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Review

Potential therapeutic effects of alpha lipoic acid in memory disorders

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Summary. With ageing, biological processes promote a gradual loss of the ability to maintain homeostasis, leading to a progressive deterioration in the body's biochemical and physiological functions, thereby increasing susceptibility to disease. ALA, a low-molecular-weight dithiol with a chiral centre, is a dietary supplement thought to have potential therapeutic effects for the prevention or treatment of neurodegenerative diseases. In addition, treatment with ALA is able to regulate inflammatory cell infiltration into the central nervous system and to down-regulate VCAM-1 and human monocyte adhesion to epithelial cells. In neurodegenerative disease models, treatment with ALA is able to improve the function of the dopamine, serotonin and norepinephrine neurotransmitters. Scientific evidence shows that ALA possesses the ability to improve memory capacity in a number of experimental neurodegenerative disease models and in age-related cognitive decline in rodents. Studies have shown that this substance is able to reduce memory loss in various behavioural paradigms of Alzheimer's disease and in age-related cognitive dysfunctions.

Key words: alpha lipoic acid, ALA, memory disorders

Cognitive decline

Ageing is a multi-factorial process that includes genetic, social and environmental factors. With ageing, biological processes promote a gradual loss of the individual ability to maintain homeostasis, followed by a progressive deterioration in the body's biochemical and physiological functions, thereby increasing susceptibility to age-related diseases. The cognitive functions also undergo a decline with age. Alzheimer's dementia and mild cognitive impairment (MCI) are common amongst the elderly and are characterised by a progressive loss of the cognitive functions, memory, speech and reasoning ability. However, even those who do not suffer from these conditions can present minor cognitive changes that affect the activities of daily living and quality of life.

Alpha lipoic acid

Over the years, increasing attention has been dedicated to alpha lipoic acid (ALA) as a dietary supplement with potential therapeutic effects for the prevention and treatment of neurodegenerative diseases and age-related cognitive dysfunctions.

ALA (1,2-dithiolane-3-pentonoic acid, or thioctic acid) was discovered in 1937 by Snell (1) and characterised by Reed in 1951 (2); however many of its properties are yet to be clarified.

ALA is a low-molecular-weight dithiol with a chiral centre and its structure is formed of eight carbon atoms, two oxygen atoms in the carboxyl group and two sulphur atoms (Figure 1). A substantial part of ALA is reduced to dihydrolipoic acid (DHLA) by lipoamide dehydrogenase with the involvement of the NADH and NADPH system (3,4). ALA contains an asymmetrical carbon atom that determines two optical isomers: the

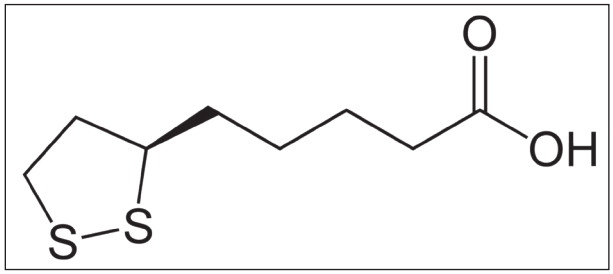

Figure 1. Structural formula of alpha lipoic acid

S form and the R form, the former being synthesised endogenously (5). ALA can be taken in through the diet and, due to its endogenous synthesis capacity, it is not considered a vitamin, rather it is structurally considered a member of the B vitamin family (6). When taken as a dietary supplement in the racemic mixture form, it contains two isomers (1:1 ratio of R-ALA and S-ALA) of which S-ALA can prevent the polymerisation of R-ALA and therefore increases its bioavailability (5). ALA is found in foods of both vegetable and animal origin. R-ALA is most abundantly present in vegetables like spinach, broccoli and tomatoes; amongst the foods of animal origin it is found most copiously in bovine kidney, heart and liver (7). Even when taken in through food and supplements, ALA is absorbed, metabolised and excreted rapidly. Up to 93% of an oral dose is absorbed in the digestive tract and undergoes considerable pre-systemic elimination. Between 27 and 34% of the oral intake is available for tissue absorption; the liver is one of the main clearance organs on account of its high absorption and storage capacity (8). Gastrointestinal absorption varies greatly and would appear to be reduced with dietary intake, suggesting that the absorption of ALA competes with that of other nutrients. ALA is rapidly absorbed in the digestive tract and its plasma presence is followed by rapid clearance. The plasma half-life of ALA is approximately 30 minutes. Peak urinary excretion occurs 3-6 hours after intake. Approximately 45% is excreted in urine within 24 hours and just 3% is excreted in stools. A small amount of ALA is excreted in an unmodified form (9). There are no guidelines regarding the recommended daily dose and the dose that could have adverse effects on human health is not known.

At cell level, ALA is an essential substrate for energy metabolism and the formation of amino acids (9). It is a fundamental cofactor for mitochondrial dehydrogenase complex enzymes including pyruvate-dehydrogenase (PDH), α-ketoglutarate-dehydrogenase (α-KGDH) and branched-chain keto acid dehydrogenase (10).

The presence of a dithiol ring in both the oxidised form (ALA) and the reduced form (DHLA), makes both forms potent natural antioxidants (11). They react with both reactive oxygen species (ROS), such as the hydroxyl, peroxyl and superoxide radicals (12), and with reactive nitrogen species (RNS), and therefore their functions are considered part of the cell protection mechanisms against those conditions in which oxidative stress plays the main aetiological role (13).

A high level of oxidative stress contributes to making the inflammatory processes chronic. A number of studies show that ALA alters nuclear factor (NF-κβ) signal transduction at cell level. NF-κβ is a redox-sensitive transcription factor that plays an important role in inflammation by regulating the expression of cytokines, internal tissue factors and adhesion factors in the endothelial cells. The expression of adhesion molecules causes an interaction between white blood cells and endothelial cells through the bloodstream. In this situation, other inflammatory mediators, such as monocyte chemo-attractant protein-1 (MCP-1), metalloprotease 9 and various cytokines, are involved by NF-κβ (14,15). As an inhibitor of NF-κβ, ALA has been studied in cytokine-mediated inflammation (16). In addition, treatment with ALA is able to regulate inflammatory cell infiltration into the central nervous system and to down-regulate vascular cell adhesion molecule-1 (VCAM-1) and the human monocyte adhesion to epithelial cells, and to inhibit the expression of NF-κβ-dependent metalloprotease 9 (17,18).

Metals can mediate the generation of free radicals, induce oxidative damage and exert a potential toxic and carcinogenic action. In addition to the direct antioxidant properties of ALA, some studies have shown that both ALA and DHLA and a great capacity to chelate redox-active metals, such as copper, free iron, zinc and magnesium, albeit in different ways (19, 20). The evidence from research seems to suggest that ALA modulates the free radical actions induced by metals in transition metal accumulation sites. More specifically, it has been shown that iron and copper chelation with DHLA may explain the low level of free radical dam-

age in the brain and the improvement in the pathobiology of Alzheimer's Disease (21). It has also been demonstrated that treatment with ALA reduces both iron absorption and the size of iron accumulations in the cerebral cortex (22).

Experimental models

Alzheimer's Disease (Figure 2) in a progressive, chronic neurodegenerative disease. It is characterised by a progressive loss of cognitive and memory capacity, as well as self-sufficiency in daily life and communication and interpersonal skills. In the past, it was postulated that the aggregation of Beta-Amyloid peptides (Aβ) to form amyloid plaques constituted the first event in the pathological cascade of Alzheimer's disease; this mechanism was known as the "amyloid cascade hypothesis". The so-called "oligomer hypothesis" now suggests that Alzheimer's disease is initiated by a synaptic dysfunction caused by soluble oligomers of Aβ (23). Furthermore, scientific evidence has shown that multiple neurotransmitters and the cholinergic system undergo a change under this condition (24,25). These changes can be defined as a deterioration of the basal cholinergic neurons of the frontal cortex and a reduction in acetylcholine production (26). As acetylcholine metabolism is associated with

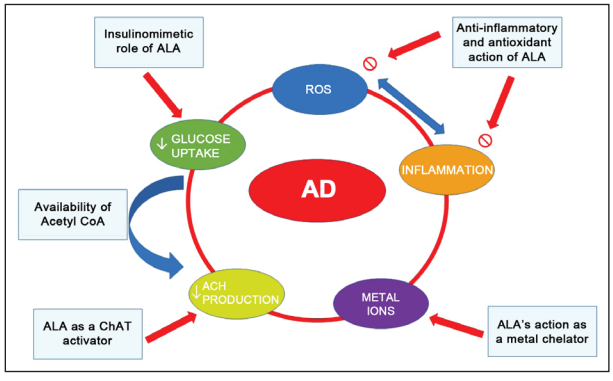

Figure 2. ALA can improve cognitive performance and could be a potential treatment for the pathogenesis of Alzheimer's disease through a number of mechanisms: (1) increased acetylcholine production; (2) increased glucose uptake and therefore greater availability of acetyl-CoA for the production of ACh; (3) inhibition of hydroxyl radical formation, removal of ROS, inflammatory process down-regulation; (4) potent metal chelator.

the glycolytic pathway and the formation of pyruvate, acetylcholine synthesis will be altered by the depletion of glucose in the brain of patients with Alzheimer's disease (27). Energy depletion and oxidative stress are therefore fundamental biochemical characteristics of the disease. Oxidative stress is triggered by the astroglia and microglia activated through an inflammatory process (28) that leads to the formation of free radicals and to extensive oxidative stress in the progression of Alzheimer's disease (29). Superoxide species and free radicals therefore cause neuronal damage in this condition (30,31). Observational studies suggest that antioxidant supplementation can modulate oxidative stress and reduce the risk of Alzheimer's disease (32). Many mechanisms have been postulated to explain the effect of ALA in Alzheimer's disease: one recent pilot study showed that combination therapy with omega-3 and ALA may reduce functional and cognitive decline in patients with mild and moderate Alzheimer's disease (33). ALA down-regulates the pro-inflammatory redox-sensitive transduction processes, including NF-ϰβ translocation, with a reduction in the release of further free radicals and cytotoxic cytokines. ALA is able to down-regulate inflammatory processes by modulating the pro-inflammatory cytokines (29), and it can influence oxidative stress by increasing intracellular glutathione levels (34,35). One study has shown that ALA improves mitochondrial enzyme activity and reduces the levels of lipid peroxidation in the hepatic and renal mitochondria of rats (36). Another study has shown that ALA may increase the mitochondrial synthesis of ATP in the brain of elderly rats, thereby increasing the activity of the mitochondrial enzymes (37). In an age-related reaction, the excess of metal ions (copper, iron and zinc) in the brain causes peptide precipitation and the formation of plaques. The abnormal combination of Aβ with copper and iron ions induces the production of hydrogen peroxide from molecular oxygen (38) with the consequent production of neurotoxic hydroxyl radicals. ALA is able to chelate transition metal ions and, therefore, modulate the iron- and copper-mediated oxidative stress in Alzheimer's plaques (39). This results in an increase in the extraction of Aβ peptide from the cortical areas (40). In an experimental mouse model of Alzheimer's, ALA was seen to increase the extraction of Aβ from the frontal cortex

that, like other metal chelators, could reduce the amyloid load in affected patients (40). ALA may also play a role in the activation of the choline acetyltransferase enzyme (ChAT), which is essential in the anabolism of acetylcholine (41,42). One experimental study has shown that in rats that had been administered ALA there was an inversion in the cognitive dysfunction with an increase in ChAT activity in the hippocampus (43). Another study showed the complete disappearance of enzymatic activity of purified ChAT after the dialytic removal of DHLA, whereas activity was restored by adding DHLA. The authors concluded that DHLA plays an essential role in the activity of this enzyme and that the relationship between reduced and oxidised ALA is important for the synthesis of acetylcholine (42). DHLA can act as a coenzyme in the ChAT reaction or it can reduce an essential functional cysteine residue of ChAT that no other physiological antioxidant, including reduced glutathione, is able to reduce.

Clinical studies

A number of clinical studies have been conducted to evaluate the effects of ALA in Alzheimer's disease. Unfortunately, as they all have methodological limitations, the conclusions that can be drawn from them have a merely indicative value.

In 2001, Hager et al. studied 9 subjects with Alzheimer's aged over 45 years. These patients received a standard treatment with acetylcholinesterase inhibitors - donepezil or rivastigmine - for three months before starting a dose of 600 mg of ALA for 12 months. The neuropsychological scales used were the Mini-Mental State Examination (MMSE) and the Alzheimer's disease assessment score cognitive subscale (ADAScog). After starting treatment with ALA, the results of these tests remained constant throughout the follow-up period of almost a year (44). A few years later, the same group published the results of a 48-month follow-up study including 43 patients with mild, moderate-early and moderate-advanced dementia. The results show a lower disease progression rate in the subjects taking ALA (600 mg/day) (45). However, the small sample size of the study and the absence of a control group constitute important limits.

Galasko et al. in 2012 conducted a double-blind, placebo-controlled trial on 78 Alzheimer's patients to evaluate biomarkers in the cerebrospinal fluid (CSF). In this trial, patients were randomised to three groups that received: (a) a combination of 800 IU/day of vitamin E (E), 500 mg/day of vitamin C (C) and 900 mg/day of ALA; (b) 1200 mg/day on co-enzyme Q; (c) placebo. Although the C/E and ALA combination reduced the CSF biomarker F2-isoprostane, showing a reduction in cerebral oxidative stress, none of the antioxidants altered the levels of CSF biomarkers associated with amyloid disease or tau protein. Furthermore, the E/C/ALA group presented a faster cognitive decline, based on MMSE scores, than the placebo group. These results suggest that further clinical studies are required to evaluate the benefits of ALA in cognitive decline (46).

In 2014, Shinto et al. studied 39 subjects with Alzheimer's Disease in a randomised, double-blind, parallel-group, 3-arm trial evaluating the efficacy of omega-3 fatty acids alone or in combination with ALA (600 mg/day) versus placebo. The purpose of the trial was to evaluate changes in oxidative stress biomarkers. The following cognitive and functional tests were also performed: MMSE, ADAScog and Activities of Daily Living / Instrumental Activities of Daily Living (ADL/IADL). After 12 months, none of the 3 groups presented significant differences in F2-isoprostane levels. The group treated with omega-3 presented a halt in decline on the IADL but no change in the MMSE and ADL scores. It is interesting to note that the omega-3 + ALA combination caused a slow-down in cognitive decline (considering both the MMSE and the IADL scores but not the ADAScog scores) (47).

In 2005, Bragin et al. suggested ALA as an approach for integrated treatment in patients with moderate dementia (MMSE < 15) and depression. In this trial, 35 subjects with an average age of 71 years were followed for 24 months. The treatment was composed of antidepressants, cholinesterase inhibitors, supplements and vitamins. Patients were also given dietary, exercise and stress control technique instructions. Neuropsychological assessment scales were used. The results showed that this treatment, administered for 2 years, slowed cognitive decline and improved the per-

formance of these patients. This effect can be partly explained by an improvement in the patients' overall mental health, due primarily to the depression treatment. The main limitations of this study were the lack of information on patient compliance and the concomitant use of other medicinal products. It is also difficult to establish which of the interventions produced a positive effect (48).

Possible mechanisms of the neuroprotective effect of alpha lipoic acid

In vivo and *in vitro* studies have been conducted to define the cellular and molecular effects of ALA underlying its activity on memory processes. The effects of ALA on oxidative markers in various areas of the brain have been discussed in a number of studies on animal models of ageing and degenerative diseases. The administration of ALA reduces lipid peroxidation in different areas of the brain and increases the activity of antioxidants such as ascorbate (vitamin C), α-tocopherol (vitamin E), glutathione, and also the activity of superoxide dismutase, catalase, glutathione-peroxidase, glutathione-reductase, glucose-6-P-dehydrogenase. Furthermore, administration of ALA inverts the increase in carbonyl protein levels in a radiation-induced cognitive dysfunction model and causes a decrease in carbonyl protein levels in elderly SAMP8 rats (49-51).

Liu et al. examined the effects of ALA on the mitochondrial structure, hippocampal neurodegeneration, and the nucleic acid oxidative damage in the hippocampus and cortex of elderly rats. ALA supplementation significantly reduced the levels of oxidised RNA and inverted age-induced structural mitochondrial damage in the hippocampus (52). In another study, conducted to evaluate the protective effect of ALA against damaged caused by arsenic-dichlorvos in rats, showed that cerebral oxidative stress and cholinergic dysfunction were significantly reduced by the administration of ALA (53).

The SAMP8 mouse is an experimental model that shows increased oxidative stress and memory decline associated with a rapid ageing process. The mechanisms underlying the inversion in the cognitive decline of SAMP 8 mice caused by ALA were determined by studying the expression and specific carbonylation of protein in the brain of 12-month-old SAMP8 mice after the administration of ALA or carrier. The levels of 3 proteins (neurofilament L triplet protein, a-enolase and ubiquitous mitochondrial creatine kinase) were significantly elevated, whereas protein carbonylation was reduced in lactate dehydrogenase B, in dihydropyraminidase-like protein 2 and in the a-enolase of elderly mice receiving ALA, suggesting that, in addition to improving learning and memory, ALA is able to restore certain proteins in the brains of elderly SAMP 8 mice (54).

In neurodegenerative disease models, treatment with ALA can improve the function of the dopamine, serotonin and norepinephrine neurotransmitters (49). In an Aβ vaccine-induced Alzheimer's disease model, mice treated with ALA presented increased levels of serotonin, dopamine and norepinephrine, whereas the concentration of the metabolites 5-hydroxyindole, acetic acid and homovalinic acid gradually normalised (55). Another study demonstrated that ALA can improve the neurological damaged induced by excess Aβ and aluminium, thereby restoring AChE activity (56). In a $AlCl_3$-induced neurodegeneration model, ALA showed the ability to improve cognitive functions and increase cholinergic system functions. Treatment with ALA increased the expression of genes encoding for muscarine receptors M1 and M2 and for choline acetyltransferase in the group treated with $AlCl_3$- (57).

Both ALA and DHLA have been seen to inhibit the formation of Aβ fibrils and their expansion, and they also weaken pre-formed fibrils in a dose-dependent manner (58). Furthermore, DHLA alone has been seen to have a significant neuroprotective action against the neurotoxicity induced by Aβ and by iron/hydrogen peroxide (59).

Conclusions

Although the mechanisms of action of ALA are not yet completely clear, it is evident that a multitude of pathways underlie its neuroprotective capacity.

Scientific evidence shows that ALA possesses the ability to improve memory capacity in a number of ex-

perimental neurodegenerative disease models and in age-related cognitive decline in rodents. Studies have shown that this substance is able to reduce memory loss in various behavioural paradigms of Alzheimer's disease and in age-related cognitive dysfunctions.

In vivo and *in vitro* studies have shown that ALA has a positive intervention in the neurodegenerative processes of the hippocampus, by reducing neuronal apoptosis and supporting a neuroprotective role mediated by the mitochondrial cell death process. ALA is also able to inhibit the formation of Aβ fibrils, thereby improving the consequent neurological damage, and it significantly restores AChE activity. This latter property suggests that ALA has a potential role in improving cholinergic and cognitive function. These neuroprotective effects can be associated with ALA's ability to improve the memory loss associated with neurodegenerative diseases.

Although they have yielded promising results, the clinical studies conducted in humans to date present a number of limitations - small sample size, open-label design, concomitant use of other antioxidants - that make it impossible to draw appropriate conclusions regarding the use of ALA in neurodegenerative diseases and memory disorders.

The improvements in memory and cognitive capacity and the neuroprotective activity shown by ALA support the hypothesis that it could be used as a supplementary treatment in neurodegenerative diseases and provide the rationale for clinical trials with an *ad hoc* design.

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