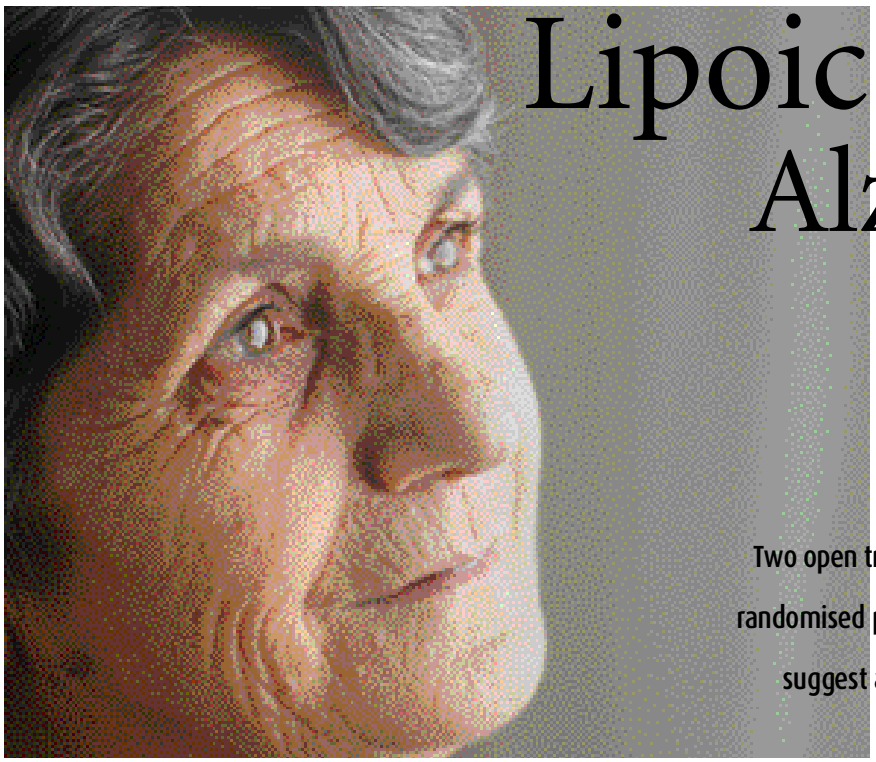

Lipoic acid for Alzheimer's disease

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Two open trials in Germany and a pilot double-blind, randomised placebo-controlled trial in the USA might suggest a long-term substantial benefit for lipoic acid in treating Alzheimer's disease.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that destroys patient memory and cognition, communication skills and ability to perform activities of daily living. It affects up to 40% of people over 85 years of age. Despite extensive research into the pathogenesis of AD, a neuroprotective treatment is still unavailable for clinical use – particularly for the early stages of disease.

Alpha lipoic acid (LA), an antioxidant that has been registered as a medicine in Germany for diabetic neuropathy since 1966, might offer benefits for patients with AD. LA has been shown to improve both neuropathic symptoms and neuropathic deficits in four clinical trials (ALADIN I, ALADIN III, SYDNEY and NATHAN II) involving a total of 1258 patients.[1] LA has been shown in clinical trials to be effective for various neurological conditions, such as sciatic pain caused by a herniated disc,[2] compressive radiculopathy syndrome from disc–nerve root conflict[3] and carpal tunnel syndrome.[4] In patients with type 2 diabetes, LA has been found to improve vascular endothelial function.[5] Some interesting positive results have been observed for intravenous LA (in combination with hydroxycitrate or low-dose naltrexone) in treating cancer progression,[6,7] and in treating weight gain in patients taking antipsychotic medications.[8]

LA is not currently used clinically to treat dementia in Australia. We propose it as a novel and cost effective therapeutic approach, particularly for mild cognitive impairment and early stage AD.

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Preparations

Most preparations of LA contain a 1:1 mixture of two enantiomers ('mirror images'). LA occurs naturally only as the R-form, but pharmacological formulations have extensively used a racemic mixture of R-lipoic acid (RLA) and S-lipoic acid (SLA), which is cheaper to manufacture and polymerises less readily than the pure enantiomers. There is ongoing debate about whether RLA has important advantages over the racemic form in terms of biological effects. However, there is increasing evidence that RLA has substantially higher bioavailability than the racemic form.[9]

Modes of action

LA is a naturally occurring cofactor in the human body, necessary for the function of enzymes involved in glucose metabolism. It has a multitude of properties that might be able to interfere with the pathogenesis of AD.[9,10] For example, it has been shown that LA can:

- increase the level of the neurotransmitter

acetylcholine (which is severely depleted in AD) by activation of choline acetyltransferase
- increase glucose uptake, providing more energy for neuronal signalling (e.g. for maintenance of ion gradients across the neuronal membrane)
- chelate redox-active transition metals such as iron, inhibiting the formation of hydroxyl radicals from hydrogen peroxide
- scavenge reactive oxygen species, regenerating other biological antioxidants such as coenzyme Q10, vitamins C and E and increasing the level of reduced glutathione (an endogenous antioxidant)
- down-regulate inflammatory processes, by interfering with signal transduction pathways that involve reactive oxygen species as intracellular signal transduction molecules
- scavenge neurotoxic lipid peroxidation products such as acrolein and hydroxynonenal, and
- up-regulate antioxidant defense enzymes, including those responsible for glutathione synthesis.

Studies in animal models

Protective effects of LA against cognitive deficits have been shown in studies conducted in rats,[11] mice[12] and dogs.[13] In one study, a diet supplemented with RLA was fed to aged rats to determine efficacy in reversing the decline in metabolism that occurs with age.[14] In the control group, ambulatory activity (a measure of general metabolic activity) was almost three-fold lower in old rats than in young rats, but this decline was reversed in the group that received the RLA supplement. In a further study, effects on cognitive function, brain mitochondrial structure and biomarkers of oxidative damage were studied after feeding old rats acetyl-l-carnitine (ALCAR) and/or RLA.[15] Dietary supplementation with ALCAR and/or RLA improved memory, the combination being the most effective for two different tests of spatial memory and for temporal memory.

Similar experiments were performed in the senescence-accelerated-prone mouse strain 8 (SAMP8), which exhibits age-related deterioration in memory and learning along with increased oxidative markers.[12] Long-term administration of LA was shown to improve the cognition of 12-month-old SAMP8 mice in the T-maze footshock avoidance paradigm and lever press appetitive task. Furthermore, treatment with LA reversed various indices of oxidative stress in the mice.

Potential beneficial effects of LA have also been investigated in the amyloid peptide overproducing Tg2576 mouse, a transgenic mouse model of AD.[16] The mice treated with LA for six months exhibited significantly improved learning and memory retention than untreated mice. Plaque load was not reduced, and the researchers concluded that long-term dietary LA supplementation can reduce hippocampal-dependent memory deficits in these mice without affecting beta-amyloid levels or plaque deposition.

In a further study, aged beagle dogs were taught how to find a food treat by identifying certain markers. The dogs received a dietary supplement of LA in combination with ALCAR or placebo. On one task, four of the six dogs receiving the supplemented diet quickly learned to find the food treat by identifying the correct marker, whereas only two of the six dogs receiving the normal diet succeeded. After 15 more weeks of training, more than 80% of dogs in the treatment group were successful at learning the new task, compared with only 50% of the placebo group. The authors concluded that the dogs that received the supplement were much more readily able to learn new things as well, even at an advanced age.

Studies in patients with Alzheimer's disease

Early studies

Although LA has been used to treat diabetic polyneuropathy in Germany since 1966, no epidemiological study has taken advantage of this large patient population and investigated the incidence of AD in the group. The first indication for a beneficial effect of LA in AD came from a patient with an unusually slow progressing form of AD.[17] In 1997, a 74-year-old woman presented at a hospital in Hannover with signs of cognitive impairment. Diabetes mellitus and a mild form of polyneuropathy were her main concomitant diseases. The patient was diagnosed with early stage AD: she satisfied clinical criteria of DSM-III-R for AD and demonstrated deficits in neuropsychological tests. A typical SPECT showed a decreased bitemporal and biparietal perfusion; an MRI did not demonstrate signs of ischaemia. Treatment with an acetylcholinesterase inhibitor was initiated; her existing LA treatment for diabetic polyneuropathy (600 mg/day) was continued.

Since 1997, several tests have been repeated for the patient and shown no substantial decline of her cognitive functions. Therefore, the diagnosis of mild AD was re-evaluated several times, but the diagnostic features did not change and neuropsychological tests showed an unusually slow progress of cognitive impairment.

This observation inspired an open pilot trial with LA at the Henriettenstiftung Hospital in Hannover in 1999.[17] LA was given once daily (600 mg, 30 minutes before breakfast) to nine patients (age, 67 ± 9 years) who were receiving standard treatment with acetylcholinesterase inhibitors (observation period, 337 ± 80 days). The patients had probable AD (Mini-Mental State Examination [MMSE], 23 ± 2 points). Cognitive performance before and after addition of LA to their standard therapy was compared. Before initiation of the LA regimen, a steady decrease in cognitive performance was observed (-2 points/year in MMSE and +4 points/year in the AD Assessment Scale-cognitive subscale ([ADAS-cog]). Treatment with LA led

to a stabilisation of cognitive functions, which was demonstrated by constant scores in the MMSE and ADAS-cog for nearly a year.

This trial was continued and finally included 43 patients, who were followed for up to 48 months.[18] In patients with mild dementia (ADAS-cog, <15), the disease progressed extremely slowly (ADAS-cog, +1.2 points/year; MMSE, -0.6 points/year) compared with the average cognitive decline of control groups in published clinical trials (ADAS-cog, +2 to 4 points/year, MMSE; -2 to 4 points/year). However, the trial was small and not randomised. In addition, patients were diagnosed with probable AD, and the diagnoses (in nearly all cases) have not yet been confirmed by postmortem analysis.

Randomised controlled trial

The first randomised, double-blind, placebo-controlled 12-month pilot study involving LA was conducted in 39 patients in Portland, Oregon, USA (ClinicalTrials.gov identifier: NCT00090402, publication in progress). Inclusion criteria included all of the following:

- age 55 years or older
- diagnosis of probable AD (mild to moderate)
- MMSE score, 15 to 26
- Clinical Dementia Rating Scale, 0.5 to 1.0
- absence of depression
- general health status that would not be expected to interfere with ability to participate in and complete the study.

Patients were allowed to continue existing doses of medications for cognitive impairment (e.g. acetylcholinesterase inhibitors, memantine) and existing doses of dietary supplements (e.g. ginkgo, vitamin E). They were excluded from the study if they were eating more than one serving of fish per week or taking fish oil or LA supplements.

Study participants were randomised to one of three treatment groups:

- placebo
- omega-3 fatty acids
- omega-3 fatty acids plus LA.

Omega-3 fatty acids were given in the form of a fish oil concentrate (3 g/day), which provided a daily dose of 675 mg docosahexaenoic acid (DHA) and 975 mg eicosapentaenoic acid (EPA). Lipoic acid was given as the racemic form (600 mg/day). The primary outcome measure was peripheral F2-isoprostane levels (a marker of oxidative stress).

Of 39 patients who were randomised, 32 completed their 12-month visit. At baseline, there was no difference between groups on medication use for cognitive impairment (p=0.50).

At the end of the study, there was no difference between the three groups in F2-isoprostane levels in blood (p=0.10). For secondary clinical measures, there was a significant delayed decline in MMSE score between groups favouring the group that received the fish oil plus LA (p=0.04) over the 12-month period. The mean change in MMSE from baseline was -4.6 (SD 4.7) for the placebo group compared with -1.0 (SD 2.3) for the group that was given omega-3 fatty acids plus LA. There was no difference between the groups in ADAS-cog scores (p=0.54). This is as yet unpublished data.

Safety

No upper limit for LA intake in humans has been established, but adverse health effects have been assessed in clinical trials. The ALADIN (I, II and III), SYDNEY (I and II) and ORPIL clinical trials used LA supplements of up to 2400 mg/day, with no reported adverse effects compared with placebo.[19] LA has also been administered intravenously in doses of 600 mg/day for three weeks with no evidence of serious side effects in humans.[20]

Drug interactions

LA can improve insulin-mediated glucose utilisation, so it is possible that LA supplementation could increase the risk of hypoglycaemia in diabetic patients using insulin or oral antidiabetic agents. Consequently, blood glucose levels should be monitored closely when LA is added to a treatment regimen for diabetes.

The chemical structure of biotin is similar to that of LA, and there is some evidence that high concentrations of LA can compete with biotin for transport across cell membranes. In rats, the administration of high doses of LA by injection has been shown to decrease the activity of two biotin-dependent enzymes by about 30%,[21] but it is not known whether LA supplementation substantially increases the requirement for biotin in humans.

Summary

AD affects a growing number of elderly people. At the moment, the most widely used medications (acetylcholinesterase inhibitors) deliver only symptomatic benefits. LA treatment has been shown to reduce markers of oxidative stress and to improve cognitive function in aged animals. The promising results found for combined omega-3 fatty acid and LA supplementation in the double-blind RCT and for LA alone in the open trial in delaying cognitive decline warrant further investigation of LA in combination with other anti-inflammatory compounds for the treatment of AD. Further research should include longer studies, conducted with patients in different stages of the disease. MT

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A list of references is available on request to the editorial office.

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