carnitine (ALCAR) stimulates the synthesis of nerve growth factor receptors (NGFR). ALCAR has also been reported to prevent some age-related impairments of the central nervous system (CNS). In particular, ALCAR reduces the loss of NGFR in the hippocampus and basal forebrain of aged rodents. On these bases, a study on the effect of NGF on the PC12 cells was carried out to ascertain whether ALCAR induction of NGFR resulted in an enhancement of NGF action. Treatment of PC12 cells for 6 days with ALCAR (10 mM) stimulated [¹²⁵I]NGF PC12 cell uptake, consistent with increased NGFR levels. Also, neurite outgrowth elicited in PC12 cells by NGF (100 ng/ml) was greatly augmented by ALCAR pretreatment. When PC12 cells were treated with 10 mM ALCAR and then exposed to NGF (1 ng/ml), an NGF concentration that is insufficient to elicit neurite outgrowth under these conditions, there was an ALCAR effect on neurite outgrowth. The concentration of NGF necessary for survival of serum-deprived PC12 cells was 100-fold lower for ALCAR-treated cells as compared to controls. The minimal effective dose of ALCAR here was between 0.1 and 0.5 mM. This is similar to the reported minimal concentration of ALCAR that stimulates the synthesis of NGFR in these cells. The data here presented indicate that one mechanism by which ALCAR rescues aged neurons may be by increasing their responsiveness to neurotrophic factors in the CNS.

20_ Neurobiol Aging. 1990 Sep-Oct;11(5):4918.

Acetyl-L-carnitine. 1: Effects on mortality, pathology and sensory-motor performance in aging rats.

Markowska AL, Ingram DK, Barnes CA, Spangler EL, Lemken VJ, Kametani H, Yee W, Olton DS.

Department of Psychology, University of Colorado, Boulder 80309.

Three different test sites assessed the effects of acetyl-L-carnitine (AC) on age-related changes in general health, sensory-motor skills, learning, and memory. Two groups of rats began the experiments at 16 months of age. One group (OLDAC) was given AC, 75 mg/kg/day, beginning at 16 months. The other group (OLDCON) was treated identically except it was not given the drug. Beginning at 22 months of age, these rats and a group of young (34 months old) rats (YGCON) were given a series of sensory-motor tasks. AC decreased mortality, and had no reliable effect on body weight, fluid intake, or the general health of the rats. These data indicate that a chronic dose of AC does not interfere with food and water intake, and may increase longevity. An age-related decline of performance occurred in most of the sensory-motor tasks; locomotor activity was reduced in a novel environment and in a runwheel, and the ability to prevent falling was reduced in tests on a taut wire, rotarod, inclined screen, and several types of elevated bridges. An age-related decline of performance did not occur in grooming, or in the latency to initiate several different behaviors. AC had no effect on performance in any sensory-motor task. These data indicate that the improvements produced by AC in some tests of spatial memory may be due to the effects of AC on cognitive abilities rather than on sensory-motor skills.

21_ Neurochem Res. 1990 Jun;15(6):597601.

Acetyl-L-Carnitine as a precursor of acetylcholine.

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Division of Pharmacology, Wellcome Research Laboratories, Research Triangle Park, North Carolina 27709.

Synthesis of [³H]acetylcholine from [³H]Acetyl-L-Carnitine was demonstrated *in vitro* by coupling the enzyme systems choline acetyltransferase and carnitine acetyltransferase. Likewise, both [³H] and [¹⁴C] labeled acetylcholine were produced when [³H] Acetyl-L-Carnitine and D[U-¹⁴C] glucose were incubated with synaptosomal membrane preparations from rat brain. Transfer of the acetyl moiety from Acetyl-L-Carnitine to acetylcholine was dependent on concentration of Acetyl-L-Carnitine and required the presence of coenzyme A, which is normally produced as an inhibitory product of choline acetyltransferase. These results provide further evidence for a role of mitochondrial carnitine acetyltransferase in facilitating transfer of acetyl groups across mitochondrial membranes, thus regulating the availability in the cytoplasm of acetylCoA, a substrate of choline acetyltransferase. They are also consistent with a possible utility of Acetyl-L-Carnitine in the treatment of age-related cholinergic deficits.

22_ Int J Clin Pharmacol Res. 1990;10(12):658.

Dietary Acetyl-L-Carnitine improves spatial behaviour of old rats.

Markowska AL, Olton DS.

Department of Psychology, Johns Hopkins University, Baltimore, Maryland.

Acetyl-L-Carnitine was given to aging rats to determine the extent to which it changed age-related impairments in several different behaviours. One group of rats was given Acetyl-L-Carnitine, 80 mg/day, beginning at 16 months of age. A second group of rats was housed and treated identically, except that no drug was administered. At 22 months of age, both groups of rats began a series of behavioural tests, along with a group of young rats, four months of age. The tests included: place learning on a circular platform,

probe reversal of place learning on a circular platform, two choice simultaneous spatial discrimination in the stem of a Tmaze spatial alternation in the arms of a Tmaze, and sensorymotor behaviour (initiation of walking, turning in an alley, walking on a square, round, and rectangular bridge, turning on an inclined grid, holding on to a wire, lightdark preference). The tasks varied in their sensitivity to agerelated impairments. These data indicate that longterm therapy with Acetyl-L-Carnitine attenuates certain agerelated cognitive deficits and may have a beneficial effect on longevity.

23_ Int J Clin Pharmacol Res. 1990;10(12):4951.

Peroxidative stress and cerebral aging.

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Department Neurological Sciences, RushPresbyterian St. Lukes Medical Center, Chicago, Illinois.

In order to test the hypothesis that cerebral nuclei showing agerelated neuronal depletion would also show signs of vulnerability in their free radical scavenger systems and accumulation of the compounds resulting from peroxidation, the regional levels of a number of compounds were measured in mouse brains. With the exception of the tocopherols all the antioxidants had lower concentrations in the Substantia nigra which showed the most severe neuronal depletion with age. Acetyl-L-Carnitine is being investigated as a determinant of neuronal longevity.

24_ J Neurosci Res. 1989 Aug;23(4):4626.

Acetyl-L-Carnitine reduces the agedependent loss of glucocorticoid receptors in the rat hippocampus: an autoradiographic study.

Patacchioli FR, Amenta F, Ramacci MT, Tagliatela G, Maccari S, Angelucci L.

Institute of Pharmacology II, Medical Faculty, University of Rome, La Sapienza, Italy.

Brain autoradiography in adrenalectomized rats injected with 3Hcorticosterone 2 hr before sacrifice was used to study the effect of aging and longterm Acetyl-L-Carnitine treatment on the hippocampal glucocorticoid receptor. Densitometric analysis of silver grains in individual nerve cells of the hippocampus showed that pyramidal neurones of the CA1 field and granular cells of the dentate gyrus are richest in 3Hcorticosterone binding sites, whereas pyramidal neurons of the CA3 field have the lowest number of binding sites. There was a significant decline in the number of glucocorticoid receptors within the various hippocampal areas, both as the total number of 3Hcorticosterone binding sites and as the number per single pyramidal or granule neuron associated with aging and perhaps due to loss of adrenocorticoidcompetent neurons. The dentate gyrus and the CA1 region were mostly affected by the agedependent decrease in glucocorticoid receptors of the hippocampus. Twentyeightmonthold rats, treated with Acetyl-L-Carnitine for 7 months, showed a significantly higher number of 3Hcorticosterone binding sites within the various hippocampal regions examined than did agematched controls. The CA1 and the dentate gyrus were the regions most susceptible to amelioration by Acetyl-L-Carnitine treatment. These findings suggest a positive effect of Acetyl-L-Carnitine treatment on agerelated changes which occur in the hippocampus.

25_ Neurochem Res. 1988 Oct;13(10):90916.

Action of Lacetylcarnitine on agedependent modifications of mitochondrial membrane proteins from rat cerebellum.

Villa RF, Turpeenoja L, Benzi G, Giuffrida Stella AM.

Institute of Pharmacology, Faculty of Science, University of Pavia, Italy.

Protein patterns of mitochondrial outer membrane, inner membrane, and matrix from nonsynaptic (free) mitochondria from rat cerebellum at different ages (4, 8, 12, 16, 20, and 24 months) were analyzed by gel electrophoresis. Acute Lacetylcarnitine treatment was performed by a single i.p. injection (100 mg/kg body weight) of the substance 60 min before the sacrifice of the animals. Different agedependent changes were obtained for the proteins of the three fractions. The amount of some protein subunits increased and/or decreased after drug treatment. In particular, protein composition of the inner mitochondrial membrane showed significant agerelated modifications. This result probably indicates differences in protein synthesis and/or turnover rates in the various mitochondrial compartments during aging. Acute Lacetylcarnitine treatment caused: a high increase in the amount of one inner membrane protein with Mw 16 kDa, at all the ages studied; a decrease in the amount of many other inner membrane proteins; modifications of some matrix proteins. Our results show that in vivo administration of Lacetylcarnitine affects mainly the inner membrane protein composition of cerebellar mitochondria.

26_ J Neurosci Res. 1988 Aug;20(4):4916.

Nerve growth factor binding in aged rat central nervous system: effect of Acetyl-L-Carnitine.

Angelucci L, Ramacci MT, Tagliatela G, Hulsebosch C, Morgan B, WerrbachPerez K, PerezPolo R.

Department of Pharmacology, University of Rome, Italy.

The nerve growth factor protein (NGF) has been demonstrated to affect neuronal development and maintenance of the differentiated state in certain neurons of the peripheral and central nervous system (CNS) of mammals. In the CNS, NGF has sparing effects on cholinergic neurons of the rodent basal forebrain (BF) following lesions where it selectively induces choline acetyltransferase (ChAT). NGF also induces ChAT in the areas to which BF provides afferents. In aged rats, there is a reduction in the NGFbinding capacity of sympathetic ganglia. Here, we wish to report that there is a decrease in the NGFbinding capacity of the hippocampus and basal forebrain of aged (26monthold) rats as compared to 4monthold controls but no change in NGF binding in cerebellum. In

all instances, equilibrium binding dissociation constants did not differ significantly. Treatment of rats with Acetyl-L-Carnitine, reported to improve cognitive performance of aged rats, ameliorates these age-related deficits.

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28_ Exp Brain Res. 2002 Jul;145(2):1829. Epub 2002 May 04.

Systemic Acetyl-L-Carnitine eliminates sensory neuronal loss after peripheral axotomy: a new clinical approach in the management of peripheral nerve trauma.

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Several hundred thousand peripheral nerve injuries occur each year in Europe alone. Largely due to the death of around 40% of primary sensory neurons, sensory outcome remains disappointingly poor despite considerable advances in surgical technique; yet no clinical therapies currently exist to prevent this neuronal death. Acetyl Lcarnitine (ALCAR) is a physiological peptide with roles in mitochondrial bioenergetic function, which may also increase binding of nerve growth factor by sensory neurons. Following unilateral sciatic nerve transection, adult rats received either one of two doses of ALCAR or sham, or no treatment. Either 2 weeks or 2 months later, L4 and L5 dorsal root ganglia were harvested bilaterally, in accordance with the Animal (Scientific Procedures) Act 1986. Neuronal death was quantified with a combination of TUNEL [TdT (terminal deoxyribonucleotidyl transferase) uptake nick end labelling] and neuron counts obtained using the optical disector technique. Sham treatment had no effect upon neuronal death. ALCAR treatment caused a large reduction in the number of TUNEL-positive neurons 2 weeks after axotomy (sham treatment 33/group; lowdose ALCAR 6/group, $P=0.132$; highdose ALCAR 3/group, $P<0.05$), and almost eliminated neuron loss (sham treatment 21%; lowdose ALCAR 0%, $P=0.007$; highdose ALCAR 2%, $P<0.013$). Two months after axotomy the neuroprotective effect of highdose ALCAR treatment was preserved for both TUNEL counts (no treatment five/group; highdose ALCAR one/group) and neuron loss (no treatment 35%; highdose ALCAR 4%, $P<0.001$). These results provide further evidence for the role of mitochondrial bioenergetic dysfunction in posttraumatic sensory neuronal death, and also suggest that acetyl Lcarnitine may be the first agent suitable for clinical use in the prevention of neuronal death after peripheral nerve trauma.

29_ Drug Saf. 1998 Dec;19(6):48194.

Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management.

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Distal symmetrical peripheral neuropathy is a common adverse experience in persons with HIV infection. This condition, which presents as a pain, numbness, burning and/or dysaesthesia initially in the feet, is often multifactorial in its origin. Nucleoside analogue reverse transcriptase inhibitors represent an important contributor to peripheral neuropathy. Specifically, around 10% of patients receiving stavudine or zalcitabine and 1 to 2% of didanosine recipients may have to discontinue therapy with these agents due to neuropathy. Prompt withdrawal of these therapies enables gradual resolution of signs and symptoms in most patients, although a period of symptom intensification may occur shortly after withdrawal. Risk factors for developing peripheral neuropathy during nucleoside analogue therapy include low CD4+ cell count (<100 cells/mm³), a prior history of an AIDS defining illness or neoplasm, a history of peripheral neuropathy, use of other neurotoxic agents including high alcohol (ethanol) consumption and nutritional deficiencies such as low serum hydroxocobalamin levels. Thus, patients at increased risk of peripheral neuropathy should potentially avoid the use of the neurotoxic nucleoside analogues or be more carefully monitored during therapy. Management of this problem includes patient education, prompt withdrawal of the likely causative agent (giving consideration not to leave the patient on a suboptimal therapy regimen) and simple analgesia, with augmentation with tricyclic antidepressants or anticonvulsant agents when pain is severe. New agents that may assist in managing this condition include levacecarnine (Acetyl-L-Carnitine) and nerve growth factors such as recombinant human nerve growth factor.

30_ Exp Gerontol. 1996 SepOct;31(5):57787.

Spatial memory and NGF levels in aged rats: natural variability and effects of Acetyl-L-Carnitine treatment.

Tagliabue G, Caprioli A, Giuliani A, Ghirardi O.

Institute for Research on Senescence, Sigma Tau S.p.A., Pomezia, Rome, Italy.

The natural variability of behavioral performance of aged rats was used to evaluate the effect of Acetyl-L-Carnitine (ALCAR) on spatial learning and NGF levels in different brain areas. We used a cluster analysis procedure to subdivide the aged animals into three classes of performance (good, intermediate, and poor). These three classes were equally subdivided into controls and ALCAR-treated animals in order to investigate its effect on spatial retention. The stratification of animals prior to treatment allowed us to highlight the state dependency of the action of ALCAR. The effect of the molecule in improving spatial retention was evident only in the intermediate performance group. Furthermore, the drug reduced the NGF levels in the basal forebrain of treated animals, especially in the intermediate performance group. These results suggest a performance-dependent effect of ALCAR and a nonlinear relationship between NGF levels and learning ability in aged rats.

31_ Neurochem Res. 1997 Mar;22(3):25765.

Acetyl-L-Carnitine arginine amide prevents beta 2535-induced neurotoxicity in cerebellar granule cells.
Scorziello A, Meucci O, Calvani M, Schettini G.
Institute of Pharmacology, School of Medicine, University of Genova, Italia.

Cerebellar granule cells (CGC) at different stages of maturation in vitro (1 or 6 DIV), were treated with beta 2535 and Acetyl-L-Carnitine arginine amide (ST857) in presence of 25 mM KCl in the culture medium, and neuronal viability was assessed. Three days of treatment slightly modified the survival of 1 DIV-treated cells, which degenerate and die five days later betaamyloid matching. Similarly, a significant neurotoxic effect was observed on 6 DIV treated cells after 5 days of exposure to the peptide, while the death occurred within 8 days. ST857 coincubated with beta 2535 was able to rescue neurons from beta 2535-induced neurotoxicity. We also studied the changes in Ca²⁺ homeostasis following glutamate stimulation, in control and betaamyloid treated single cells, either in presence or in absence of ST857. beta 2535 did not affect basal [Ca²⁺]_i, while modified glutamate-induced [Ca²⁺]_i increase, causing a sustained plateau phase of [Ca²⁺]_i, that persisted after the removal of the agonist. ST857 pretreatment completely reverted this effect suggesting that, in CGC chronically treated with beta 2535, ST857 could protect the cells by neurotoxic insults of the peptide likely interfering with the cellular mechanisms involved in the control of Ca²⁺ homeostasis.

32_ Prog Neuropsychopharmacol Biol Psychiatry. 1995 Jan;19(1):11733.

Effects of Acetyl-L-Carnitine treatment and stress exposure on the nerve growth factor receptor (p75NGFR) mRNA level in the central nervous system of aged rats.

Foreman PJ, PerezPolo JR, Angelucci L, Ramacci MT, Tagliatela G.
Institute for Research on Senescence Sigma Tau, Pomezia, Italy.

1. There is growing evidence that the nerve growth factor protein (NGF), a neurotrophic factor for peripheral and central nervous system (CNS) neurons, may play a role in the modulation of the hypothalamopituitaryadrenocortical axis (HPAA). While NGF binding is decreased in rodent CNS after stress exposure, this reduction is prevented by treatment with Acetyl-L-Carnitine (ALCAR), a chemical substance able to prevent some degenerative events associated with aging. 2. The authors studied the effect of cold stress on the lowaffinity NGF receptor (p75NGFR) mRNA levels in the basal forebrain and cerebellum of aged rats chronically treated with ALCAR. 3. The present results show that ALCAR abolished the age-associated reduction of p75NGFR mRNA levels in the basal forebrain of old animals, but did not affect the response to stress stimuli. 4. Also, treatment with ALCAR maintained p75NGFR mRNA levels in the cerebellum of old animals at levels almost identical to those observed in young control animals. 5. These results suggest a neuroprotective effect for ALCAR on central cholinergic neurons exerted at the level of transcription of p75NGFR. The restoration of p75NGFR levels could increase trophic support by NGF of these CNS cholinergic neurons which are implicated in degenerative events associated with aging.

33_ Neurochem Res. 1995 Jan;20(1):19.

Neurite outgrowth in PC12 cells stimulated by Acetyl-L-Carnitine arginine amide.

Tagliatela G, Navarra D, Olivi A, Ramacci MT, WerrbachPerez K, PerezPolo JR, Angelucci L.
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Senescence of the central nervous system is characterized by a progressive loss of neurons that can result in physiological and behavioral impairments. Reduction in the levels of central neurotrophic factors or of neurotrophin receptors may be one of the causes of the onset of these degenerative events. Thus, a proper therapeutic approach would be to increase support to degenerating neurons with trophic factors or to stimulate endogenous neurotrophic activity. Here we report that Acetyl-L-Carnitine arginine amide (ST857) is able to stimulate neurite outgrowth in rat pheochromocytoma PC12 cells in a manner similar to that elicited by nerve growth factor (NGF). Neurite induction by ST857 requires de novo mRNA synthesis and is independent of the action of several common trophic factors. The integrity of the molecular structure of ST857 is essential for its activity, as the single moieties of the molecule have no effect on PC12 cells, whether they are tested separately or together. Also, minor chemical modifications of ST857, such as the presence of the arginine moiety at a position other than the amino one, completely abolish its neuritogenic effect. Lastly, the presence of ST857 in the culture medium competes with the high affinity NGF binding in a dose dependent fashion. These results, although preliminary, are suggestive of a possible role for ST857 in the development of therapeutic strategies to counteract degenerative diseases of the CNS.

34_ Int J Dev Neurosci. 1995 Feb;13(1):139.

Acetyl-L-Carnitine restores choline acetyltransferase activity in the hippocampus of rats with partial unilateral fimbria fornix transection.

Piovesan P, Quatrini G, Pacifici L, Tagliatela G, Angelucci L.
Institute for Research on Senescence, SigmaTau, Pomezia, Italy.

Transection of the fimbria fornix bundle in adult rats results in degeneration of the septohippocampal cholinergic pathway, reminiscent of that occurring in aging as well as Alzheimer disease. We report here a study of the effect of a treatment with Acetyl-L-Carnitine (ALCAR) in threemonthold Fischer 344 rats bearing a partial unilateral fimbria fornix transection. ALCAR is known to ameliorate some morphological and functional disturbances in the aged central nervous system (CNS). We used choline acetyltransferase (ChAT) and acetyl cholinesterase (AChE) as markers of central cholinergic function, and nerve growth factor

(NGF) levels as indicative of the trophic regulation of the mesioseptal cholinergic system. ChAT and AChE activities were significantly reduced in the hippocampus (HIPP) ipsilateral to the lesion as compared to the contralateral one, while no changes were observed in the septum (SPT), nucleus basalis magnocellularis (NBM) or frontal cortex (FCX). ALCAR treatment restored ChAT activity in the ipsilateral HIPP, while AChE levels were not different from those of untreated animals, and did not affect NGF content in either SPT or HIPP.

35_ *Neurol Res.* 1995 Oct;17(5):3736.

Effects of levoacetylcarnitine on second motoneuron survival after axotomy.

Fernandez E, Pallini R, Tamburrini G, Lauretti L, Tancredi A, La Marca F.

Department of Neurosurgery, Catholic University Medical School, Rome, Italy.

Little is known about factors that regulate the survival of cranial motoneurons which project to peripheral targets. Various neurotrophic factors of central and peripheral origin have been isolated. In this study, we examined thirteen newborn Wistar rats to determine the effects of Acetyl-L-Carnitine treatment on the survival of motoneurons within the facial nucleus after transection of the facial nerve. Acetyl-L-Carnitine was administered for 7 days in seven rats after nerve transection, while saline solution was injected in 6 rats used as controls. Both the motoneuron number and the motoneuron diameter were significantly higher in the facial nucleus of the rats treated with Acetyl-L-Carnitine than in the facial nucleus of the control rats. The results obtained suggest that Acetyl-L-Carnitine can rescue a substantial number of facial motoneurons from axotomy-induced cell death. Compared to neurotrophic factors, because of its simple molecular structure, Acetyl-L-Carnitine permits a safe oral and parenteral administration. It is suggested that Acetyl-L-Carnitine could be considered for use as a therapeutic agent in neurodegenerative disorders.

36_ *J Pharmacol Exp Ther.* 1995 Jul;274(1):43743.

Developmental deficiency of the cholinergic system in congenitally hyperammonemic spf mice: effect of Acetyl-L-Carnitine.

Ratnakumari L, Qureshi IA, Maysinger D, Butterworth RF.

Division of Medical Genetics, SainteJustine Hospital, Montreal, Quebec, Canada.

The sparsefur (spf) mutant mouse has an Xlinked deficiency of hepatic ornithine transcarbamylase (OTC) and develops hyperammonemia in the postnatal period similar to that seen in human patients. We studied the effect of congenital hyperammonemia on the development of cerebral cholinergic parameters such as choline acetyltransferase (ChAT), acetylcholinesterase (AChE) and highaffinity choline uptake (HACU) in spf mice. The serum ammonia levels of spf mutant mice were significantly elevated after weaning compared with control animals. ChAT activity levels started decreasing in mutant spf mice from the age of 30 days (i.e., immediately after weaning); it reached significantly lower levels in the adult animals. HACU was consistently lower ($P < .01$) in spf/Y mice compared with controls up to the adult stage. However, there were no marked changes in the activity of AChE between control and hyperammonemic spf mice. The levels of betaNGF, which is essential for cholinergic differentiation and function, were significantly lower in different brain regions of adult mutant mice compared with normal controls. A treatment of spf/spf breeding females with Acetyl-L-Carnitine, at a dose of 1.5 mM in drinking water, starting from day 1 of conception, resulted in a significant restoration of ChAT activity levels in some brain regions of the spf/Y offspring. The betaNGF levels were also significantly elevated after supplementation with ALCAR in mutant mice compared with untreated mutant mice. These data are suggestive of a neurotrophic property of ALCAR during cholinergic deficiency caused by congenital hyperammonemia.

37_ *Int J Dev Neurosci.* 1995 Feb;13(1):139.

Acetyl-L-Carnitine restores choline acetyltransferase activity in the hippocampus of rats with partial unilateral fimbria fornix transection.

Piovesan P, Quatrini G, Pacifici L, Tagliatalata G, Angelucci L.

Institute for Research on Senescence, SigmaTau, Pomezia, Italy.

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38_ *Neurochem Res.* 1995 Jan;20(1):19.

Neurite outgrowth in PC12 cells stimulated by Acetyl-L-Carnitine arginine amide.

Tagliatalata G, Navarra D, Olivi A, Ramacci MT, WerrbachPerez K, PerezPolo JR, Angelucci L.

Senescence of the central nervous system is characterized by a progressive loss of neurons that can result in physiological and behavioral impairments. Reduction in the levels of central neurotrophic factors or of neurotrophin receptors may be one of the causes of the onset of these degenerative events. Thus, a proper therapeutic approach would be to increase support to degenerating neurons with trophic factors or to stimulate endogenous neurotrophic activity. Here we report that Acetyl-L-Carnitine arginine amide (ST857) is able to stimulate neurite outgrowth in rat pheochromocytoma PC12 cells in a manner similar to that elicited by nerve growth factor (NGF). Neurite induction by ST857 requires de novo mRNA synthesis and is independent of the action of several common trophic factors. The integrity of the molecular structure of ST857 is essential for its activity, as the single moieties of the molecule have no effect on PC12 cells, whether they are tested separately or together. Also, minor chemical modifications of ST857, such as the presence of the arginine moiety at a position other than the amino one, completely abolish its neurotogenic effect. Lastly, the presence of ST857 in the culture medium competes with the high affinity NGF binding in a dose dependent fashion. These results, although preliminary, are suggestive of a possible role for ST857 in the development of therapeutic strategies to counteract degenerative diseases of the CNS.

39_ Prog Neuropsychopharmacol Biol Psychiatry. 1995 Jan;19(1):11733.

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1. There is growing evidence that the nerve growth factor protein (NGF), a neurotrophic factor for peripheral and central nervous system (CNS) neurons, may play a role in the modulation of the hypothalamopituitaryadrenocortical axis (HPAA). While NGF binding is decreased in rodent CNS after stress exposure, this reduction is prevented by treatment with Acetyl-L-Carnitine (ALCAR), a chemical substance able to prevent some degenerative events associated with aging. 2. The authors studied the effect of cold stress on the lowaffinity NGF receptor (p75NGFR) mRNA levels in the basal forebrain and cerebellum of aged rats chronically treated with ALCAR. 3. The present results show that ALCAR abolished the age-associated reduction of p75NGFR mRNA levels in the basal forebrain of old animals, but did not affect the response to stress stimuli. 4. Also, treatment with ALCAR maintained p75NGFR mRNA levels in the cerebellum of old animals at levels almost identical to those observed in young control animals. 5. These results suggest a neuroprotective effect for ALCAR on central cholinergic neurons exerted at the level of transcription of p75NGFR. The restoration of p75NGFR levels could increase trophic support by NGF of these CNS cholinergic neurons which are implicated in degenerative events associated with aging.

40_ Neurobiol Aging. 1995 JanFeb;16(1):14.

Clinical and neurochemical effects of Acetyl-L-Carnitine in Alzheimer's disease.

Pettegrew JW, Klunk WE, Panchalingam K, Kanfer JN, McClure RJ.

Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, School of Medicine, PA 15213, USA.

In a doubleblind, placebo study, Acetyl-L-Carnitine was administered to 7 probable Alzheimer's disease patients who were then compared by clinical and ³¹P magnetic resonance spectroscopic measures to 5 placebotreated probable AD patients and 21 agematched healthy controls over the course of 1 year. Compared to AD patients on placebo, Acetyl-L-Carnitinetreated patients showed significantly less deterioration in their MiniMental Status and Alzheimer's Disease Assessment Scale test scores. Furthermore, the decrease in phosphomonoester levels observed in both the Acetyl-L-Carnitine and placebo AD groups at entry was normalized in the Acetyl-L-Carnitinetreated but not in the placebotreated patients. Similar normalization of highenergy phosphate levels was observed in the Acetyl-L-Carnitinetreated but not in the placebotreated patients. This is the first direct in vivo demonstration of a beneficial effect of a drug on both clinical and CNS neurochemical parameters in AD.

41_ Brain Res. 1995 Mar 13;674(1):1426.

Spatial discrimination learning and choline acetyltransferase activity in streptozotocintreated rats: effects of chronic treatment with Acetyl-L-Carnitine.

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Treatment of rats with i.c.v. injected streptozotocin (STREP) may provide a relevant model of neurodegeneration that is induced by a decrease in the central metabolism of glucose. Acetyl-L-Carnitine (ALCAR) enhances the utilization of alternative energy sources and by such a mechanism of action ALCAR could antagonize the effects of STREP treatment. In this study the effects of chronic treatment with ALCAR were evaluated on spatial discrimination learning in the Morris task and choline acetyltransferase (ChAT) activity of middleaged STREPtreated rats. Chronic treatment with ALCAR attenuated both the STREPinduced impairment in spatial bias and the decrease in hippocampal ChAT activity. These findings indicate that ALCAR treatment has a neuroprotective effect, although further studies are needed to characterize the mechanism of action of ALCAR in this model.

42_ Brain Res. 1994 Jan 7;633(12):7782.

Acetyl-L-Carnitine treatment increases choline acetyltransferase activity and NGF levels in the CNS of adult rats following total fimbria-fornix transection.

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Transection of the fimbria-fornix in adult rats is a useful model for producing impairments of cholinergic activity in the hippocampus (HIPPO) and atrophy of the medial septum cholinergic perikarya, similar to those observed during senescence, that are possibly due to the lack of nerve growth factor (NGF) retrogradely transported from the hippocampus. In our investigation we used choline acetyltransferase (ChAT) as an index of cholinergic activity in HIPPO, frontal cortex (FCX), septum and nucleus basalis magnocellularis (NBM) along with measurements of NGF levels in the HIPPO. Threemonthold rats with unilateral total fimbria transection received Acetyl-L-Carnitine (ALCAR) (150 mg/kg/day) in drinking water for 1 week before and 4 weeks after the lesion). ALCAR is a substance known to ameliorate some morphological and functional disturbances in the aging central nervous system (CNS). ChAT activity in septum and FCX, and NGF levels in HIPPO were significantly increased in the treated group, compared with untreated control groups, while no changes were found in the NBM. On the other hand, a similar ALCAR treatment in unoperated animals induced an increase in ChAT activity in FCX but not in septum nor in NBM. These data are suggestive of a neurotrophic property of ALCAR exerted on those central cholinergic pathways typically damaged by aging.

43_ Exp Gerontol.

1994 JanFeb;29(1):5566.

Acetyl-L-Carnitine treatment increases nerve growth factor levels and choline acetyltransferase activity in the central nervous system of aged rats.

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The hypothesis that some neurodegenerative events associated with ageing of the central nervous system (CNS) may be due to a lack of neurotrophic support to neurons is suggestive of a possible reparative pharmacological strategy intended to enhance the activity of endogenous neurotrophic agents. Here we report that treatment with Acetyl-L-Carnitine (ALCAR), a substance which has been shown to prevent some impairments of the aged CNS in experimental animals as well as in patients, is able to increase the levels and utilization of nerve growth factor (NGF) in the CNS of old rats. The stimulation of NGF levels in the CNS can be attained when ALCAR is given either for long or short periods to senescent animals of various ages, thus indicating a direct effect of the substance on the NGF system which is independent of the actual degenerative stage of the neurons. Furthermore, longterm treatment with ALCAR completely prevents the loss of choline acetyltransferase (ChAT) activity in the CNS of aged rats, suggesting that ALCAR may rescue cholinergic pathways from age-associated degeneration due to lack of retrogradely transported NGF.

44_ Life Sci. 1994;54(17):120514.

Acetyl-L-Carnitine affects aged brain receptorial system in rodents.

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Acetyl-L-Carnitine (ALCAR), the acetyl ester of carnitine, is regarded as a compound of considerable interest because of its capacity to counteract several physiological and pathological modifications typical of brain ageing processes. In particular, it has been demonstrated that ALCAR can counteract the agedependent reduction of several receptors in the central nervous system of rodents, such as the NMDA receptorial system, the Nerve Growth Factor (NGF) receptors, those of glucocorticoids, neurotransmitters and others, thereby enhancing the efficiency of synaptic transmission, which is considerably slowed down by ageing. The present review thus postulates the importance of ALCAR administration in preserving and/or facilitating the functionality of carnitines, the concentrations of which are diminished in the brain of old animals.

45_ Biochem Pharmacol. 1992 Aug 4;44(3):57785.

Stimulation of nerve growth factor receptors in PC12 by Acetyl-L-Carnitine.

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Acetyl-L-Carnitine (ALCAR) prevents some deficits associated with aging in the central nervous system (CNS), such as the agedrelated reduction of nerve growth factor (NGF) binding. The aim of this study was to ascertain whether ALCAR could affect the expression of an NGF receptor (p75NGFR). Treatment of PC12 cells with ALCAR increased equilibrium binding of 125I-NGF. ALCAR treatment also increased the amount of immunoprecipitable p75NGFR from PC12 cells. Lastly, the level of p75NGFR messenger RNA (mRNA) in PC12 was increased following ALCAR treatment. These results are in agreement with the hypothesis that there is a direct action of ALCAR on p75NGFR expression in aged rodent CNS.

46_ Int J Dev Neurosci. 1992 Aug;10(4):3219.

Culture of dorsal root ganglion neurons from aged rats: effects of Acetyl-L-Carnitine and NGF.

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In vitro neuronal preparations are used to study the action mechanism of substances which are active in normal and pathological brain aging. One major concern with in vitro assays is that the use of embryonic or adult neurons may hamper an appreciation of the relevance of these substances on aged nervous tissue. In the present study for the first time cultures of aged dorsal root ganglia from 24-month-old rats were maintained in vitro up to 2 weeks. This model was used to investigate the neurotrophic/neuroprotective action of nerve growth factor and Acetyl-L-Carnitine. A large population of aged dorsal root ganglia neurons was responsive to nerve growth factor (100 ng/ml). Nerve growth factor induced an increase of initial rate of axonal regeneration and influenced the survival time of these neurons. Acetyl-L-Carnitine (250 microM) did not affect the axonal regeneration but substantially attenuated the rate of neuronal mortality. A significant difference was evident between the Acetyl-L-Carnitine-treated and the untreated neurons from the first cell counting (day 3 in culture). After 2 weeks the number of aged neurons treated with Acetyl-L-Carnitine was almost double that of the controls. The effects of Acetyl-L-Carnitine on aged DRG neurons potentially explain the positive effects in clinical and in vivo experimental studies.

47_ Brain Res Dev Brain Res. 1991 Apr 24;59(2):22130.

Acetyl-L-Carnitine enhances the response of PC12 cells to nerve growth factor.

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We have demonstrated that treatment of rat pheochromocytoma (PC12) cells with Acetyl-L-Carnitine (ALCAR) stimulates the synthesis of nerve growth factor receptors (NGFR). ALCAR has also been reported to prevent some age-related impairments of the central nervous system (CNS). In particular, ALCAR reduces the loss of NGFR in the hippocampus and basal forebrain of aged rodents. On these bases, a study on the effect of NGF on the PC12 cells was carried out to ascertain whether ALCAR induction of NGFR resulted in an enhancement of NGF action. Treatment of PC12 cells for 6 days with ALCAR (10 mM) stimulated [¹²⁵I]NGF PC12 cell uptake, consistent with increased NGFR levels. Also, neurite outgrowth elicited in PC12 cells by NGF (100 ng/ml) was greatly augmented by ALCAR pretreatment. When PC12 cells were treated with 10 mM ALCAR and then exposed to NGF (1 ng/ml), an NGF concentration that is insufficient to elicit neurite outgrowth under these conditions, there was an ALCAR effect on neurite outgrowth. The concentration of NGF necessary for survival of serum-deprived PC12 cells was 100-fold lower for ALCAR-treated cells as compared to controls. The minimal effective dose of ALCAR here was between 0.1 and 0.5 mM. This is similar to the reported minimal concentration of ALCAR that stimulates the synthesis of NGFR in these cells. The data here presented indicate that one mechanism by which ALCAR rescues aged neurons may be by increasing their responsiveness to neurotrophic factors in the CNS.

48_ Int J Dev Neurosci. 1991;9(1):3946.

Effect of Acetyl-L-Carnitine on forebrain cholinergic neurons of developing rats.

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It has been shown that the endogenous compound, Acetyl-L-Carnitine (ALCAR), acts in the brain as a metabolic cofactor in the synthesis of acetylcholine. In these studies, ALCAR was injected into the brain of developing rats every other day for the first three weeks after birth in order to assess its effect on forebrain cholinergic neurons. The results showed that intracerebroventricular (icv) administration of ALCAR causes an increase of choline acetyltransferase (ChAT) activity and of nerve growth factor receptor expression in the striatum. Biological assays of brain tissues revealed that the level of nerve growth factor (NGF) in the hippocampus also increases. The ability of brain cholinergic tissues to respond to exogenous administration of ALCAR is discussed.

49_ J Neurosci Res. 1990 Mar;25(3):3315.

¹²⁵I-nerve growth factor binding is reduced in rat brain after stress exposure.

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In the central nervous system (CNS), the presence of nerve growth factor (NGF) and its receptor, NGFR, in cholinergic neurons has been demonstrated. In this study we report that, after exposure to stress, there was a reduction in total binding of NGF in the hippocampus and basal forebrain of 3.5-month-old rats without significant changes in the frontal cortex or cerebellum. Chronic treatment with Acetyl-L-Carnitine (ALCAR), that prevents some age-related impairments of CNS, for 1.5 months, decreased NGF binding in hippocampus and basal forebrain but abolished the stress-related reduction of NGF binding observed in the hippocampus of untreated rats.

50_ J Neurosci Res. 1988 Aug;20(4):4916.

Nerve growth factor binding in aged rat central nervous system: effect of Acetyl-L-Carnitine.

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The nerve growth factor protein (NGF) has been demonstrated to affect neuronal development and maintenance of the differentiated state in certain neurons of the peripheral and central nervous system (CNS) of mammals. In the CNS, NGF has sparing effects on cholinergic neurons of the rodent basal forebrain (BF) following lesions where it selectively induces choline acetyltransferase (ChAT). NGF also induces ChAT in the areas to which BF provides afferents. In aged rats, there is a reduction in the NGF binding capacity of sympathetic ganglia. Here, we wish to report that there is a decrease in the NGF binding capacity of the hippocampus and basal forebrain of aged (26 month old) rats as compared to 4 month old controls but no change in NGF binding in cerebellum. In all instances, equilibrium binding dissociation constants did not differ significantly. Treatment of rats with Acetyl-L-Carnitine, reported to improve cognitive performance of aged rats, ameliorates these age related deficits.

Acetyl-L-Carnitine: 11 Citations

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