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The neurobiology of acetyl-L-carnitine

Giovanna Traina[1]

[1]*Dipartimento di Scienze Farmaceutiche, Universita degli Studi di Perugia, Via S. Costanzo, 06126 Perugia, Italy*

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1. ABSTRACT

A large body of evidence points to the positive effects of dietary supplementation of acetyl-L-carnitine (ALC). Its use has shown health benefits in neuroinflammation, which is a common denominator in a host of neurodegenerative diseases. ALC is the principal acetyl ester of L-Carnitine (LC), and it plays an essential role in intermediary metabolism, acting as a donor of acetyl groups and facilitating the transfer of fatty acids from cytosol to mitochondria during beta-oxidation. Dietary supplementation of ALC exerts neuroprotective, neurotrophic, antidepressive and analgesic effects in painful neuropathies. ALC also has antioxidant and anti-apoptotic activity. Moreover, ALC exhibits positive effects on mitochondrial metabolism, and shows promise in the treatment of aging and neurodegenerative pathologies by slowing the progression of mental deterioration. In addition, ALC plays neuromodulatory effects on both synaptic morphology and synaptic transmission. These effects are likely due to affects of ALC through modulation of gene expression on several targets in the central nervous system.

Here, we review the current state of knowledge on effects of ALC in the nervous system.

2. INTRODUCTION

There is a growing interest in the scientific community about the use of nutraceutical substances supplementation. In this context, the use of metabolic compounds such as acetyl-L-carnitine (ALC) as putative candidate in neuroprotection suggests new strategies for increasing protection through a natural molecule that can be effective in inducing health-promoting genes and/or reducing the expression of disease-promoting genes.

ALC is widespread in the medical practice since it is highly tolerated and without any adverse effects. Thus, ALC can be a useful pharmacological tool to examine the validity of the epigenetic hypothesis of various disorders in humans. The ability to esterify and to transport metabolites throughout the body has singled out ALC as a unique metabolite, and suggests that the acylcarnitine profile might be a useful marker of metabolic changes, particularly related to diseases.

The effects of ALC have led researchers to investigate carnitine's involvement in several neuropathological conditions and treatments, including Alzheimer's disease (AD), depression, chronic fatigue, cerebellar ataxia, ammonia neurotoxicity, hepatic encephalopathy, and age-associated mental decline,

as well as to investigate the genetic and epigenetic mechanisms underlying its actions (1-7).

3. ROLE OF THE CARNITINES IN THE BRAIN

3.1. Modulation in neurotransmission

Carnitine and its acylcarnitines have chemical structures comparable to choline and acetylcholine (ACh). It has been suggested that they are involved in cholinergic neurotransmission (8,9). Actually, ALC provides acetyl groups for ACh synthesis, it exerts a cholinergic effect, and it optimizes the balance of energy processes. Many studies have shown a modulation of synaptic transmission by LC and ALC, through an increase in ACh synthesis and release (10-13). Evidence of the influence of ALC on the cholinergic system have been provided by Janiri et al. (14), whose *in vivo* microiontophoretic studies on rat showed that ALC exerts excitatory effects on cholinergic receptors. Such effects are blocked by atropine, indicating that ALC is a weak muscarinic receptor agonist (14).

Other neuromodulatory actions of ALC involve enhancement of dopamine release and increase in gamma-aminobutirric acid (GABA) (10,13). In particular, ALC has beneficial effects on the dopaminergic system of the aging brain. The 50% loss of D1 dopamine receptor activity with age is reduced by prior ALC treatment, while the electrically evoked stimulation of dopamine release from aged striatal tissue is enhanced by *in vivo* pretreatment with ALC (15).

Dysfunction of glutamatergic neurotransmission is considered to be a core feature of stress-related disorders, including depression. In this context, ALC corrected the deficit of glutamate release in a spontaneously depressed model of rats, by strengthening the antidepressant activity of ALC (6,15). Finally, ALC influences functional aspects of serotonergic, noradrenergic and GABA neurotransmission (4,16,17).

3. 2. Carnitines and mitochondrial energetic

Carnitine plays a critical role in energy balance across cell membranes and in energy metabolism of tissues. LC is the biologically active carnitine stereoisomer, a widely distributed compound in the food from animal sources. In humans, about 75% of carnitine is obtained from the diet. Endogenous part is synthesized in kidney, liver, and brain from the essential amino acids lysine and methionine (18-21). Carnitine has two major functions:

1. It transports long-chain fatty acids as acylcarnitines from the cytoplasm into the mitochondria for their subsequent use as a source of energy (via acetyl-CoA formation in the beta-oxidation).
2. It removes short- and medium-chain fatty acids formed from metabolic processes, preventing their accumulation in the mitochondria, leading to an increase of free CoA, and contributing to the protection of cells from potential destabilizing acyl-CoAs.

Carnitine is not simply a cofactor in beta-oxidation. Its importance in the brain is emphasized by carnitine deficiency symptoms, many of which involve major harmful effects (4). Two states of carnitine deficiency exist:

1. Primary carnitine deficiency is a genetic disorder consisting in a recessive mutation of the cellular carnitine-transporter system, namely Na+-dependent organic cation/carnitine transporter (OCTN2) (22).
2. Secondary carnitine deficiency is an acquired carnitine depletion that may occur in some disorders such as chronic renal failure, or under particular conditions, such as the use of antibiotics, which can reduce carnitine absorption or increase its excretion (22).

The brain is one of the organs with higher lipid content. It cannot employ the exogenous lipids, neither as energy substrate nor as material, because fatty acids conveyed through plasmatic albumin cannot cross the blood-brain barrier (BBB).

The specific function of “active acetate donor” played by ALC acquires particular importance in the context of neuronal lipid metabolism. In fact, the synthesis of all fatty acids presents in the composition of phospholipids, cerebrosides and sphingomyelins, takes place in the cytoplasm, starting from active acetate, which is exclusively formed inside the mitochondrion (23). Furthermore, the active acetate is the only material used by the human body for the synthesis of cholesterol (24).

A portion of the newly synthesized lipids and those arising from turnover of lipid components of membranes are used as energetic material and, subsequently, metabolized by neurons. In such processes the role of LC is essential for the transport of acyl groups through the mitochondrial membrane, and their complete oxidation. An increase of acyl groups into the cell inhibits the transfer of ATP produced in the mitochondria, negatively influencing the energy metabolism of the whole cell.

In addition, although glucose is the primary energy source for the adult brain under normal conditions, fatty acids become pivotal energy substrates for the brain under metabolically compromised conditions such as fasting or starvation. For this reason, carnitine and acylcarnitines function in fatty acid metabolism, ketosis and are crucial in brain metabolism, particularly in metabolic disturbances present in neurological diseases.

Carnitine and acylcarnitines cross the BBB primarily through the high affinity through OCTN2, and

secondarily via $ATB0^+$, a unique Na^+-, Cl^--dependent amino acid transporter with broad substrate specificity and concentrative ability (25-28). In particular, ALC spreads across membranes much better than LC and its efflux in the systemic circulation is four times greater than that one of LC.

It is known that both a decline in mitochondrial energetics and an increase in oxidative stress are the basic processes in many neurotoxic and neurodegenerative disorders and represent some of the effects of aging (see below). The oxidative stress affects the activities of the respiratory chain complexes I–V. In this regard, ALC up-regulates cytochrome b oxidase, and complex bc1 gene expression (29), and it increases the cellular energy status, thus maintaining the energy levels of the cells and stabilizing mitochondrial activity. ALC activates the peroxisome proliferator-activated receptor-gamma co-activators PGC-1alpha/PGC-1beta-dependent signalling cascade of mitochondrial biogenesis (30). ALC enhances the mitochondrial DNA transcription, the stability of mitochondrial mRNA and the mitochondrial protein synthesis. In addition, ALC protects membrane integrity against lipid peroxidation and membrane breakdown (31,32). ALC exhibits protective effect on mitochondrial structure and function through different mechanisms:

1. By preventing the production of oxidants or by inducing radical scavenging activity;
2. By increasing the mitochondrial antioxidant defences; increasing mitochondrial metabolism to facilitate either the repair of less damaged mitochondria or the degradation of the most damaged ones;
3. By protecting mitochondrial enzymes as well as by stimulating enzyme activity (33).

Moreover, ALC functions as a stress modulator in various cell processes and it might play protective functions against chemotherapy-induced neurotoxicity (34,35).

In vitro experiments reported antioxidant properties of ALC mediated by its iron chelating properties (36). As cellular antioxidant defence mechanism, ALC decreases brain lipid peroxidation in old rats (37). The supplementation of ALC to the older rats decreased both 4-hydroxy-2-nonenal (HNE) formation and protein carbonyls, two indicators of oxidative stress and neurotoxicity (38,39). ALC treatment leads to the activation of phosphoinositol-3 kinase, protein kinase G, and ERK1/2 signalling pathways that are important in neuronal cell survival and differentiation processes (40). In streptozotocin-induced diabetic rats, ALC improved the speed of nerve conduction, in combination with a reduction in malonyldialdehyde (MDA) levels, another indicator of lipid peroxidation (41). ALC improves mitochondrial respiration in neurons and it has neuroprotective effect through a variety of further mechanisms such as the increase in protein kinase-C (PKC) activity (42). Interestingly, 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 (15,42).

For all these considerations, ALC has been considered a “mitochondrial nutrient” (33,43) that reverses both aging-related mitochondrial dysfunction and the reaction of elderly mitochondria to challenge (44).

ALC can be protective against oxidative stress. In particular, i) ALC reduces tissue lactic acidosis, which brings about the formation of reactive oxygen species (ROS); ii) ALC shifts in both the mitochondrial and cytosolic redox state; (45) and/or iii) ALC induces antioxidant gene expression (45,46). In addition, treatment with both carnitine and acylcarnitines has shown to decrease the contents of circulating oxidative stress biomarkers such as tumour necrosis factor-alpha and interleukins, which could protect against oxidative stress (47,48). Such events could lead to an increase of reducing power necessary for detoxification through the glutathione system (46,49).

3.3. Genetic modulations

3.3.1. ALC and Heme Oxigenase -1 regulation

ALC up-regulates the expression of Heme Oxidase-1 gene (HO-1). HO-1 is an early and ubiquitous gene induced by moderate or severe oxidative stress. It is controlled by inflammation or pro-oxidant states, and it produces antioxidant molecules. ALC up-regulates HO-1, reducing the amyloid beta (Abeta) toxicity in primary cortical neuronal cultures (50). ALC prevents age-related changes in mitochondrial respiration through the induction of heat shock proteins (Hsp70, Hsp60), and Thioredoxin Reductase, which together with HO-1 are components of the vitagene system, the main intracellular redox system involved in neuroprotection, and decreasing oxidative stress biomarkers in senescent rats (51-53). HO-1 is a rate-limiting enzyme for the production of the potent antioxidant bilirubin from heme and iron. ALC increases amount and activity of HO-1 in astrocytes, and pre-incubation with ALC before the initiation of stress with lipopolysaccharide and interferon, prevents the decrease in complex IV activity, protein nitration and restores the reduced glutathione (GSH) (54,55). Supplementation of ALC enhances the antioxidant status by directly quenching the free radicals, thus decreasing the use of GSH and subsequent production of oxidized glutathione (GSSG) (45,49). All these data suggest a role of ALC as defence mechanism after an external damage of the homeostatic equilibrium or as pre-conditioning agent.

Acetyl ester group of LC may modulate critical processes such as gene transcription and apoptosis. Acetylation of proteins is a crucial step in epigenetic modulations. This evidence implies the possibility that

the ALC-mediated acetylation of DNA binding proteins can induce post-translational modifications of critical target proteins involved in DNA competence and trans-activating activity (45,51,55).

The described mode of action is that ALC acetylates Kelch-like ECH-associated protein (Keap 1). This is a cytoplasmatic repressor of the nuclear factor erythroid-derived 2-like 2 (Nrf2) that controls the expression of several enzymes protective against oxidative stress (45,54). The activity of Nrf2 is so normally suppressed in the cytosol by specific binding to the chaperone Keap 1 (54). Keap 1 interacts with Nrf2 in a redox-sensitive manner, and the dissociation of the proteins in the cytoplasm is followed by translocation of Nrf2 to the nucleus (45). Here, Nrf2 is bound to antioxidant responsive elements (ARE) and it allows the expression of genes, such as HO-1 gene (56,57).

Moreover, ALC induces Hsps, specialized proteins that mediate various cellular functions. Hsps are up-regulated in response to stress conditions in order to restore cellular integrity (58). Hsps are chaperones that protect against damage by misfolded proteins, prevention of aggregation, dissolution and refolding of aggregated proteins. Up-regulation of hsp70 reduces apoptosis. Heat shock response decreases in aging cells; hsps play a protective role against brain oxidative stress, and they work as relevant cellular protection molecules against protein aggregation (59). Such changes restore the ratio of GSH to GSSG and reverse the inhibition of complex IV. *In vivo* treatment with ALC induces up-regulation of the expression of amma isoform of 14-3-3 protein and hsp72 (the inducible form of hsp70) genes in rat brain (60). The gamma 14-3-3 protein is a component of a family of proteins acting as chaperones to a very wide variety of proteins and nucleic acids. Taken together, these responses might contribute to a strategy for improving outcomes via protection from the risk of macromolecular oxidation and misfolding during aging, and reducing the tendency of tissues to develop disease.

3.3.2. ALC and apoptosis

ALC exerts modulatory functions in critical cellular processes including apoptosis. Acetyl ester groups of LC modulate apoptosis. It has been shown that ALC and LC reduce apoptosis through the mitochondrial pathway (61,62). Their anti-apoptotic effect has been observed in different cell types, including neurons, myocytes, teratocarcinoma cells, hepatocytes and lymphocytes (60-68).

A reduction in apoptosis was observed in mouse fibroblasts treated with different concentrations of ALC, an effect that was confirmed by an assessment of cytochrome c release and immunoreactivity to caspase 3 (69). ALC and LC promoted neuronal survival and mitochondrial activity in addition to having anti-apoptotic effects in serum deprived primary culture neurons (62). A recent study reports that ALC treatment induced both apoptotic and anti-apoptotic gene expressions *in vitro* through activation of antiapoptotic Bcl family members and attenuating pro-inflammatory cytokines levels (70). The antiapoptotic effect of ALC is likely related to the activation of HO-1, which increases the level of antiapoptotic bcl-2 protein and it inactivates the pro-apoptotic transcription factor p53 in neurons (71).

Supplemented ALC in rats decreases caspase activation by increasing the level of X-linked inhibitor of apoptosis protein, thus limiting the apoptotic pathway in peripheral neurons (72). Moreover, ALC up-regulates the voltage-dependent anion channel gene expression in rat brain (73). This protein exerts an important role in cellular homeostasis, apoptosis and synaptic plasticity.

3.3.3. ALC in neuroprotection/neuromodulation

Actually, ALC treatment induces important changes in gene expression. In this regard, Traina et al. (29,60,73-76) have identified a group of differentially expressed genes in the healthy rat brain in response to chronic ALC treatment. The gene expression was compared to the mRNA level using suppression subtractive hybridization (SSH)(60). These studies proved that the majority of detected clones are involved in the neuroprotection and/or in neuromodulation. It has been observed that ALC influences the expression of genes involved in a group of autosomal recessively inherited monogenetic storage disorders, the neuronal ceroid lipofuscinoses (NCL), considered as lysosomal storage diseases (LSDs)(74). At present there are no available and effective therapies to treat these disorders, so that all forms of NCL invariably prove to be fatal after a prolonged period of disability. ALC treatment: 1) up-regulates the expression of the lysosomal H+/ATPase, V1 subunit D gene; 2) down-regulates the expression of both the myelin basic protein (MBP) and the ATP synthase lipid-binding protein, subunit c genes (74).

In NCLs, the ceroid lipopigments, such as subunit c of mitochondrial ATP synthase lipid-binding protein, are accumulated in the lysosomes. A loss of H+/ATPase function determines a strong accumulation of the subunit c of mitochondrial ATP synthase and an increased amount of lysosomal enzymes (77). 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. In this respect, studies reported that the highest alkalinization was found in lysosomes of fibroblast cell lines of patients affected by the most severe form of NCL (78). Thus the upgrading of the lysosomal protonic pump by ALC treatment might be a compensatory mechanism of the abnormal higher lysosomal pH (74).

The fact that ATP synthase lipid-binding protein, subunit c, 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. ALC supplementation eliminates the mitochondrial damage, and it prevents the formation of lipofuscin and/or myelin-like structures in neurons (77). In addition, apoptosis due to lipid peroxidation brings about neuronal damage in NCL (79).

Finally, it has been shown that endoplasmic reticulum (ER) and oxidative stresses (ER stress) are common manifestations in cells from both neurodegenerative and non-neurodegenerative LSD. The ER stresses might cause apoptosis (80). A lysosomal dysfunction, through the alteration of pH, produces ER and oxidative stress, supporting the idea that all these abnormalities originate from an alteration of the pH of organelles.

Interestingly, in a mouse model of a human NCL form, the motor-neuron-degeneration (*mnd*) mouse, which summarizes many clinical and histopathological features in NCL patients, the altered expression of genes in both central and peripheral organs is associated with lipopigment accumulation. In addition, in the *mnd* model some genes are expressed in a manner exactly opposite respect that seen in wild-type mice and to ALC modulation, sustaining further neuroprotective ALC role (81).

3.3.4. Further modulations

ALC treatment up-regulates the expression of brain-specific Na+-dependent inorganic phosphate transporter gene in rat brain (29). This evidence is consistent with studies that have ascribed to vesicular glutamate transporter 1 a role in the protection against excitotoxic injury. ALC up-regulates the expression of prostaglandin D2 synthase gene (PGD2S) (29). The activation of a receptor of PGD2 can prevent neuronal injury in paradigms of acute excitotoxicity (82), and Lin et al. (83) indicated that a product of PGD2 exhibits anti-inflammatory properties, supporting an emerging neuronal protective role for prostaglandins.

ALC down-regulates the expression of ferritin-H gene in rat brain (29). Studies suggest that multiple independent pathways exist converging in the increase of ferritin synthesis in response to oxidative insults. With its ability to oxidize and sequester intracellular iron in an internal mineral core, ferritin limits the levels of catalytically available iron, owing to the generation of free radicals, functioning as a critical cytoprotective protein in the antioxidant response. It has been reported that ALC exerts antioxidant effect and reverses iron-induced oxidative stress in human fibroblast (84). It is possible that ALC might reduce available iron by decreasing ferritin gene expression (29).

3.4. Aging and neurodegeneration

As already reported, the use of ALC is justified by its ability to improve energy metabolism. In aging there is a negative impairment of both energy substrates and enzymatic systems involved in the production of energy. A deficit in energy production has important implications in brain tissue. In the elderly, there are reductions in the plasma concentration of carnitine, in parallel with the reduction in body mass index and muscle mass (85,86). Moreover, variations in the diet, as result of gastrointestinal diseases, can affect the concentration of carnitine in the body. In this context, the exogenous administration of LC and ALC may allow the correction of immunological functions and improvement of energy metabolism and functions in aging (87). In the brain of aged animals the mitochondrial mass does not vary compared to young ones, whereas the mitochondria function is affected (88).

The effect of ALC on aged mitochondria has been evaluated. The supplemented ALC is transported into the cardiac mitochondria where the acetyl group favours the production of acetyl-CoA both directly and through activation of carnitine acetyltransferase (CAT), which is decreased in aging. The acetyl-CoA acts on the acetylation status of mitochondrial proteins that increase mitochondrial transcription and protein synthesis. As a result, cytochrome *b* content increases, leading to increased activity of electron transport chain (ETC) complexes and stimulating the oxidative phosphorylation. This sequence of events leads to the restoration of the aging-related mitochondrial defects (89-91).

ALC is involved in cognitive functions in rats (11). Supplementation with ALC improves attention, learning and spatial working memory deficits, reduces oxidative stress and inhibits apoptotic cascade induced by hypoxia (48). Moreover, ALC showed significant effects on the expression of biomarkers of aging in the cerebellum (92). Chronic ALC treatment increases life-span, it improves cognitive behaviour in aged rats and it guarantees long-term memory performance. Aged rats showed also significant improvements in cognitive tasks, including the Morris water maze test (93,94).

ALC is able to counter age-related decline in tissue carnitine levels and improves fatty acid utilization, but high levels of ALC also lowered hepatocellular antioxidant status (95). This problem is overcomed by combining ALC with the antioxidant lipoic acid (LA) (96). Additional benefits include a variety of metabolic functions, restoration of the age related decrease in cardiolipin (a phospholipid cofactor for protein complexes in ETC), increase of glucose uptake, decrease of MDA and HNE formation, and reduction of the age-related accumulation of iron and copper (96). These findings established in hepatocytes have been extended to brain mitochondria and cortical tissues with similar results (91,97), including restoration of glutathione system, superoxide dismutase, and protein carbonyl formation. The effect of ALC plus LA treatment *in vivo* appears to significantly block or to

reverse various factors underlying the vicious cycle of age-related mitochondrial decay and cellular dysfunction. Finally, the density of neuronal mitochondria associated with lipofuscin and vacuoles has been reduced by feeding aged rats with ALC and LA. This observation is in agreement with ALC role on the modulation of genes involved in lipofuscinosis pathologies (74).

In summary, dietary supplementation with ALC in old rats reverses the age-associated decline of mitochondrial functions. ALC plays also interesting roles to manage aging risk factors in models of Parkinson's disease (PD). ALC protected the dopaminergic system against the intraventricular injection of 1-methyl-4-phenylpyridinium (MPP^+), an inhibitor of complex I, in rats (98). In primate models ALC provides some protection against MPTP-induced PD (99). Studies *in vitro* reported protective effects of LC and ALC on the neurotoxicity induced by mitochondrial uncoupling agents (31). In neuroblastoma cells exposed to rotenone, an inhibitor of the complex I, the pretreatment of ALC in combination with LA protects against reduction of mitochondrial membrane potential, ATP, and GSH, and it reduces the level of protein and DNA oxidation, accumulation of alpha-synuclein, ubiquitin, and ROS. In the absence of rotenone, ALC plus LA increases the number of viable mitochondria and mitochondrial DNA expression, likely through the induction of the signalling molecule PGC-1alpha, a regulator of the transcription factor for mitochondrial biogenesis and respiration, supporting the effectiveness of the combination against risks of disease.

Due to the reduction of both mortality and neuronal degeneration, LC appeared to be protective against neurotoxicity. As reported, LC inhibited the increase in oxidized glutathione and mitochondrial dysfunction in the hippocampus and prevented neuronal hypoglycemia-induced damage (100,101). Several studies have described an association between autism spectrum disorders and mitochondrial dysfunction. Also carnitine deficiency is commonly found in autistic patients (102). Carnitine deficiency results in impaired beta-oxidation. In autistic patients, as a consequence of impaired beta-oxidation polyunsaturated long-chain fatty acids and/or saturated very long chain fatty acids were elevated (103).

3.4.1. ALC and aged-related diseases

Preclinical studies suggested that ALC administration could be beneficial for the treatment of age-related diseases, the treatment of symptoms of cerebral dysfunction caused by aging and in some disorders of aging associated with cholinergic deficiency, such as Alzheimer's disease (AD), one of the most disabling conditions that affect the elderly (1,2,104,105). The clinical efficacy of ALC was previously reported, and several molecular mechanisms were evoked to support it (2). In such respect, Traina and coll. have provided a potential mechanism of action of ALC (75). ALC up-regulates kinesin light chain 1 (KLC1) gene expression in the brain of rats chronically treated with ALC (75). Kinesin-1 is needed to transport different types of cargoes along neuronal axons. The amyloid precursor protein (APP) is a receptor that attaches KLC1 to vesicular cargoes. It is known that the deposition of APP degradative products 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 (107). Reduction in KLC1 increases Abeta levels in the brain, accelerates and enhances amyloid deposition in an AD mice model (107). Reductions in microtubule-dependent transport may stimulate proteolitic processing of APP, resulting in the development of senile plaques and AD. ALC may therefore modify key pathogenic elements in AD, such as amyloid processing. In addition, supplementation of ALC normalizes the levels of phosphate in the brain of AD patients (1).

It was hypothesized that the well-established antioxidant properties of ALC on compromised mitochondrial function could be also involved on gamma-secretase activity and APP metabolism. Accumulation of the Abeta peptide has been implicated as the cause of the cognitive decline seen with AD. In cases of neurotoxicity from Abeta fragments, ALC was able to attenuate the oxidative stress, ATP depletion and cell death (106).

3.5. Epigenetic modulation

The acetylation and deacetylation of core histone tails are important factors in the regulation of DNA transcription (108,109). Generally a highly acetylated histone core corresponds to activation of transcription, while when histones are poorly acetylated the transcriptional repression occurs. The limiting factor for histone acetylation is the acetyl-CoA availability in the nucleus-cytosolic pool (110). Acetylation can control the activity of mitochondrial enzymes, and possibly *de novo* synthesis of acetyl-CoA in mitochondria. Mitochondrial matrix-acetyl-CoA synthetase is reversibly acetylated at a lysine residue in the active site of the enzyme. Sirtuins are an evolutionarily conserved family comprising 7 proteins with NAD+-dependent deacetylase activity in mammals, three of which (SIRT3–SIRT5) are mainly localized in the mitochondrion, regulating energy metabolism and oxidative stress (111). The deacetylation of this site induced by SIRT3 activates the acetyl-CoA synthetase (112,113). Recently, in a murine model, it has been shown that ALC up-regulates SIRT3, improving mitochondrial function against acute kidney injury (114).

3.5.1. ALC and neuropathies of pain

Several studies showed the effect of ALC in diseases characterized by neuropathies and neuropathic

pain: diabetic neuropathy, HIV and antiretroviral therapy–induced neuropathies, neuropathies due to compression and chemotherapeutic agents (115; for reviews, see 4,5).

Actually, ALC is currently used for the treatment of neuropathic pain. Its long-term analgesic effects are dependent on epigenetic modifications, such as reversible modifications in gene activity, but not associated with changes in DNA sequence. Thus ALC represents a consistent therapeutic option for peripheral neuropathies, and its complex neurotrophic and analgesic effects, based on epigenetic mechanism, open new pathways in the study of peripheral nerve disease management.

Evaluations evidenced reduction of pain, improvements of nerve function and trophism. ALC determines analgesia increasing type 2-metabotropic glutamate receptor (mGlu2) expression (115,116). ALC enhances transcription of *Grm2* gene encoding mGlu2 receptor. In particular, it acts as donor of acetyl group to transcription factor NF-kappaB p65/RelA, inducing long-term up-regulation of the mGlu2 receptor (117).

3.5.2. ALC and antidepressant effects

Studies on animal and cellular models suggest that ALC exerts neuroplastic effect, membrane modulation, and neurotransmitter regulation, and it could also have an important role as antidepressant. ALC brings about a rapid, robust, and long-lasting antidepressant effect in spontaneously depressed Flinders Sensitive Line (FSL) rat, a genetic model of depression, and in mice exposed to chronic unpredictable stress. FSL rats exhibit sleep, immune and neurochemical changes, as well as behaviours similar to those observed in depressed patients (6). ALC treatment of stressed and genetically vulnerable animals rapidly reversed these behaviours. It has been suggested that ALC has an antidepressant effect by increasing brain-derived neurotrophic factor (BDNF) level and glutamate release (6). This effect was selectively associated with mGlu2 receptors in brain regions that are critically involved in the pathophysiology of depression, such as the hippocampus and prefrontal cortex, suggesting that ALC, as well as compounds with similar mechanisms of action, could represent a truly unique approach to treat depressive disorders.

The putative mechanism of ALC on antidepressive effect via improving neuroplasticity suggests that ALC, by providing acetyl groups, causes acetylation of p65 at LYS(310) located in NF-kappaB binding sites. The acetylation of NF-κappaB-p65 subunit amplifies the transcriptional activity of NF-κappaB (38). The mGlu2 receptor promoter harbors numerous NF-kappaB–responsive elements as opposed to mGlu3 promoter. The effect of ALC on the expression of mGlu2 receptors was prevented by a combined treatment with sodium salicylate, a nonselective inhibitor of NF-alphaB. Finally, the role of epigenetic mechanisms in the regulation of mGlu2 receptors is further supported by the use of MS-275, a histone deacetylase inhibitor that mimicked the action of ALC in enhancing mGlu2 receptor expression in the prefrontal cortex (6). Summing up, ALC behaves as an antidepressant by the epigenetic regulation of mGlu2 receptors. The mGlu2 and mGlu3 receptors are coupled to Gi/Go proteins and they are preferentially localized in the preterminal region of axons, where they negatively modulate neurotransmitter release (118).

3.6. ALC and neurotrophic effects

Many studies have focused on the neurotrophic effects of ALC in the nervous system. As reported above, ALC improves motor and cognitive deficits in several disease models through a variety of mechanisms including increased acetylcholine synthesis and neurotrophin expression, as well as improved mitochondrial function. ALC modulates the activity of nerve growth factor (NGF) and a number of hormones (2). ALC increases NGF production and NGF binding in vivo (119,120). NGF affects neuronal development and maintenance of neurons in the peripheral and central nervous system. ALC influences 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 alterations, and prevent structural changes associated with diabetes pathology (121). ALC prevents the age-dependent structural changes in rat peripheral nerves and in lesioned animals it promotes nerve regeneration by increasing both the density of regenerating myelinated fibers and axon diameter (122). ALC also exhibits both neuroprotective and neurotrophic activity in primary motoneurons exposed to excitotoxic agents or deprived of BDNF (123).

4. ALC IN AN INVERTEBRATE ANIMAL MODEL

There are very few studies on the effects of ALC in invertebrate models. The invertebrate models exhibit simple behaviours that are sustained by neural circuits easily accessible to experimentation and already complex enough to provide information on the cellular and molecular mechanisms that control the function of the most evolved nervous system in the vertebrates. Recently, a simple animal model, the leech *Hirudo medicinalis* has been used to investigate the ALC-induced modulation of elementary forms of learning such as behavioural sensitization and dishabituation. These studies provide evidences for interesting long-term effects of the drug on non-associative learning processes triggered by brush strokes (124). In nearly-intact leeches repetitive application of weak electrical shocks onto the caudal portion of the body wall produces habituation of swim induction, whereas brush stroke on the dorsal skin produces sensitization or dishabituation when the nociceptive stimulus is delivered on previously

habituated animals. The neurotransmitter 5-HT is involved in both sensitization and dishabituation acting through the second messenger cAMP (125,126). The effects of a single treatment with ALC on the behavioural sensitization and dishabituation processes have been studied. In particular, ALC strongly impaired sensitization in a dose and time-dependent manner (124). In addition, ALC prevented 5-HT-induced behavioural paradigm, and inhibitors of transcription and protein synthesis influenced the learning process (127,128).

It has been observed that a single administration of ALC has a lasting effect on behavioural processes suggesting a regulation of gene expression in nervous system of the leech. SSH methodology has been applied for generating subtracted cDNA libraries and identifying differentially expressed genes (129). Some of the identified genes code for proteins involved in neuromodulatory and neuroprotective mechanisms, such as hsp90 and biosynthetic enzyme for thiazole, confirming the ALC role.

Finally, at cellular level, ALC induced a sustained potentiation of the afterhypolarization that accompanies bursting in tactile cells of the leech, thus modulating the electrical activity and the synaptic efficacy of the sensory neurons (130). In particular, ALC seems to be able to exert a positive sustained effect on the Na+/K+ ATPase activity in leech T sensory neurons. Moreover, in these widely arborized cells, the AHP seems to play a crucial role in determining the action potential transmission at neuritic bifurcations of the branching points and to influence the conduction of action potentials to the synaptic terminals (130).

5. SUMMARY AND PERSPECTIVES

ALC has a wide spectrum of pharmacological effects on nervous system. Its supplementation induces neuroprotective and neurotrophic effects. It influences expression of many genes, some of these are involved in controlling the development of free radicals, cellular antioxidant capacity and repair, restoring and stabilizing mithocondrial activity. Many of the neuronal responses may result not only from ALC acting via improved energy supply, and gene activity, but also by acting more directly to provide acetyl moieties to be used, for example in acetylcholine synthesis, or by providing activated acyl groups for the acylation of membrane phospholipids. Many studies suggest that the mode of action of ALC may involve, as well as synaptic function, an increase of cholinergic activity, acetylation of proteins and neurotrophic effects stimulating NGF, as well as enhancing anterograde axonal transport. ALC activates the Keap 1/Nrf2/ARE pathway, an important network of protective mechanisms. Neuroprotective therapeutic strategies through natural substances that reduce the risk of neurodegeneration, are emerging. These substances, such as ALC, are 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. Finally, the rapid and long-lasting action of ALC strongly suggests an approach to examine the epigenetic hypothesis of disorders in humans.

6. REFERENCES

1. JW Pettegrew, WE Klunk, K Panchalingam, JN Kanfer, RJ McClure: Clinical and neurochemical effects of acetyl-L-carnitine in Alzheimer's disease. *Neurobiol Aging* 16(1), 1-4 (1995)
DOI: 10.1016/0197-4580(95)80001-8
2. JW Pettegrew, J Levine, RJ McClure: Acetyl-L-carnitine physical-chemical, metabolic, and therapeutic properties: relevance for its mode of action in Alzheimer's disease and geriatric depression. *Mol Psychiatry* 5(6), 616-632 (2000)
DOI: 10.1038/sj.mp.4000805
3. HM Abdul, V Calabrese, M Calvani, DA Butterfield: Acetyl-L-carnitine-induced up-regulation of heat shock proteins protects cortical neurons against amyloid-beta peptide 1-42-mediated oxidative stress and neurotoxicity: implications for Alzheimer's disease. *J Neurosci Res* 84(2), 398-408 (2006)
DOI: 10.1002/jnr.20877
4. LL Jones, DA McDonald, PR Borum: Acylcarnitines: role in brain. *Prog Lipid Res* 49, 61-75 (2010)
DOI: 10.1016/j.plipres.2009.08.004
5. G Traina: Update on critical evidence for use of carnitine analogs in clinical practice in CNS disorders. *Nutr Diet Suppl* 3, 77 -87 (2011)
DOI: 10.2147/NDS.S7119
6. C Nasca, D Xenos, Y Barone, A Caruso, S Scaccianoce, F Matrisciano, G Battaglia, AA Mathé, A Pittaluga, L Lionetto, M Simmaco, F Nicoletti: L-acetylcarnitine causes rapid antidepressant effects through the epigenetic induction of mGlu2 receptors. *Proc Natl Acad Sci U S A* 110(12), 4804-4809 (2013)
DOI: 10.1073/pnas.1216100110
7. L Ratnakumari, IA Qureshi, D Maysinger, RF Butterworth: Developmental deficiency of the cholinergic system in congenitally

hyperammonemic spf mice: effect of acetyl-L-carnitine. *J Pharmacol Exp Ther* 274(1), 437-443 (1995)

8. M Malaguarnera, MP Gargante, E Cristaldi, V Colonna, M Messano, A Koverech, S Neri, M Vacante, L Cammalleri, M Motta: Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Arch Gerontol Geriatr* 46(2), 181-190 (2008)
DOI: 10.1016/j.archger.2007.03.012

9. A Wawrzenczyk, KA Nalecz, MJ Nalecz: Effect of externally added carnitine on the synthesis of acetylcholine in rat cerebral cortex cells. *Neurochem Int* 26(6), 635-641 (1995)
DOI: 10.1016/0197-0186(94)00162-N

10. S Falchetto, G Kato, L Provini: The action of carnitines on cortical neurons. *Can J Physiol Pharmacol* 49(1), 1-7 (1971)
DOI: 10.1139/y71-001

11. S Ando, T Tadenuma, Y Tanaka, F Fukui, S Kobayashi, Y Ohashi, T Kawabata: Enhancement of learning capacity and cholinergic synaptic function by carnitine in aging rats. *J Neurosci Res* 66(2), 266-271 (2001)
DOI: 10.1002/jnr.1220

12. H Sershen, LG. Harsing, Jr, M Banay-Schwartz, A Hashim, MT Ramacci, A Lajtha: Effect of acetyl-L-carnitine on the dopaminergic system in aging brain. *J Neurosci Res* 30(3), 555-559 (1991)
DOI: 10.1002/jnr.490300313

13. A Imperato, MT Ramacci, L Angelucci: Acetyl-L-carnitine enhances acetylcholine release in the striatum and hippocampus of awake freely mo ving rats. *Neurosci Lett* 107(1-3), 251-255 (1989)
DOI: 10.1016/0304-3940(89)90826-4

14. L Janiri, M Falcone, A Persico, E Tempesta: Activity of L-carnitine and L-acetylcarnitine on cholinoceptive neocortical neurons of the rat in vivo. *J Neural Transm Gen Sect* 86(2), 135-146 (1991)
DOI: 10.1007/BF01250574

15. MA McDaniel, SF Maier, GO Einstein: "Brain-specific" nutrients: a memory cure? *Nutrition* 19(11-12), 957-975 (2003)
DOI: 10.1016/S0899-9007(03)00024-8

16. B Smeland, TW Meisingset, K Borges, U Sonnewald: Chronic acetyl-L-carnitine alters brain energy metabolism and increases noradrenaline and serotonin content in healthy mice. *Neurochem Int* 61(1), 100-107 (2012)
DOI: 10.1016/j.neuint.2012.04.008

17. E Tempesta, L Janiri, C Pirrongelli: Stereospecific effects of acetylcarnitine on the spontaneous activity of brainstem neurones and their responses to acetylcholine and serotonin. *Neuropharmacology* 24(1), 43-50 (1985)
DOI: 10.1016/0028-3908(85)90094-2

18. A Steiber, J Kerner, CL Hoppel: Carnitine: a nutritional, biosynthetic, and functional perspective. *Mol Aspects Med* 25(5-6), 455-473 (2004)
DOI: 10.1016/j.neuint.2012.04.008

19. LL Bieber: Carnitine. *Annu Rev Biochem* 57, 261-283 (1988)
DOI: 10.1146/annurev.bi.57.070188.001401

20. MC Cave, RT Hurt, TH Frazier, PJ Matheson, RN Garrison, CJ McClain, SA McClave: Obesity, inflammation, and the potential application of pharmaconutrition. *Nutr Clin Pract* 23(1), 16-34 (2008)
DOI: 10.1177/011542650802300116

21. BS Kendler: Carnitine: an overview of its role in preventive medicine. *Prev Med* 15(4), 373-390 (1986)
DOI: 10.1016/0091-7435(86)90005-8

22. CA Stanley: Carnitine deficiency disorders in children. *Ann N Y Acad Sci* 1033, 42-51 (2004)
DOI: 10.1196/annals.1320.004

23. G Goodridge, DW Back, SB Wilson, MJ Goldman: Regulation of genes for enzymes involved in fatty acid synthesis. *Ann N Y Acad Sci* 478, 46-62 (1986)
DOI: 10.1111/j.1749-6632.1986.tb15520.x

24. KE Bloch: Sterol structure and membrane function. *CRC Crit Rev Biochem* 14(1), 47-92 (1983)
DOI: 10.3109/10409238309102790

25. Y Kido, I Tamai, A Ohnari, Y Sai, T Kagami, J Nezu, H Nikaido, N Hashimoto, M Asano, A Tsuji: Functional relevance of carnitine transporter OCTN2 to brain distribution of L-carnitine and acetyl-L-carnitine across the blood-brain barrier. *J Neurochem* 79(5), 959-969 (2001)
DOI: 10.1046/j.1471-4159.2001.00621.x

26. T Nakanishi, T Hatanaka, W Huang, PD

Prasad, FH Leibach, ME Ganapathy, V Ganapathy: Na+- and Cl--coupled active transport of carnitine by the amino acid transporter ATB(0,+) from mouse colon expressed in HRPE cells and Xenopus oocytes. *J Physiol* 532(Pt 2), 297-304 (2001) DOI: 10.1111/j.1469-7793.2001.0297f.x

27. JL Sloan, S Mager: Cloning and functional expression of a human Na(+) and Cl(-)-dependent neutral and cationic amino acid transporter B(0+). *J Biol Chem* 274(34), 23740-23745 (1999) DOI: 10.1074/jbc.274.34.23740

28. D Miecz, E Januszewicz, M Czeredys, BT Hinton, V Berezowski, R Cecchelli, KA Nalecz: Localization of organic cation/carnitine transporter (OCTN2) in cells forming the blood-brain barrier. *J Neurochem* 104(1), 113-123 (2008) DOI: 10.1111/j.1471-4159.2007.05024.x

29. G Traina, G Federighi, M Brunelli, R Scuri: Cytoprotective effect of acetyl-L-carnitine evidenced by analysis of gene expression in the rat brain. *Mol Neurobiol* 39(2), 101-106 (2009) DOI: 10.1007/s12035-009-8056-1

30. V Pesce, L Nicassio, F Fracasso, C Musicco, P Cantatore, MN Gadaleta: Acetyl-L-carnitine activates the peroxisome proliferator-activated receptor-γ coactivators PGC-1α/PGC-1β-dependent signaling cascade of mitochondrial biogenesis and decreases the oxidized peroxiredoxins content in old rat liver. *Rejuvenation Res* 15(2), 136-139 (2012) DOI: 10.1089/rej.2011.1255

31. MA Virmani, R Biselli, A Spadoni, S Rossi, N Corsico, M Calvani, A Fattorossi, C De Simone, E Arrigoni-Martelli: Protective actions of L-carnitine and acetyl-L-carnitine on the neurotoxicity evoked by mitochondrial uncoupling or inhibitors. *Pharmacol Res* 32(6), 383-389 (1995) DOI: 10.1016/S1043-6618(05)80044-1

32. MA Virmani, V Caso, A Spadoni, S Rossi, F Russo, F Gaetani: The action of acetyl-L-carnitine on the neurotoxicity evoked by amyloid fragments and peroxide on primary rat cortical neurones. *Ann N Y Acad Sci* 939, 162-178 (2001) DOI: 10.1111/j.1749-6632.2001.tb03623.x

33. J Liu, BN Ames: Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease. *Nutr Neurosci* 8(2), 67-89 (2005) DOI: 10.1080/10284150500047161

34. ZS Altun, D Güneş, S Aktaş, Z Erbayraktar, N Olgun: Protective effects of acetyl-L-carnitine on cisplatin cytotoxicity and oxidative stress in neuroblastoma. *Neurochem Res* 35(3):437-443 (2010) DOI: 10.1007/s11064-009-0076-8

35. Z Altun, Y Olgun, P Ercetin, S Aktas, G Kirkim, B Serbetcioglu, N Olgun, E A Guneri: Protective effect of acetyl-l-carnitine against cisplatin ototoxicity: role of apoptosis-related genes and pro-inflammatory cytokines. *Cell Prolif* 47(1), 72-80 (2014) DOI: 10.1111/cpr.12080

36. ML Schinetti, D Rossini, R Greco, A Bertelli: Protective action of acetylcarnitine on NADPH-induced lipid peroxidation of cardiac microsomes. *Drugs Exp Clin Res* 13(8), 509-515 (1987)

37. J Liu, E Head, H Kuratsune, CW Cotman, BN Ames: Comparison of the effects of L-carnitine and acetyl-L-carnitine on carnitine levels, ambulatory activity, and oxidative stress biomarkers in the brain of old rats. *Ann N Y Acad Sci* 1033, 117-131 (2004) DOI: 10.1196/annals.1320.011

38. HF Poon, V Calabrese, M Calvani, DA Butterfield: Proteomics analyses of specific protein oxidation and protein expression in aged rat brain and its modulation by L-acetylcarnitine: insights into the mechanisms of action of this proposed therapeutic agent for CNS disorders associated with oxidative. *Antioxid Redox Signal* 8(3-4), 381-394 (2006) DOI: 10.1089/ars.2006.8.381

39. V Calabrese, AM Giuffrida Stella, M Calvani, DA Butterfield: Acetylcarnitine and cellular stress response: roles in nutritional redox homeostasis and regulation of longevity genes. *J Nutr Biochem* 17(2), 73-88 (2006) DOI: 10.1016/j.jnutbio.2005.03.027

40. HM Abdul, DA Butterfield: Involvement of PI3K/PKG/ERK1/2 signaling pathways in cortical neurons to trigger protection by cotreatment of acetyl-L-carnitine and alpha-lipoic acid against HNE-mediated oxidative stress and neurotoxicity: implications for

Alzheimer's disease. *Free Radic Biol Med* 42(3), 371-384 (2007)
DOI: 10.1016/j.freeradbiomed.2006.11.006

41. S Lowitt, JI Malone, AF Salem, J Korthals, S Benford: Acetyl-L-carnitine corrects the altered peripheral nerve function of experimental diabetes. *Metabolism* 44(5), 677-680 (1995)
DOI: 10.1016/0026-0495(95)90128-0

42. A Pascale, S Milano, N Corsico, L Lucchi, F Battaini, EA Martelli, M Trabucchi, S Govoni: Protein kinase C activation and anti-amnesic effect of acetyl-L-carnitine.: in vitro and in vivo studies. *Eur J Pharmacol* 265(1-2), 1-7 (1994)
DOI: 10.1016/0014-2999(94)90216-X

43. W Shen, K. Liu, C Tian, L Yang, X Li, J Ren, L Packer, E Head, E Sharman, J Liu: Protective effects of R-alpha-lipoic acid and acetyl-L-carnitine in MIN6 and isolated rat islet cells chronically exposed to oleic acid. *J Cell Biochem* 104(4), 1232-1243 (2008)
DOI: 10.1002/jcb.21701

44. EJ Lesnefsky: Reversal of mitochondrial defects before ischemia protects the aged heart. *FASEB J* 20, 1543-1545 (2006)
DOI: 10.1096/fj.05-4535fje

45. V Calabrese, A Ravagna, C Colombrita, G Scapagnini, E Guagliano, M Calvani, D A Butterfield, A M Giuffrida Stella: Acetylcarnitine induces heme oxygenase in rat astrocytes and protects against oxidative stress: involvement of the transcription factor Nrf2. *J Neurosci Res* 79(4), 509-521 (2005)
DOI: 10.1002/jnr.20386

46. SA Zanelli, NJ Solenski, RE Rosenthal, G Fiskum: Mechanisms of ischemic neuroprotection by acetyl-L-carnitine. *Ann N Y Acad Sci* 1053, 153-161 (2005)
DOI: 10.1196/annals.1344.013

47. BK Winter, G Fiskum, LL Gallo: Effects of L-carnitine on serum triglyceride and cytokine levels in rat models of cachexia and septic shock. *Br J Cancer* 72(5), 1173-1179 (1995)
DOI: 10.1038/bjc.1995.482

48. K Barhwal, SB Singh, SK Hota, K Jayalakshmi, G Ilavazhagan: Acetyl-L-carnitine ameliorates hypobaric hypoxic impairment and spatial memory deficits in rats. *Eur J Pharmacol* 570(1-3), 97-107 (2007)
DOI: 10.1016/j.ejphar.2007.05.063

49. K Barhwal, SK Hota, D Prasad, SB Singh, G Ilavazhagan: Hypoxia-induced deactivation of NGF-mediated ERK1/2 signaling in hippocampal cells neuroprotection by acetyl-L-carnitine. *J Neurosci Res* 86(12), 2705-2721 (2008)
DOI: 10.1002/jnr.21722

50. V Calabrese, M Calvani, DA Butterfield: Increased formation of short-chain organic acids after chronic ethanol administration and its interaction with the carnitine pool in rat. *Arch Biochem Biophys* 431(2), 271-278 (2004)
DOI: 10.1016/j.abb.2004.08.020

51. V Calabrese, DA Butterfield, G Scapagnini, AM Stella, MD Maines: Redox regulation of heat shock protein expression by signaling involving nitric oxide and carbon monoxide: relevance to brain aging, neurodegenerative disorders, and longevity. *Antioxid Redox Signal* 8(3-4), 444-477 (2006)
DOI: 10.1089/ars.2006.8.444

52. V Calabrese, G Pennisi, M Calvani, DA Butterfield, C Mancuso, AM Giuffrida Stella. Heme Oxygenase as a Therapeutic Funnel in Nutritional Redox Homeostasis and Cellular Stress Response. In: Heat Shock Proteins in Neural Cells. Ed: C Richter-Landsberg, Springer New York, New York, NY, 39-52 (2009)
DOI: 10.1007/978-0-387-39954-6_4

53. V Calabrese, C Cornelius, C Mancuso, G Pennisi, S Calafato, F Bellia, TE Bates, AM Giuffrida Stella, T Schapira, AT Dinkova Kostova, E Rizzarelli: Cellular stress response: a novel target for chemoprevention and nutritional neuroprotection in aging, neurodegenerative disorders and longevity. *Neurochem Res* 33(12), 2444-2471 (2008)
DOI: 10.1007/s11064-008-9775-9

54. K Itoh, N Wakabayashi, Y Katoh, T Ishii, K Igarashi, JD Engel, M Yamamoto: Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. *Genes Dev* 13(1), 76-86 (1999)
DOI: 10.1007/s11064-008-9775-9

55. V Calabrese, C Colombrita, E Guagliano, M Sapienza, A Ravagna, V Cardile, G Scapagnini, AM Santoro, A Mangiameli, DA Butterfield, AM Giuffrida Stella, E Rizzarelli: Protective effect of carnosine during nitrosative stress in astroglial cell cultures.

Neurochem Res 30(6-7), 797-807 (2005)
DOI: 10.1007/s11064-005-6874-8

56. A Virmani, L Pinto, Z Binienda, S Ali: Food, nutrigenomics, and neurodegeneration--neuroprotection by what you eat! *Mol Neurobiol* 48(2), 353-362 (2013)
DOI: 10.1007/s12035-013-8498-3

57. A Kravets, Z Hu, T Miralem, MD Torno, MD Maines: Biliverdin reductase, a novel regulator for induction of activating transcription factor-2 and heme oxygenase-1. *J Biol Chem* 279, 19916-19923 (2004)
DOI: 10.1074/jbc.M314251200

58. C Sõti, E Nagy, Z Giricz, L Vígh, P Csermely, P Ferdinandy: Heat shock proteins as emerging therapeutic targets. *Br J Pharmacol* 146(6), 769-780 (2005)
DOI: 10.1038/sj.bjp.0706396

59. JR Glover, S Lindquist: Hsp104, Hsp70, and Hsp40. *Cell* 94, 73-82 (1998)
DOI: 10.1016/S0092-8674(00)81223-4

60. G Traina, S Valleggi, R Bernardi, M Rizzo, M Calvani, R Nicolai, L Mosconi, M Durante, M Brunelli: Identification of differentially expressed genes induced in the rat brain by acetyl-L-carnitine as evidenced by suppression subtractive hybridisation. *Brain Res Mol Brain Res* 132(1), 57-63 (2004)
DOI: 10.1016/j.molbrainres.2004.09.006

61. T Furuno, T Kanno, K Arita, M Asami, T Utsumi, Y Doi, M Inoue, K Utsumi: Roles of long chain fatty acids and carnitine in mitochondrial membrane permeability transition. *Biochem Pharmacol* 62(8), 1037-1046 (2001)
DOI: 10.1016/S0006-2952(01)00745-6

62. T Ishii, Y Shimpo, Y Matsuoka, K Kinoshita: Anti-apoptotic effect of acetyl-L-carnitine and L-carnitine in primary cultured neurons. *Jpn J Pharmacol* 83(2), 119-124 (2000)
DOI: 10.1254/jjp.83.119

63. E Arrigoni-Martelli, V Caso: Carnitine protects mitochondria and removes toxic acyls from xenobiotics. *Drugs Exp Clin Res* 27, 27–49 (2001)

64. G Galli, M Fratelli: Activation of apoptosis by serum deprivation in a teratocarcinoma cell line: inhibition by L-acetylcarnitine. *Exp Cell Res* 204, 54–60, (1993)
DOI: 10.1006/excr.1993.1008

65. RP Revoltella, B Dal Canto, L Caracciolo, CM D'Urso: L-Carnitine and some of its analogs delay the onset of apoptotic cell death initiated in murine C2.8 hepatocytic cells after hepatocyte growth factor deprivation. *Biochim Biophys Acta* 1224, 333–341 (1994)
DOI: 10.1016/0167-4889(94)90265-8

66. JW Snyder, ME Kyle, TN Ferraro: L-carnitine delays the killing of cultured hepatocytes by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Arch Biochem Biophys* 276, 132–138 (1990)
DOI: 10.1016/0003-9861(90)90019-U

67. S Moretti, G Famularo, S Marcellini: L-Carnitine reduces lymphocyte apoptosis and oxidant stress in HIV-1 infected subjects treated with zidovudine and di- danosine. *Antioxid Redox Signal* 4, 391–403 (2002)
DOI: 10.1089/15230860260196191

68. A Virmani, F Gaetani, Z Binienda, A Xu, H Duhart, SF Ali: Role of mitochondrial dysfunction in neurotoxicity of MPP+: partial protection of PC12 cells by acetyl-L-carnitine. *Ann N Y Acad Sci* 1025, 267–273 (2004)
DOI: 10.1196/annals.1316.033

69. RT Pillich, G Scarsella, G Risuleo: Reduction of apoptosis through the mitochondrial pathway by the administration of acetyl-L-carnitine to mouse fibroblasts in culture. *Exp Cell Res* 306(1), 1-8 (2005)
DOI: 10.1016/j.yexcr.2005.01.019

70. Z Altun, Y Olgun, P Ercetin, S Aktas, G Kirkim, B Serbetcioglu, N Olgun, EA Guneri: Protective effect of acetyl-l-carnitine against cisplatin ototoxicity: role of apoptosis-related genes and pro-inflammatory cytokines. *Cell Prolif* 47(1), 72-80
DOI: 10.1111/cpr.12080

71. N Panahian, M Yoshiura, MD Maines: Overexpression of heme oxygenase-1 is neuroprotective in a model of permanent middle cerebral artery occlusion in transgenic mice. *J Neurochem* 72(3), 1187-1203 (1999)
DOI: 10.1111/j.1471-4159.1999.721187.x

72. L Di Cesare Mannelli, C Ghelardini, M Calvani, R Nicolai, L Mosconi, E Vivoli, A Pacini, A Bartolini: Protective effect of acetyl-L-carnitine on the apoptotic pathway of peripheral neuropathy. *Eur J Neurosci* 26, 820–827 (2007)
DOI: 10.1111/j.1460-9568.2007.05722.x

73. G Traina, R Bernardi, M Rizzo, M Calvani,

M Durante, M Brunelli: Acetyl-L-carnitine up-regulates expression of voltage-dependent anion channel in the rat brain. *Neurochem Int* 48(8), 673-678 (2006)
DOI: 10.1016/j.neuint.2005.11.005

74. G Traina, R Bernardi, E Cataldo, M Macchi, M Durante, M Brunelli: In the rat brain acetyl-L-carnitine treatment modulates the expression of genes involved in neuronal ceroid lipofuscinosis. *Mol Neurobiol* 38(2), 146-152 (2008)
DOI: 10.1007/s12035-008-8038-8

75. G Traina, G Federighi, M Brunelli: Up-regulation of kinesin light-chain 1 gene expression by acetyl-L-carnitine: therapeutic possibility in Alzheimer's disease. *Neurochem Int* 53(6-8), 244-247 (2008)
DOI: 10.1016/j.neuint.2008.08.001

76. G Traina, G Federighi, M Macchi, R Bernardi, M Durante, M Brunelli: Modulation of myelin basic protein gene expression by acetyl-L-carnitine. *Mol Neurobiol* 44(1), 1-6 (2011)
DOI: 10.1007/s12035-011-8189-x

77. D Kasper, R Planells-Cases, J C Fuhrmann, O Scheel, O Zeitz, K Ruether, A Schmitt, M Poët, R Steinfeld, M Schweizer, U Kornak, TJ Jentsch: Loss of the chloride channel ClC-7 leads to lysosomal storage disease and neurodegeneration. *EMBO J* 24, 1079-1091 (2005)
DOI: 10.1038/sj.emboj.7600576

78. JM Holopainen, J Saarikoski, PK Kinnunen, I Järvelä: Elevated lysosomal pH in neuronal ceroid lipofuscinoses (NCLs). *Eur J Biochem/ FEBS* 268, 5851-5856 (2001)
DOI: 10.1046/j.0014-2956.2001.02530.x

79. M Hayashi, R Miyata, N Tanuma: Oxidative stress in developmental brain disorders. *Adv Exp Med Biol* 724, 278-90 (2012)
DOI: 10.1007/978-1-4614-0653-2_21

80. H Wei, SJ Kim, Z Zhang, PC Tsai, KE Wisniewski, AB Mukherjee: ER and oxidative stresses are common mediators of apoptosis in both neurodegenerative and non-neurodegenerative lysosomal storage disorders and are alleviated by chemical chaperones. *Hum Mol Genet* 17(4), 469-477 (2008)
DOI: 10.1093/hmg/ddm324

81. G Traina, P Bigini, G Federighi, L Sitia, G Paroni, F Fiordaliso, M Salio, C Bendotti, M Brunelli: Lipofuscin accumulation and gene expression in different tissues of mnd mice. *Mol Neurobiol* 45(2), 247-257 (2012)
DOI: 10.1007/s12035-012-8248-y

82. X Liang, L Wu, T Hand, K Andreasson: Prostaglandin D2 mediates neuronal protection via the DP1 receptor. *J Neurochem* 92(3), 477-486 (2005)
DOI: 10.1111/j.1471-4159.2004.02870.x

83. TN Lin, WM Cheung, JS Wu, JJ Chen, H Lin, JJ Chen, JY Liou, SK Shyue, KK Wu: 15d-prostaglandin J2 protects brain from ischemia-reperfusion injury. *Arterioscler Thromb Vasc Biol* 26(3), 481-487 (2006)
DOI: 10.1161/01.ATV.0000201933.53964.5b

84. A Lal, W Atamna, DW Killilea, JH Suh, BN Ames: Lipoic acid and acetyl-carnitine reverse iron-induced oxidative stress in human fibroblasts. *Redox Rep* 13(1), 2-10 (2008)
DOI: 10.1179/135100008X259150

85. M Malaguarnera, L Cammalleri, MP Gargante, M Vacante, V Colonna, M Motta: L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial. *Am J Clin Nutr* 86(6), 1738-1744 (2007)
DOI not found

86. M Malaguarnera, G Pistone, G Receputo, R Rapisarda, FB Tomasello, M Motta, D Maugeri: Serum Carnitine Levels in Centenarians. *Clin Drug Investig* 17, 321-327 (1999)
DOI: 10.2165/00044011-199917040-00008

87. M Malaguarnera: Carnitine derivatives: clinical usefulness. *Curr Opin Gastroenterol* 28(2), 166-176 (2012)
DOI: 10.1097/MOG.0b013e3283505a3b

88. M Frenzel, H Rommelspacher, MD Sugawa, NA Dencher: Ageing alters the supramolecular architecture of OxPhos complexes in rat brain cortex. *Exp Gerontol* 45(7-8), 563-572 (2010)
DOI: 10.1016/j.exger.2010.02.003

89. G Aliev, J Liu, JC Shenk, K Fischbach, GJ Pacheco, SG Chen, ME Obrenovich, WF Ward, AG Richardson, MA Smith, E Gasimov, G Perry, BN Ames: Neuronal mitochondrial amelioration by feeding acetyl-L-carnitine and lipoic acid to aged rats. *J Cell Mol Med* 13(2), 320-333 (2009)

DOI: 10.1111/j.1582-4934.2008.00324.x

90. TM Hagen, J Liu, J Lykkesfeldt, CM Wehr, RT Ingersoll, V Vinarsky, JC Bartholomew, BN Ames: Feeding acetyl-L-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc Natl Acad Sci U S A* 99, 1870-1875 (2002)
DOI: 10.1073/pnas.261708898

91. J Long, F Gao, L Tong, CW Cotman, BN Ames, J Liu: Mitochondrial decay in the brains of old rats: ameliorating effect of alpha-lipoic acid and acetyl-L-carnitine. *Neurochem Res* 34(4), 755-763 (2009)
DOI: 10.1007/s11064-008-9850-2

92. SK Park, K Kim, GP Page, DB Allison, R Weindruch, TA Prolla: Gene expression profiling of aging in multiple mouse strains: identification of aging biomarkers and impact of dietary antioxidants. *Aging Cell* 8(4), 484-495 (2009)
DOI: 10.1111/j.1474-9726.2009.00496.x

93. M D Seidman, MJ Khan, U Bai, N Shirwany, WS Quirk: Biologic activity of mitochondrial metabolites on aging and age-related hearing loss. *Am J Otol* 21(2), 161-167 (2000)
DOI: 10.1016/S0196-0709(00)80003-4

94. MF Beal: Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol* 53 Suppl 3, S39-47, S47-48 (2003)
DOI: 10.1002/ana.10479

95. TM Hagen, RT Ingersoll, CM Wehr, J Lykkesfeldt, VVinarsky, JC Bartholomew, MH Song, BN Ames: Acetyl-L-carnitine fed to old rats partially restores mitochondrial function and ambulatory activity. *Proc Natl Acad Sci U S A* 95(16), 9562-9566 (1998)
DOI: 10.1073/pnas.95.16.9562

96. TM Hagen, R Moreau, JH Suh, F Visioli: Mitochondrial decay in the aging rat heart: evidence for improvement by dietary supplementation with acetyl-L-carnitine and/or lipoic acid. *Ann N Y Acad Sci* 959, 491-507 (2002)
DOI: 10.1111/j.1749-6632.2002.tb02119.x

97. JH Suh, R Moreau, SH Heath, TM Hagen: Dietary supplementation with (R)-alpha-lipoic acid reverses the age-related accumulation of iron and depletion of antioxidants in the rat cerebral cortex. *Redox Rep* 10(1), 52-60 (2005)
DOI: 10.1179/135100005X21624

98. V Steffen, M Santiago, CP de la Cruz, E Revilla, A Machado, J Cano: Effect of intraventricular injection of 1-methyl-4-phenylpyridinium: protection by acetyl-L-carnitine. *Hum Exp Toxicol* 14(11), 865-871 (1995)
DOI: 10.1177/096032719501401102

99. I Bodis Wollner, E Chung, MF Ghilardi, A Glover, M Onofrj, P Pasik, Y Samson: Acetyl-levo-carnitine protects against MPTP-induced parkinsonism in primates. *J Neural Transm Park Dis Dement Sect* 3(1), 63-72 (1991)
DOI: 10.1007/BF02251137

100. Z Binienda, A Virmani, B Przybyla-Zawislak, L Schmued: Neuroprotective effect of L-carnitine in the 3-nitropropionic acid (3-NPA)-evoked neurotoxicity in rats. *Neurosci Lett* 367(2), 264-267 (2004)
DOI: 10.1016/j.neulet.2004.05.031

101. K Hino, M Nishikawa, E Sato, M Inoue: L-carnitine inhibits hypoglycemia-induced brain damage in the rat. *Brain Res* 1053, 77-87 (2005)
DOI: 10.1016/j.brainres.2005.06.062

102. L Palmieri, AM. Persico: Mitochondrial dysfunction in autism spectrum disorders: cause or effect? *Biochim Biophys Acta* 1797(6-7), 1130-1137 (2010)
DOI: 10.1016/j.bbabio.2010.04.018

103. PA Filipek, J Juranek, MT Nguyen, C Cummings, JJ Gargus: Relative carnitine deficiency in autism. *J Autism Dev Disord* 34(6), 615-623 (2004)
DOI: 10.1007/s10803-004-5283-1

104. M Calvani, M Lannuccelli, D Colasimone, Z Orfalian. Chronicle of the development of an endogenous substance for dementia: acetyl-lcarnitine. In: Senile Dementias: Early Detection. Ed: A Bes, John Libbey Eurotext (1986)

105. E Bonavita: Study of the efficacy and tolerability of L-acetylcarnitine therapy in the senile brain. *Int J Clin Pharmacol Ther Toxicol* 24(9), 511-516 (1986)

106. A Virmani, Z Binienda: Role of carnitine esters in brain neuropathology. *Mol Aspects Med* 25(5-6), 533-549 (2004)
DOI: 10.1016/j.mam.2004.06.003

107. G.B Stokin, C Lillo, TL Falzone, RG Brusch, E

Rockenstein, SL Mount, R Raman, P Davies, E Masliah, DS Williams, LS Goldstein: Axonopathy and transport deficits early in the pathogenesis of Alzheimer's disease. *Science* 307(5713), 1282-1288 (2005)
DOI: 10.1126/science.1105681

108. H Takahashi, JM McCaffery, RA Irizarry, JD Boeke: Nucleocytosolic acetyl-coenzyme a synthetase is required for histone acetylation and global transcription. *Mol Cell* 23, 207–217 (2006)
DOI: 10.1016/j.molcel.2006.05.040

109. MG Rosca, H Lemieux, CL Hoppel: Mitochondria in the elderly: is acetylcarnitine a rejuvenator? *Adv Drug Deliv Rev* 61, 1332–1342 (2009)
DOI: 10.1016/j.addr.2009.06.009

110. B Schwer, J Bunkenborg, RO Verdin, JS Andersen, E Verdin: Reversible lysine acetylation controls the activity of the mitochondrial enzyme acetyl-CoA synthetase 2. *Proc Natl Acad Sci U S A* 103, 10224–10229 (2006)
DOI: 10.1073/pnas.0603968103

111. DB Lombard, FW Alt, HL Cheng, J Bunkenborg, RS Streeper, R Mostoslavsky, J Kim, G Yancopoulos, D Valenzuela, A Murphy, Y Yang, Y Chen, MD Hirschey, RT Bronson, M Haigis, LP Guarente, RV Farese, Jr, S Weissman, E Verdin, B Schwer: Mammalian Sir2 homolog SIRT3 regulates global mitochondrial lysine acetylation. *Mol Cell Biol* 27(24), 8807-8814 (2007)
DOI: 10.1128/MCB.01636-07

112. MC Haigis, R Mostoslavsky, KM Haigis, K Fahie, DC Christodoulou, AJ Murphy, DM Valenzuela, GD Yancopoulos, M Karow, G Blander, C Wolberger, TA Prolla, R Weindruch, FW Alt, L. Guarente: SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell* 126, 941–954 (2006)
DOI: 10.1016/j.cell.2006.06.057

113. BH Ahn, HS Kim, S Song, IH Lee, J Liu, A Vassilopoulos, CX Deng, T Finkel: A role for the mitochondrial deacetylase SIRT3 in regulat ing energy homeostasis. *Proc Natl Acad Sci U S A* 105, 14447–14452 (2008)
DOI: 10.1073/pnas.0803790105

114. M Morigi, L Perico, C Rota, L Longaretti, S Conti, D Rottoli, R Novelli, G Remuzzi, A Benigni: Sirtuin 3-dependent mitochondrial dynamic improvements protect against acute kidney injury. *J Clin Invest* 125(2), 715-726 (2015)
DOI: 10.1172/JCI77632

115. S Chiechio, A Caricasole, E Barletta, M Storto, MV Catania, A Copani, M Vertechy, R Nicolai, M Calvani, D Melchiorri, F Nicoletti: L-Acetylcarnitine induces analgesia by selectively up-regulating mGlu2 metabotropic glutamate receptors. *Mol Pharmacol* 61(5), 989-996 (2002)
DOI: 10.1124/mol.61.5.989

116. S Chiechio, A Copani, M Zammataro, G Battaglia, RW 4th Gereau, F Nicoletti: Transcriptional regulation of type-2 metabotropic glutamate receptors: an epigenetic path to novel treatments for chronic pain.*Trends Pharmacol Sci* 31(4), 153-160 (2010)
DOI: 10.1016/j.tips.2009.12.003

117. S Chiechio, FNicoletti: Metabotropic glutamate receptors and the control of chronic pain. *Curr Opin Pharmacol* 12(1), 28-34 (2012)
DOI: 10.1016/j.coph.2011.10.010

118. F Nicoletti, J Bockaert, GL Collingridge, PJ Conn, F Ferraguti, DD Schoepp, JT Wroblewski, JP Pin: Metabotropic glutamate receptors: from the workbench to the bedside. *Neuropharmacology* 60(7-8), 1017-1041 (2011)
DOI: 10.1016/j.neuropharm.2010.10.022

119. PJ Foreman, JR Perez-Polo, L Angelucci, MT Ramacci, G Taglialatela: 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. *Prog Neuropsychopharmacol Biol Psychiatry* 19(1), 117-133 (1995)
DOI: 10.1016/0278-5846(94)00109-U

120. JH Furlong: Acetyl-l-carnitine: metabolism and applications in clinical practice. *Altern Med Rev* 1, 85-93 (1996)
DOI not found

121. AA Sima, H Ristic, A Merry, M Kamijo, SA Lattimer, MJ Stevens, DA Greene: Primary preventive and secondary interventionary effects of acetyl-L-carnitine on diabetic neuropathy in the bio-breeding Worcester rat. *J Clin Invest* 97(8), 1900-1907 (1996)
DOI: 10.1172/JCI118621

122. C De Angelis, C Scarfo, M Falcinelli, E Perna, E Reda, MT Ramacci, L Angelucci: Acetyl-L-carnitine prevents age-dependent structural alterations in rat peripheral nerves and promotes regeneration following sciatic nerve injury in young and senescent rats. *Exp Neurol* 128(1), 103-114 (1994) DOI: 10.1006/exnr.1994.1117

123. P Bigini, S Larini, C Pasquali, V Muzio, T Mennini: Acetyl-L-carnitine shows neuroprotective and neurotrophic activity in primary culture of rat embryo motoneurons. *Neurosci Lett* 329(3), 334-338 (2002) DOI: 10.1016/S0304-3940(02)00667-5

124. C Ristori, E Cataldo, ML Zaccardi, G Traina, M Calvani, P Lombardo, R Scuri, M Brunelli: Acetyl-L-carnitine affects nonassociative learning processes in the leech Hirudo medicinalis. *Neuroscience* 142(4), 931-939 (2006) DOI: 10.1016/S0304-3940(02)00667-5

125. ML Zaccardi, G Traina, E Cataldo, M Brunelli: Nonassociative learning in the leech Hirudo medicinalis. *Behav Brain Res* 126(1-2), 81-92 (2001) DOI: 10.1016/S0166-4328(01)00247-9

126. ML Zaccardi, G Traina, E Cataldo, M Brunelli: Sensitization and dishabituation of swim induction in the leech Hirudo medicinalis: role of serotonin and cyclic AMP. *Behav Brain Res* 153(2), 317-326 (2004) DOI: 10.1016/j.bbr.2003.12.008

127. G Traina, C Ristori, M Brunelli, R Scuri: Acetyl-l-carnitine prevents serotonin-induced behavioural sensitization and dishabituation in Hirudo medicinalis. *Behav Brain Res* 253, 323-328 (2013) DOI: 10.1016/j.bbr.2013.07.030

128. G Traina, R Scuri: Transcription and protein synthesis inhibitors influence long-term effects of acetyl-l-carnitine on non-associative learning in the leech. *Neurochem Int* 80, 72-78 (2015) DOI: 10.1016/j.neuint.2014.11.007

129. G Federighi, M Macchi, R Bernardi, R Scuri, M Brunelli, M Durante, G Traina: Differentially expressed genes in Hirudo medicinalis ganglia after acetyl-L-carnitine treatment. *PLoS One* 8(1), e53605 (2013) DOI: 10.1371/journal.pone.0053605

130. P Lombardo, R Scuri, E Cataldo, M Calvani, R Nicolai, L Mosconi, M Brunelli: Acetyl-L-carnitine induces a sustained potentiation of the afterhyperpolarization. *Neuroscience* 128(2), 293-303 (2004) DOI: 10.1016/j.neuroscience.2004.06.028

Abbreviations: 5-HT: serotonin; ACh: acetylcholine; AD: Alzheimer's disease; ALC: acetyl-L-carnitine; APP: amyloid precursor protein; ARE: antioxidant responsive elements; BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; ER: endoplasmic reticulum; ETC: electron transport chain; FSL: flinders sensitive line; GABA: gamma-aminobutirric acid; GSH: reduced glutathione; HNE: 4-hydroxy-2-nonenal; HO-1: heme oxidase-1; hsp: heat shock protein; KEAP1: kealch-like ECH-associated protein; KLC1: kinesin light chain 1; LA: lipoic acid; LC: L-carnitine; LSD: lysosomal storage disorder; MBP: myelin basic protein; MDA: malonyldialdehyde; mGlu2: type 2 metabotropic glutamate receptor; NCL: neuronal ceroid lipofuscinosis; NGF: neurotrophic factor; OCTN2: organic cation/carnitine transporter; PD: Parkinson's disease; SIRT: sirtuine; SSH: suppression subtractive hybridization.

Key Words: Acetyl-L-carnitine, Nervous System, Gene Expression, Neuroprotection, Review

Send correspondence to: Giovanna Traina, Dipartimento di Scienze Farmaceutiche, Universita degli Studi di Perugia, Via S. Costanzo, 06126 Perugia, Italy**,** Tel: 39 075 5857977**,** Fax: 39 075 5857904 E-mail: giovanna.traina@unipg.it