Nutrition and Dietary Supplements

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REVIEW

Update on critical evidence for use of carnitine analogs in clinical practice in CNS disorders

This article was published in the following Dove Press journal:
Nutrition and Dietary Supplements
27 April 2011
Number of times this article has been viewed

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Abstract: L-carnitine (LC) is part of the carnitine shuttle system at the mitochondrial inner membrane (MIM) and transports long chain fatty acids over the MIM route. Acetyl-L-carnitine (ALC), the acetyl ester of LC, plays an essential role in intermediary metabolism. To ALC are ascribed neurotrophic actions, antioxidant and antiapoptotic activity, positive effects on mitochondrial metabolism, and stabilization of intracellular membranes. Acylcarnitine and LC supplementation have shown beneficial effects in the treatment of aging, chronic degenerative pathologies and the slowing of the progression of mental deterioration in neurodegenerative diseases, and painful neuropathies. ALC is reported to affect brain energy and phospholipid metabolism and to interact with cell membranes, proteins, and enzymes. It also shows a neuromodulatory effect on synaptic morphology and neurotransmitter synaptic transmission, including that of acetylcholine and dopamine. All these data suggest that ALC can affect several targets in the central nervous system. The roles and effects of LC and ALC have led researchers to investigate carnitine's involvement in a variety of neuropathological states and treatments, including autism, Parkinson's disease, Alzheimer's disease, Down's syndrome, Huntington's disease, cerebellar ataxia, age-associated mental decline, hepatic encephalopathy, and ammonia neurotoxicity. This review summarizes evidence that carnitine analogs play many roles in serious neurological pathologies.

Keywords: L-carnitine, acetyl-L-carnitine, brain, neural disorders

Introduction

Carnitine metabolism

Carnitine plays a critical role in energy balance across cell membranes and in energy metabolism of tissues, in particular in carnitine free fatty acid metabolism.

L-Carnitine (LC) is the biologically active carnitine stereoisomer, a compound widely distributed in the food from animal sources. In humans, about 75% of carnitine is obtained from the diet.[1] The endogenous part is synthesized in kidney, liver, and brain from the essential amino acids lysine and methionine.[2] Ascorbic acid, ferrous iron, pyroxidine, and niacin are necessary cofactors.[3] In mammals the pathway is unique, using protein-bound lysine methylated to form trimethyllysine (TML) as post-translational modification of protein synthesis.[1,4] The normal plasma concentration of LC in healthy adults with a mixed diet is 40 to 50 μM. Omnivorous humans ingest 2 to 12 μmol/kg of body weight/day.[5] The absorption of LC decreases as the intake of LC increases, maintaining a constant LC concentration. Unabsorbed LC is degraded by microorganisms in the large intestine.[5] Carnitine is not metabolized and is excreted, mostly as free carnitine in the urine, with daily urinary carnitine excretion equal to the sum of dietary absorption and

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Dovepress
DOI: 10.2147/NDS.S7119

endogenous synthesis.[6] Exogenous LC is almost completely excreted during the first 12 hours after administration whereas dietary LC is reabsorbed.

The main biological role of LC is to facilitate the transport of fatty acids to mitochondria. In fact, LC performs several biochemical and physiological roles, including: i) transporting fatty acids acetyl-CoA across the mitochondrial inner membrane (MIM) for β-oxidation; ii) providing acyl deposit that keeps appropriate levels of free CoA; iii) facilitating the oxidation of pyruvate and branched-chain ketoacids and, by preventing their accumulation, contributing to the protection of cells from potentially membrane-destabilizing acyl-CoAs.[7] LC has an amphiphilic structure, making it very mobile throughout the cell. The free hydroxyl group has the potential for many different molecules to attach, creating a wide array of possible acylcarnitines. The ability to esterify and transport metabolites throughout the body distinguishes LC as a unique metabolite and suggests that the acylcarnitine profile might be a useful indicator of metabolic changes, particularly related to disease states. In addition, this wide array of possibilities also leads to a broad range of structures that are very different both chemically and metabolically.

Plasma concentration of free carnitine is in dynamic balance with acylcarnitine. Acylcarnitine esters are formed intracellularly during regular metabolic activity. LC undergoes acetylation in rodents and human intestine thus forming esterified compounds such as acetyl-L-carnitine (ALC). ALC is the principal acylcarnitine ester, an endogenous intermediate synthetized in many tissues including brain, liver, heart, kidney, and muscle.[8] It is involved in trans-mithocondrial membrane traffic of acetyl units, participating in both anabolic and catabolic pathways in cellular metabolism.[8,9] When injected into the brain, the acetyl groups were mostly incorporated into saturated fatty acids. ALC plays an essential role in energy production as 'shuttles' of long-chain fatty acids between the cytosol and the mitochondria for subsequent β-oxidation.[10–12] Together with LC, ALC is involved in the control of mitochondrial acetyl-CoA ratio, and peroxisomal oxidation of fatty acids.[7]

Carnitine and acylcarnitines cross the blood–brain barrier primarily via the high affinity through Na^+-dependent organic cation/carnitine transporter (OCTN2), and secondarily via $ATB^{0,+}$, a Na^+-, Cl^--dependent amino acid transporter expressed in the hippocampus.[13–16] ALC spreads across membranes much better than LC and its efflux in the systemic circulation was 4 times greater than that of LC.

Cao et al[17] have shown that LC has a greater maximum plasma concentration than ALC and palmitoyl-L-carnitine (PLC), and LC has a longer half-life than ALC and PLC. Yet a long-chain acylcarnitine, such as PLC, needs a transporter to cross the plasma membrane and, therefore, may be more restricted in its actions. As a result, changes in individual acylcarnitines may imply changes in specific metabolic pathways.

The roles of long-chain acylcarnitines, specifically PLC, in the brain have been investigated. Owing to the amphiphilic nature of PLC, it can react on the membrane surface and influence membrane fluidity and the activity of membrane enzymes and transporters.[18,19] PLC is involved in phospholipid and fatty acid turnover in rat fetal neurons.[20]

Carnitine in the brain

The importance of carnitine in the brain is emphasized by carnitine deficiency symptoms, many of which involve major deleterious effects.[21]

Carnitine deficiency

Two types of carnitine deficiency states exist. Primary carnitine deficiency is a genetic disorder consisting in a recessive mutation of the cellular carnitine-transporter system (OCTN2) that usually manifests itself by 5 years of age with symptoms of cardiomyopathy, skeletal-muscle weakness, and hypoglycemia. Secondary carnitine deficiency is an acquired carnitine depletion that may occur due to certain disorders (chronic renal failure) or under particular conditions, such as the use of antibiotics, which can reduce carnitine absorption or increase its excretion.[6,7]

Since the brain is dependent on oxidative metabolism, impairment of fatty acid metabolism and energy production due to lack of carnitine leads to metabolic encephalopathy.[22] The majority of the brain is composed of fatty acids, which are needed for incorporation into structural lipids.[23] Glucose is the primary energy source for the adult brain under normal conditions, but fatty acids become pivotal energy substrates for the brain under metabolically compromised conditions such as fasting or starvation. For this reason, carnitine and acylcarnitines functions in fatty acid metabolism, ketosis, and buffering of the concentration ratio of acyl-CoA to free CoA, are significant in brain metabolism, particularly metabolic disturbances present in neurological disease.

The enzymes required for the synthesis of carnitine are present in brain tissue.[24] LC is stored in neurons of the cerebral cortex and forms acylcarnitines. Isolated neurons of the adult brain contain approximately 80% free carnitine, 10% to 15% ALC, and less than 10% long-chain acylcarnitines. Since carnitine and its acylcarnitines have chemical structures comparable to choline and acetylcholine (ACh), it has been suggested that they are involved in neurotransmission. In

particular, many studies showed a modulation of synaptic transmission by LC and ALC, through an increase in ACh synthesis and release, an enhancement of dopamine release, and an increase in γ-aminobutirric acid (GABA).[21,25–27] The transporters OCTN1, OCTN2, and OCTN3 are expressed in the central nervous system of the mouse in regions that suggest they play a role in modulating cerebral bioenergetics and in synthesis of ACh.[28]

Acetyl-L-carnitine in the brain

ALC is present at relatively high levels in the brain.[29] It is highest in the hypothalamus,[30] where the level of the ALC-synthesizing enzyme, carnitine acetyltransferase (CAT), is high. Since ALC can readily cross the blood–brain barrier,[31] its supplementation could possibly affect brain metabolism. Injection of ALC in rats leads to reduced oxidation of glucose and increased glycogen synthesis in brain.[32]

ALC has been proposed to have beneficial effects in preventing the loss of brain function which typically occurs during aging and neurodegenerative disorders (Table 1). The main mechanism of action of ALC is the improvement of mitochondrial respiration which allows the neuron to produce ATP necessary to maintain the normal membrane potential.[33]

The main effects of ALC on the nervous system can be summarized as follows:

1. ALC has been shown to be neuroprotective through a variety of effects (see below) such as the increase in protein kinase C (PKC)[34] activity and gene expression.[21,35,36] In particular, an increase in PKC in the rat brain cortex is correlated with an improvement of the performance in a spatial learning task, reversing the age-related decline.[33,34]
2. ALC counteracts the loss of N-Methyl D-Aspartate (NMDA) receptors in neuronal membrane.[33]
3. ALC increases the production of neurotrophins.[33] Many studies have focused on the neurotrophic effects of ALC in the nervous system. ALC modulates the activity of nerve growth factor (NGF) and a number of hormones.[37] In particular, ALC increases NGF production and NGF binding in vivo.[38,39] NGF affects neuronal development and maintenance of neurons in the peripheral and central nervous system. ALC has influence on neuronal repair and nerve fiber regeneration. In diabetic Worcester rats prolonged treatments with ALC promote nerve fiber regeneration, correct both the Na^+/K^+ ATPase and nerve conduction defect, and prevent structural changes associated with diabetes pathology.[40] ALC prevents the age-dependent structural changes in rat peripheral nerves and, in lesioned animals, ALC treatment promotes regeneration of nerves by significantly increasing both the density of regenerating myelinated fibers and axon diameter.[41] ALC has also exhibited both neuroprotective and neurotrophic activity in primary motoneurons exposed to excitotoxic agents or deprived of brain-derived neurotrophic factor (BDNF).[42] ALC exerts cytoprotective, antioxidant, and antiapoptotic activity, and there is some experimental evidence that ALC might also have antiaging effects and cardioprotective activity.[33,43,44] Feeding ALC to older Fisher rats (22–28 months of age) increases the cellular consumption of oxygen, and reverses the declines in mitochondrial membrane potential and cardiolipin content.[45] ALC improves different aspects of the neuronal metabolism,[33,46–48] and has wide neuromodulatory effects.[7,26,43,46] It plays a neuromodulatory role by increasing the synthesis of phospholipids for membrane formation and integrity.[7] When ALC was added to α-lipoic acid (LA) to rats, reversals in the age-associated decline of mitochondrial membrane potential and the levels of ascorbate and malondialdehyde were observed.[49,50] The density of neuronal mitochondria associated with lipofuscin and vacuoles has been reduced by feeding ALC and LA to aged rats. In addition, an increase of the number of intact mitochondria has been observed.[51] Aged rats showed significant improvements on cognitive tasks, including the Morris water maze test.[52]

Table 1 Role of acetyl-L-carnitine in nervous system diseases

Neural disorders	Cited references
Alzheimers' disease	31,37,53,54,80,100–103,105,106
Parkinson's disease	84,87,90
Autism spectrum disorders	93,94
Neuronal ceroid lipofuscinosis	99,116–121
Cerebeller ataxia	72
Huntington's disease	81,90
Down's syndrome	79,108
Aging	27,31,33,56,57,58,60
Neurodegeneration	50,51
Intractable epilepsy	21,85,115
Chronic fatigue	21,109–111
Antioxidant and antiapoptosis	56,61–71

Anti-aging and neurodegenation

ALC has been shown to have beneficial effects treating symptoms of cerebral dysfunction caused by aging and in some disorders of aging associated with cholinergic deficiency, such as Alzheimer's disease (AD).[53,54]

Listed below are the most important examples of ALC effects on aging.

a. Sershen et al[27] studied the effect of ALC on dopamine release and age-related changes in dopamine receptors. These receptors declined with age, and treatment with ALC for 3 months diminished the reduction in receptor binding.
b. Both sphingomyelin and cholesterol tend to accumulate in the brain of older rats. Such increments are reduced by long-term ALC supplementation.[55]
c. ALC can reverse alterations in membrane lipid content and function, and it can improve age-related changes in metabolism, either directly through supplying high-energy acyl groups or indirectly through restoring membranes.
d. In rats, chronic ALC treatment increases life-span, improves cognitive behavior in aged animals, and guarantees long-term memory performance.[33]
e. Aging produces both a decline in mitochondrial energetics and an augment in oxidative stress. ALC prevents age-related changes in mitochondrial respiration and decreases oxidative stress biomarkers through the upregulation of heme oxygenase-1 (HO-1), Hsp70, and superoxide dismutase-2 in senescent rats, and a high expression of the redox-sensitive transcription factor Nrf2.[56–58] ALC is involved in cognitive functions in rats.[26] A recent study suggests that supplementation with ALC improves attention, learning, and spatial working memory deficits, reduces oxidative stress, and inhibits apoptotic cascade induced by hypoxia.[59]
f. ALC restores the age-associated decline of learning and memory in aging animals.[60]

Antioxidant and antiapoptotic functions

ALC can be protective against oxidative stress by: 1) a reduction in tissue lactic acidosis, which brings about the formation of reactive oxygen species (ROS); 2) shifts in both the mitochondrial and cytosolic redox state;[61] and/or 3) the induction of antioxidant genes.[56,61] Such events could lead to an increase of reducing power necessary for detoxification through the glutathione system.[61] Protection against mitochondrial alterations and cell death from cytokines along with an increased expression of HO-1 has been observed in primary rat cortical astrocytes treated with ALC.[56] Traina et al[35] reported an upregulation of hsp72 gene expression in rat brain after chronic treatment with ALC. Hsp72 gene plays a protective role against brain oxidative stress, and works as a relevant cellular protection molecule against protein aggregation.[62–64] These changes restored the ratio of reduced to oxidized glutathione and reversed the inhibition of complex IV. Further studies have evidenced that ALC decreases both 4-hydroxy-2-nonenal (HNE) formation and protein carbonyls, indicators of oxidative stress.[58,65] Pretreatment of cortical neurons with ALC and LA decreased HNE-mediated neurotoxicity, protein and lipid oxidation, and apoptosis in a dose-dependent manner as well as increased cellular reduced glutathione and heat-shock proteins hsps).[66] These results showed that ALC induces upregulation of HO-1, hsp60, and hsp72, and that this effect may involve the transcription factor Nrf2, implying the possibility that ALC, by promoting acetylation of DNA-binding proteins, can induce post-translational modifications of critical target proteins. Such a new role of ALC as a molecule able to enhance the cellular stress response pathways appears to be promising as an alternative therapeutic approach for those pathophysiological conditions where stimulation of the HO pathway is guaranteed.[56]

Oxidative stress underlies the neuropathology of AD and other disorders. ALC treatment leads to the activation of phosphoinositol-3 kinase, protein kinase, and extracellular signal-regulated kinase pathways that are important in neuronal cell survival and differentiation.[66] Both ALC and LC treatments have also been shown to reduce apoptosis through the mitochondrial pathway.[67–69] Oxidative stress from insults such as hypoxia and deprivation of trophic factors can cause apoptosis both in vitro and in vivo. ALC treatment reduced apoptosis in serum-deprived mouse fibroblasts, an effect that was confirmed by an assessment of cytochrome c release and immunoreactivity to caspase 3. ALC as well as LC promoted neuronal survival and mitochondrial activity and have antiapoptotic effects in serum-deprived primary culture neurons.[69] ALC is involved in the energy response and maintenance and appears to stimulate cell proliferation.

Traina et al[70] reported that ALC upregulates the voltage-dependent anion channel. This channel exerts an important role in cellular homeostasis, in apoptosis, and in synaptic plasticity.

ALC downregulates ferritin-H gene expression.[36] Several studies suggest that multiple independent pathways exist which converge in the increase of ferritin synthesis in response to various forms of oxidative insult. Ferritin, with its ability to oxidize and sequester intracellular iron in an internal mineral core, limits the levels of catalytically available iron, owing to the generation of free radicals, as a critical cytoprotective protein that constitutes an integral part of the

antioxidant response. A recent study reported that ALC exerts antioxidant effect and reverses iron-induced oxidative stress in human fibroblast.[71] It is possible that ALC might reduce available iron, by reducing ferritin expression.[36]

Finally, despite the different genetic defects underlying degenerative cerebellar ataxia, it has been suggested that mithochondrial energy production and antioxidative metabolism dysfunction may be common biochemical alterations related to this disease. Treatments with ALC in patients with degenerative ataxia produced an improvement of some symptoms and reduced the progression of the disease.[72]

Energy metabolism

According to its role in whole energy metabolism, ALC can repair neurological injury through metabolic pathways.[21] In rats, ALC supplementation enhances the level of phosphocreatine and decreases the concentrations of lactate and inorganic phosphate in aging and post-ischemic brain models, providing protection during metabolic stress, such as ischemia, hypoxia, reperfusion of the brain, alcohol, and brain injury.[7,73,74] In particular, studies by ^{31}P and ^{1}H-NMR spectroscopy suggested a therapeutic role for ALC in the treatment of cerebral ischemia through a faster recovery.[21,74] Dogs treated with ALC exhibited a reduction in neurological deficit scores after cerebral ischemia and reperfusion, suggesting that ALC improves neurological effect, as a result of potentiating brain energy metabolism.[21,75] ALC increases fluidity in rat brain microsomes and liposomes.[76,77] ALC, as well as LC, may affect membrane fluidity due to its amphiphilic structure.[78] Alterations in neural phospholipid composition and further effects on signal transduction pathways have been found to be characteristic of many neurological disorders such as AD, Down syndrome, and Huntington's disease.[79–81]

Evidence suggests that ALC exerts a function in the elongation–desaturation of the *n*−3 polyunsaturated fatty acids to form 22:6*n*−3, docosahexaenoic acid (DHA), in mitochondria.[82] It is believed that ALC represents an intramitochondrial source of acetyl groups and supplies them in the elongation pathway. Changes in DHA content of membranes can affect synaptic plasticity, enzymatic activities, immunity, inflammatory response, gene expression, ion channels, membrane-bound proteins, and neurotransmission.[83]

Neuroprotection mechanisms from excitotoxicity

It is known that either the formation of ROS or mitochondrial dysfunction lead to metabolic and oxidative stress and are the basic processes in many neurotoxic and neurodegenerative disorders, such as AD and Parkinson's disease (PD).[84] The oxidative stress affects the activities of the respiratory chain complexes I–V, changes that are crucial in many neurological disorders. ALC treatment is neuroprotective. ALC upregulates cytochrome b oxidase, and complex bc 1 gene expression.[36] ALC increases the energy status of the cell by increasing the activities of cytochrome b oxidase, thus maintaining energy levels of the cells and stabilizing mitochondrial activity. Cassano et al[85] have found an increase in transcripts related to mitochondrial biogenesis with ALC supplementation in a rat model for hind-limb muscle atrophy. ALC could also help to generate more mitochondria under certain conditions, preserving or improving overall metabolic function.[85]

Pretreatment of young rats with ALC exerted effect neuroprotection at the mitochondrial level against 3,4-methylenedioximethamphetamine (ecstasy).[86] Neurotoxicity was induced in vitro by rotenone, an inhibitor of mitochondrial complex I, in rat cortical neurons. Coincubation of the cells with ALC increases survival and partial protection from cell death. An inhibitor of complex I, 1-methyl-4-phenylpyridinium (MPP+), results in symptoms similar to those in patients with PD. Virmani et al[87] reported that the inhibitory action of MPP+ was partly reversed by incubation of cells with ALC. In neuroblastoma cells, treatment with ALC, but not LC, prevented MPP(+) toxicity and partially restored intracellular ATP concentrations. However, ALC did not reverse the MPP(+)-induced loss of mitochondrial oxygen consumption suggesting that protective effects are independent of oxidative phosphorylation. ALC may exert protection through maximizing cellular glucose efficiency under both normal and MPP+-treated conditions.[88] Studies suggest that the mechanism of neuroprotection may be through restoration of mitochondrial function and/or improved energy use since at least part of the toxicity of MPP+ is due to mitochondrial inhibition.[87,88]

It has been observed that neurons are protected by LC after inducing neurotoxicity through 3-nitropropionic acid, a molecule that induces neurotoxicity through irreversible binding to succinate dehydrogenase (complex II of the mitochondrial respiratory chain), suggesting that LC's protective effects against neurotoxicity mainly seem to be due to its antioxidant ability.[89] Defects in the function of complexes II and III have been observed in Huntington's disease patients.[90] Due to the reduction of both mortality and neuronal degeneration, LC appeared to be protective against neurotoxicity. More-

over, LC inhibited the increase in oxidized glutathione and mitochondrial dysfunction in the hippocampus and prevented neuronal hypoglycemia-induced damage.[91,92]

Several studies have described an association between autism spectrum disorders and mitochondrial dysfunction. Also carnitine deficiency is commonly found in autistic patients.[93] Carnitine deficiency results in impaired β-oxidation. In autistic patients, as a consequence of impaired β-oxidation polyunsatured long-chain fatty acids and/or satured very long chain fatty acids were elevated. None of the autistic patients had a well-recognized cause of a primary deficiency. None had the carnitine deficiency or the clinical picture seen with the classical OCTN2 transport defect.[94]

Traina et al[36] reported that ALC treatment upregulates the expression of brain-specific Na^+-dependent inorganic phosphate transporter gene. This evidence is consistent with studies that have ascribed to vesicular glutamate transporter 1 a role in the protection against excitotoxic injury. In addition, ALC upregulates prostaglandin D2 synthase (PGD2S) gene expression.[36] Liang et al[95] showed that in the brain the activation of DP1, a receptor of PGD2, can prevent neuronal injury in paradigms of acute excitotoxicity, and Lin et al[96] indicated that a product of PGD2 exhibits anti-inflammatory properties, supporting an emerging and neuronal protective role for prostaglandins that may present novel therapeutic targets in neurological diseases.

Both a decline in mitochondrial energetics and an increase in oxidative stress are some of the effects of aging. ALC can decrease brain lipid peroxidation in old rats whereas LC was ineffective. However, treatment with both carnitine and acylcarnitines has shown to significantly reduce the levels of circulating tumor necrosis factor-α (TNF-α) and interleukins, which could then protect against oxidative stress.[97,98]

Alzheimer's disease

Preclinical studies suggested that ALC treatment could be beneficial for the treatment of age-related diseases. ALC exerts advantageous effects on AD, the most common disorder in the geriatric population. The clinical efficacy of ALC was previously reported, and several molecular mechanisms were evoked to support it.[37] Many studies suggest that the mode of action of ALC in AD may involve, as well as synaptic function, an increase of cholinergic activity, restoration, protection against toxins, acetylation of proteins, and neurotrophic effects stimulating NGF. Patients affected by AD treated with ALC at doses ranging from 1 to 2 g/day for 6 to 12 months have shown an improved performance on several cognitive tests.

Recent studies reported that chronic ALC treatment induces modulation of expression of genes involved in neural disorders.[99,100] In particular, ALC upregulates kinesin light chain 1 (KLC1) gene expression.[100] Kinesin-1 is needed to move different types of cargoes in neuronal axons. A receptor that attaches KLC1 to vesicular cargoes is the amyloid precursor protein (APP). It is known that the deposition of APP degradative product in the brain is a major pathological finding in AD. Axonal transport of APP is mediated by direct binding of the KLC1, and leads to the suggestion that abnormal interaction of APP and KLC1 could play a role in the pathogenesis of AD.[101] Reduction in KLC1 increases Aβ levels in the brain, and accelerates and enhances amyloid deposition. Reductions in microtubule-dependent transport may stimulate proteolitic processing of APP, resulting in the development of senile plaques and AD.[101]

ALC may therefore, in some way, modify key pathogenic elements in AD, such as amyloid processing. Another hypothesis is that it can alter membrane fluidity or composition and that this modification can influence disintegrin and metalloprotease domain 10 (ADAM10) activity. This is supported by findings that describe the activation of ADAM10 as the major target of the cholesterol effects on APP metabolism because of increased membrane fluidity.[102] Supplementation of ALC has been shown to normalize the levels of high-energy phosphate in the brain of AD patients as measured by ^{31}P magnetic resonance spectroscopy.[103]

ALC has well-established antioxidant properties and studies in humans and animals suggest ALC has a favorable role in restoring cerebral energy metabolism, ie, ALC increases the activity of both cytochrome oxidase and α-ketoglutarate dehydrogenase in intrasynaptic but not in nonsynaptic mitochondria from rat cerebral cortex.[32,104] It was hypothesized that the antioxidant properties of ALC on compromised mitochondrial function could be involved in the effect of this compound on α-secretase activity and APP metabolism. Accumulation of the Aβ peptide has been implicated as the cause of the cognitive decline seen with AD. The Aβ peptide can suppress levels of acetyl-CoA and the activity of choline acetyltransferase in cell culture.[105] In this study ALC reversed these effects, but it did not change the mortality of the undifferentiated cells. In other cases of neurotoxicity from Aβ fragments, ALC was able to attenuate the oxidative stress, ATP depletion, and cell death.[7] ALC may be acting through buffering of oxidative stress and maintaining energy levels.

However, results are variable on the extent to which ALC improves clinical symptoms of AD: some studies have observed significant improvements in biochemical assays and psychometric tests, whereas others have not observed such large differences on a large scale.[106,107]

Finally, since there is an increased prevalence of AD in people with Down's syndrome, it was suggested that ALC administration might affect central nervous function positively and decrease mental deterioration in older people with Down's syndrome.[108]

Chronic fatigue and neurotransmitter modulation

Chronic fatigue patients show reduced biosynthesis of neurotransmitters.[21,109] ALC treatment reduces physical and mental fatigue in the elderly, and improve cognitive status, suggesting effects on endogenous ACh levels.[110] ALC supplementation induces an increase in choline uptake, ACh synthesis, and ACh release in synaptosomes, striatum, and hippocampus of rats.[11] Together with choline, carnitine was found to stimulate ACh synthesis in a synergistic way in rat cortex cells.[111] Pretreatment with ALC determines a progressive and dose-dependent recovery of field potential amplitude, which is an index of functional activity of striatal neurons. The addition of a choline transporter inhibitor blocks this protective effect of ALC. It is believed that choline transporters support presynaptic ACh synthesis and release. Neuroprotection by ALC is prevented by the addition of a nonselective muscarinic antagonist and by an M2-like receptor antagonist. By changing the ACh production in the brain, ALC increases cholinergic neurotransmission.[11,21,38] Studies suggest that ALC may improve transmitter function of cholinergic neurons by enhancing the acetyl-CoA concentration in the cytosol.[105]

Intractable epilepsy

The ketogenic therapy (KT) is a therapeutic, alternative diet for pharmacoresistant epilepsies. It mimics the state of starvation through a low-carbohydrate, high-fat regimen. Since dietary sources of glucose are dramatically reduced, during KT treatment the body synthesizes ketones as an energy supplement to the brain.

A study on rat hippocampus identified modulation of expression of genes after KT treatment, including genes involved in energy metabolism, signal transduction, oxidative phosphorylation, accompanied with mitochondrial biogenesis.[112] ALC upregulates mitochondrial transcripts in soleus muscle and improves mitochondrial morphology and function reinforcing the effects of KT.[85,113]

Both KT and ALC have comparable effects: increased β-oxidation, mitochondrial biogenesis, and enhanced energy reserves by reducing "the levels of circulating proinflammatory cytokines (TNF-α and IL-1β). Many of the neuroprotective functions of ALC could have beneficial effects for epileptic patients, such as neurotransmitter modulation, upregulation of hsps, and protection against excitotoxicity. Since free radical concentrations and apoptosis may be elevated in states of enhanced fat metabolism, a free radical quencher with antiapoptotic effects such as ALC may be useful". [21,114,115] Future studies will be needed to improve our knowledge on ALC's role in KT.

Neuronal ceroid lipofuscinosis

In order to study the role of ALC in molecular mechanisms Traina et al[35,36,70,99,100] have identified the differentially expressed genes in the rat brain in response to ALC treatment and gene expression was compared at the mRNA level using suppression subtractive hybridization (SSH). These authors comprehensively ana1yzed all the genes that are up- or downregulated after long-lasting ALC treatment. SSH combines normalization and subtraction of cDNAs in a single procedure and allows enrichment of differentially expressed sequences, generating an equalized representation of differentially expressed genes irrespective of their relative abundance. It is an excellent technology to search for differentially expressed genes in the tissues, and, in particular, for rare transcripts and unknown genes. Two different mRNA populations are compared so as to obtain clones of genes that are differentially expressed. The studies proved that chronic ALC treatments modulate different gene expression in the rat brain, and that the majority of detected clones are involved in the neuroprotection and/or in neuromodulation.

In particular, Traina et al[99] observed the effects of ALC on important molecular elements involved, to different degrees, in neuronal ceroid lipofuscinosis (NCL). ALC treatment: 1) upregulates the expression of the lysosomal H^+/ATPase, V1 subunit D gene; 2) downregulates the expression of the myelin basic protein (MBP) gene; 3) downregulates the expression of the ATP synthase lipid-binding protein, subunit c gene. The neurona1 ceroid lipofuscinoses (NCLs) are a group of autosomal recessively inherited monogenetic storage disorders. Since there are no effective therapies available, all forms of NCL invariably prove to be fatal after a prolonged period of disability. Indeed, for the forms of NCL that are the result of mutations in transmembrane proteins, the therapeutic outlook remains uniformly bleak. NCLs are considered as lysosomal storage diseases (LSDs). In NCLs the ceroid lipopigments are accumulated in the lysosomes, such as subunit c of mitochondrial ATP synthase. In particular, a loss of H^+/ATPases determines a strong accumulation

of the subunit c of mitochondrial ATP synthase and increased amounts of lysosomal enzymes.[116] Since the low pH of lysosomes is necessary to maintain the activity of acid hydrolases in the lysosomal lumen, a deficit in proton pump leads to severe neurodegeneration. The upgrading of the lysosomal protonic pump by ALC treatment might be a compensatory mechanism of the abnormal higher lysosomal pH.[99] Holopainen et al[117] have measured intracellular and lysosomal pH in fibroblast cell lines of patients with 6 different types of NCLs. The highest alkalinization was found in lysosomes of the most severe form of NCL. The elevated lysosomal pH might interfer with the catalytic activity of the lysosome by inactivating hydrolases.[117] There are studies suggesting that the regulation of lysosomal pH may be the underlying cause of Batten disease. In the CLN3 form, the lysosomal pH has been shown to be elevated.[117]

It has been observed that ALC exerts a downregulation of the subunit c of ATP synthase gene expression.[35,99] This protein is the major protein accumulated in the storage bodies of animals or humans affected by NCL. The fact that this protein, initially located in the mitochondria, is accumulated in lysosomes of NCL cells strongly suggests that the intracellular trafficking of specific molecules to lysosome is severely altered. In a canine model for the juvenile form of the human disease, a major constituent of the storage bodies is the subunit c protein of mitochondrial ATP synthase that contains an ε-N-TML residue.[118] TML is a precursor in carnitine biosynthesis. The changes in plasma carnitine and TML levels support the possibility that the disease involves a defect in the carnitine biosynthetic pathway.[118] Both TML and carnitine levels were significantly depressed in the affected individuals. In addition, dietary supplementation with carnitine delayed the progression of cognitive decline in NCL dogs.[119] Prolonged treatment with LC in isolated fibroblast cells from NCL patients fully restored the mitochondrial enzyme activities.[120] ALC and LA supplementation diet not only eliminated the mithocondrial damage, but also prevented the formation of lipofuscin and/or myelin-like structures in neurones.[51]

These results are the first studies in which, by applying a molecular biological approach, it has been possible to identify a direct effect of ALC on gene expression related to neuronal activity. The results are of relevant importance for possible therapeutic intervention, contributing to the increasingly recognized importance of the role of ALC in neuroprotection and suggesting a pathway for the treatment of NCL.[99]

Wei et al[121] have shown that endoplasmic reticulum (ER) and oxidative stresses (ER stress) are common manifestations in cells from both neurodegenerative and non-neurodegenerative LSD. These ER stresses might cause apoptosis. Wei et al[121] claim that lysosomal dysfunction, through the alteration of pH, produces ER and oxidative stress, supporting the idea that all the abnormalities originate by altering the pH of organelles. According to these findings, neuroprotective therapeutic strategies, involving substances that reduce the risk of neurodegeneration, are emerging. These substances are chemical and pharmacological chaperones that stabilize the conformation of proteins, increase the protein-folding capacity of the ER, and facilitate the trafficking of mutant proteins, including one of the main intracellular redox systems involved in neuroprotection, the vitagene system, as a potential target for novel cytoprotective intervention. Vitagenes encode for cytoprotective hsp70 and HO-1 as well as thioredoxin reductase and sirtuins proteins.[63] In addition, dietary antioxidants, including curcumin, ALC, and carnosine, have neuroprotective roles. In conclusion, these chemical chaperones might protect LSD cells.

Disclosure

The author reports no conflicts of interest in this work.

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