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# α-Lipoic Acid in the Treatment of Diabetic Polyneuropathy and Alzheimer's Disease

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## ABSTRACT

α-lipoic acid (LA) is a naturally occurring cofactor for mitochondrial enzymes, including pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). LA acts as a powerful micronutrient with diverse pharmacological properties. LA improves glucose uptake and insulin sensitivity, and thus decreases blood glucose levels and increases mitochondrial energy levels. LA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals from hydrogen peroxide and also scavenges reactive oxygen species, thereby increasing the levels of reduced glutathione. Via the same mechanisms, down-regulation of redox-sensitive inflammatory processes is achieved. Furthermore, LA can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. LA is currently studied for the treatment of some neurodegenerative diseases with diverse pathophysiology, including diabetic polyneuropathy and Alzheimer's disease (AD). For diabetic polyneuropathy, LA has been used for decades in Germany with a number of clinical trials showing benefits in insulin-stimulated glucose uptake and attenuating symptoms of neuropathy. In AD, an open-label trial in patients with mild and moderate AD is currently conducted at a at the memory clinic of the Henriettenstiftung hospital in Hannover, Germany. Interim analysis of the data after 4 years show that the progression rate of the patient treated with 600 mg LA daily is significantly slower than to the non-treated control group – particularly in early stages of dementia – and other control groups in published studies.

**Keywords:** antioxidants, clinical trials, inflammation, glucose metabolism, neurodegeneration

## CONTENTS



## INTRODUCTION

α-lipoic acid (LA) is currently being investigated for the treatment of a variety of neurological and neurodegenerative diseases with diverse pathophysiologies, including Alzheimer's disease (AD). This review advances the hypothesis that the multiple pharmacological properties of LA target the defined pathogenic processes known to be common to all neurodegenerative diseases.

## DIABETIC POLYNEUROPATHY

Diabetic polyneuropathy (DPN) is one of the most common long-term sequelae of diabetes mellitus, one of the most rapidly growing health problems in the world. All types of diabetic patient may develop neuropathy with prevalence increasing with the duration of diabetes; up to 50% of all patients develop neuropathic symptoms within 25 years of the onset of diabetes. DPN leads to serious disability and increased mortality. Patients with this syndrome show a gene-

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ral lower quality of life since they may also become depressed or anxious and may have trouble with work, social obligations, sleep and other daily activities. There are varied clinical presentations of DPN with involvement of proximal or distal peripheral sensory and motor nerves (diabetic peripheral neuropathy), as well as autonomic nerves (diabetic autonomic neuropathy) (Little *et al.* 2007; Said 2007).

The causes of neuropathy are not fully understood and are probably different for different types of diabetic neuropathy. Nerve damage is probably caused by a number of factors, of which three are accepted to be primary:

a) metabolic factors: predominantly high blood glucose levels (with an element of duration), possibly low levels of insulin (not in type II diabetes), and abnormal blood fat levels (Hayden and Tyagi 2004),

b) neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to the nerves (Dickinson *et al.* 2002), and

c) inflammation caused by advanced glycation end products (AGEs) or factors released from dying and degenerating neurons (Bierhaus *et al.* 2005).

## ALZHEIMER'S DISEASE

AD is a progressive neurodegenerative brain disorder that gradually destroys a patient's memory and ability to learn, make judgments, communicate with the social environment and carry out daily activities. Initially, short-term memory is affected, due to neuronal dysfunction and degeneration in the hippocampus and amygdala. As the disease progresses, neurons degenerate and die in other cortical regions of the brain, leading to dramatic changes in personality and behaviour; typically mainifesting as anxiety, suspiciousness or agitation, as well as delusions or hallucinations.

AD is characterized by two major morphopathological hallmarks: the deposition of extracellular neuritic, β-amyloid peptide-containing senile plaques in hippocampal and cerebral cortical regions of Alzheimer's patients is accompanied by the presence of intracellular neurofibrillary tangles that occupy much of the cytoplasm of particular pyramidal neurons (Kosik 1994). Inflammation, as evidenced by the activation of microglia cells and astrocytes, is another hallmark of AD. Accumulation of AGEs and inflammation, particularly the induction of superoxide production ("oxidative burst"), is an important source of oxidative stress in AD patients. The inflammatory process occurs mainly around the amyloid plaques and is characterized by pro-inflammatory substances released from activated microglia (Wong *et al.* 2001). Reactive oxygen species (ROS) are the most prominent molecules in the inflammatory process, along with prostaglandins, IL-1β, IL-6, M-CSF and TNF-α. Besides these morphological alterations, AD is associated also with a markedly impaired cerebral glucose metabolism as detected by reduced cortical [$^{18}$F]desoxyglucose utilization in positron emission tomography (PET) of Alzheimer's patients and by reduced densities in cortical glucose transporter subtypes (Ishii and Minoshima 2005).

## LA – A MULTISPECIFIC DRUG FOR MULTIFACTORIAL DISEASES

### LA - the universal antioxidant

LA (1,2-dithiolane-3-pentanoic acid and known as thioctic acid in Europe) is a naturally occurring disulfide that has long been known to be an essential cofactor for mitochondrial bioenergetic enzymes including pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. In addition to the enzymatic role, *in vitro* and *in vivo* studies suggest LA acid also acts as a powerful micronutrient with diverse pharmacologic and antioxidant properties (Bilska and Wlodek 2005). Often described as "nature's perfect antioxidant" LA has been used for decades in Germany for the treatment of diabetic polyneuropathy.

LA is a very small molecule that is efficiently absorbed and easily crosses cell membranes. Unlike vitamin E (primarily fat-soluble) and vitamin C (readily water-soluble), LA can quench either water- or fat-soluble free radicals both inside and outside the cell. These diverse actions suggest that LA can act by multiple mechanisms in different cell compartments both physiologically and pharmacologically, many of which are only now being explored. It should be noted that the reduced form of LA, dihydrolipoic acid (DHLA) is the active compound providing nearly all the pharmacological benefits but is readily oxidized precluding long-term storage. For most indications, however, LA may be administered as this is reduced by mitochondrial lipoamide dehydrogenase (part of the pyruvate dehydrogenase complex) to yield DHLA *in situ*. The human body produces only very small quantities of LA – importantly, this is manufactured in its enzyme bound form rather than being freely available. Thus, the only way to provide free LA in pharmacological dose is by intravenous or oral supplementation, usually in doses of 600 mg to 1800 mg daily. LA contains an asymmetric carbon, yielding the optical isomers R-LA and S-LA. Only the R-isomer is endogenously synthesized but LA supplements may contain either R-LA or a 50/50 (racemic) mixture of R-LA and S-LA.

### Safety profile of LA

LA has been used in Germany for decades and is considered safe for humans at the recommended dosages of 600 to 1800 mg per day. The oral $LD_{50}$ for experimental rodents was found to be between 500 and 1000 mg kg$^{-1}$. In a recent safety study in rats, no significant difference between control and groups treated with 31.6 or 61.9 mg kg$^{-1}$ day$^{-1}$ with regard to body weight gain, feed consumption, animal behaviour, or haematological and clinical chemistry parameters was observed (Cremer *et al.* 2006). The only notable finding in rats of both sexes dosed at 180 mg kg$^{-1}$ day$^{-1}$ was a reduction in food intake relative to the controls and a concomitant decrease in body weight. In LA treated groups, mortality was slightly lower as compared to the untreated control (Cremer *et al.* 2006). In humans, the most frequently reported side effects to oral LA supplementation are allergic reactions affecting the skin, including rashes, hives and itching. Gastrointestinal symptoms, including abdominal pain, nausea, vomiting and diarrhoea have also been reported (Cremer *et al*. 2006).

In a further safety study, co-administration of LA with other anti-diabetic medications such metformin, sulfonylureas, acarbose, troglitazone and insulin (either as monotherapy or in combination) orally to 21 patients with type 2 diabetes (900 mg of R-LA daily for 6 weeks, followed by 1,200 mg of R-LA daily for an additional 6 weeks) did not lead to changes in either liver or kidney function or hematologic profiles (Evans *et al.* 2002).

Since the chemical structure of biotin is similar to that of LA, is might be possible that high concentrations of LA can compete with biotin for transport across cell membranes. The administration of high doses of LA by injection to rats decreased the activity of two biotin-dependent enzymes by about 30-35%; but it is not known whether LA supplementation substantially increases the requirement for biotin in humans (Zempleni *et al.* 1997).

### Pharmacokinetics of LA

Consumption of LA in foods has not yet been found to result in detectable increases of free LA in human plasma or cells. In contrast, high intravenous or oral doses of free LA (50 mg or more) result in significant but transient increases in free LA in plasma and cells. Exogenous racemic LA orally administered for the symptomatic treatment of diabetic polyneuropathy is readily and nearly completely absorbed, with a limited absolute bioavailability of about 30% caused by high pre-systemic elimination. Oral LA supplements are better absorbed on an empty stomach than with food. Taking racemic LA with food decreased peak plasma

concentrations by about 30% and total plasma concentrations by about 20% compared to fasting. After oral dosing with racemic LA, peak plasma concentrations of R-LA were found to be 40-50% higher than S-LA, suggesting R-LA is better absorbed than S-LA (Teichert *et al.* 2003), supporting the hypothesis that this isomer may be actively absorbed by the biotin carrier.

## BIOCHEMICAL PROPERTIES AND PHYSIOLOGICAL EFFECTS OF LA

### Antioxidant effect of LA including its regenerating effect for other antioxidants

LA is a potent lipophilic and hydrophilic antioxidant, which is able to scavenge a variety of reactive oxygen species such as hydroxyl radicals, hypochlorous acid, and singlet oxygen. LA itself is not able to scavenge the superoxide radical, but the reduced form DHLA is able to scavenge superoxide and peroxyl radicals. One of the most beneficial effects of DHLA is its ability to regenerate other essential antioxidants such as vitamin C, vitamin E, coenzyme Q10 and glutathione, strengthening the view that LA is a "catalytical" antioxidant (Kagan *et al.* 1992; Nohl and Gille 1998). The evidence is especially strong for the ability of DHLA to recycle vitamin E, which is apparently achieved directly by quenching tocopherol radicals or indirectly by reducing vitamin C or increasing the levels of ubiquinol (a derivative of CoQ) and glutathione, which, in turn, help to regenerate tissue levels of vitamin E. GSH is an essential antioxidant, which scavenges hydroxyl radicals, the most dangerous type of free radicals found in the body. Recent studies have shown that when LA is added to various types of animal and human cells in tissue culture, it causes a significant increase in cellular GSH levels (Deuther-Conrad *et al.* 2001; Hultberg and Hultberg 2006).

### LA as an anti-inflammatory agent (via inhibition of redox-signalling)

Increased formation of AGEs through higher extracellular glucose and intracellular methylglyoxal levels is a characteristic of diabetes. Binding of AGEs to the receptor for advanced glycation end products (RAGE) results in activation of the transcription factor nuclear factor kappa B (NF-κB), and subsequent expression of NF-κB-regulated cytokines (Dukic-Stefanovic *et al.* 2003). This has been shown to be a relevant pathomechanism in diabetic complications including polyneuropathies (Bierhaus *et al*. 2005). In this pathway, much attention has been paid to reactive oxygen species (ROS) as mediators in signalling processes – termed "redox-sensitive signal transduction". ROS modulate the activity of cytoplasmic signal transducing enzymes by two different mechanisms: oxidation of cysteine residues or reaction with iron-sulphur clusters. LA can scavenge intracellular free radicals (acting as second messengers), downregulate pro-inflammatory redox-sensitive signal transduction processes including NF-κB translocation, and thus attenuates the release of more free radicals and cytotoxic cytokines (Wong *et al.* 2001).

### LA stimulates glucose uptake and utilization ("insulinomimetic") and increases insulin sensitivity

Reactive oxygen and nitrogen molecules serve as signaling molecules that are involved in the regulation of cellular function. The chronic and/or increased production of these reactive molecules or a reduced capacity for their elimination, termed oxidative stress, can lead to abnormal changes in intracellular signaling and result in chronic inflammation and insulin resistance. Although LA's primary effect in improving neuropathy is thought to be the result of its antioxidant effects, it has also been shown to lead to an improvement in blood sugar metabolism, improve blood flow to peripheral nerves and to stimulate the regeneration of nerve fibers in animal models. Improved blood sugar metabolism is a result of both effects on glucose metabolism and an increase in insulin sensitivity in insulin-sensitive tissues (e.g. liver and muscle). At the cellular level, one described cause of insulin resistance is impaired signalling between the insulin receptor and downstream effectors such as insulin-receptor substrate 1 (IRS-1). Activation of stress activated kinases by oxygen free radicals leads to the phosporylation of IRS-1 on serine and threonine residues, thus impairing normal signalling function (Evans *et al.* 2005).

A decrease in oxidative stress attenuates the activation of these stress kinases and thus normalizes insulin signalling and decreases insulin resistance. Furthermore, recent investigations indicate that LA can affect central and peripheral modulation of 5'-AMP-activated protein kinase, activate PPAR-α and PPAR-χ, modulate PPAR-regulated genes and upregulate the expression of PPAR-χmRNA (Pershadsingh 2007).

### LA as a metal chelator

LA has been used for decades as a metal chelator to treat acute heavy metal poisoning (Pande and Flora 2002; Sumathi *et al.* 1996). In Alzheimer's disease, there is now compelling evidence that Aβ, the main component of amyloid plaques in the AD brain, does not spontaneously aggregate, but that there is an age-dependent reaction with excess brain metal ions (copper, iron and zinc), which induces the peptide to precipitate and form plaques. The abnormal combination of Aβ with $Cu^{+}$ or $Fe^{++}$ induces the production of hydrogen peroxide from molecular oxygen, which then further react to yield the neurotoxic hydroxyl radical by the Fenton or Haber-Weiss reactions. Because LA is a potent chelator of divalent metal ions *in vitro*, Suh et al monitored whether feeding R-LA could lower cortical iron and improve antioxidant status. Results show that cerebral iron levels in old LA-fed animals were lower when compared to controls and were similar to levels seen in young rats. These results demonstrate that LA supplementation may be a means to modulate the age-related accumulation of cortical iron content, thereby lowering oxidative stress associated with aging (Suh *et al.* 2005). Although it has not been tested yet whether LA reduces the amount of redox-active transition metal ions in plaques of patients, these experimental data strongly suggest that LA could be able to remove transition metals from plaques and lower oxidative stress in AD patients (Fonte *et al.* 2001; Veurink *et al.* 2003).

### LA as a carbonyl scavenger

Cell and mitochondrial membranes contain a significant amount of arachidonic and linoleic acids, precursors of lipid peroxidation products (LPOs), 4-hydroxynonenal (HNE) and 2-propen-1-al (acrolein) that are extremely reactive. Acrolein decreases PDH and KGDH activities by binding to LA, a component in both the PDH and KGDH complexes, probably explaining the loss of enzyme activity. However, supplemented LA could assist in scavenging LPOs or help replace inactivated LA from damaged PDH and KGDH. Acrolein, which is increased in AD brain, may be partially responsible for the dysfunction of mitochondria and loss of energy found in AD brain by inhibition of PDH and KGDH activities, potentially contributing to the neurodegeneration in this disorder (Pocernich and Butterfield 2003).

## BENEFICIAL EFFECTS OF LA IN CELL CULTURE AND ANIMAL MODELS OF DPN AND AD

### Potential beneficial effects of LA in animal models of DPN

A variety of animal models of diabetic polyneuropathy (most notably streptozotocin-induced diabetic neuropathy) have been used to evaluate potential beneficial effects of

LA. In one study, a rise in erythrocyte glutathione by 27% and a trend towards decreased plasma malondialdehyde in LA treated animals in comparison with the placebo group was observed. Simultaneously, sciatic nerve blood flow and vascular resistance were improved by daily LA administration by 38%. However, peripheral nerve conduction velocity and endoneurial glutathione were not significantly influenced by LA treatment (van Dam 2002). In another study, the efficacy of LA supplementation in improving nerve blood flow (NBF) in streptozotocin-induced diabetic neuropathy (SDN) electrophysiology and indexes of oxidative stress in peripheral nerves affected by SDN, at 1 month after onset of diabetes and in age-matched control rats was investigated. LA, in doses of 20, 50, and 100 mg per kg, was administered intraperitoneally five times per week after onset of diabetes. NBF in SDN was reduced by 50%; LA did not affect the NBF of normal nerves but improved that of SDN in a dose-dependent manner. After 1 month of treatment, LA supplemented rats (100 mg $kg^{-1}$) exhibited normal NBF. The most sensitive and reliable indicator of oxidative stress was reduction in reduced glutathione, which was significantly reduced in streptozotocin-induced diabetic and α-tocopherol-deficient nerves; which was improved in a dose-dependent manner in LA supplemented rats. The conduction velocity of the digital nerve was reduced in SDN and was significantly improved by LA (Nagamatsu *et al.* 1995).

A further study reports highly selective effects of administration of LA to streptozotocin-injected diabetic rats. LA improved digital sensory but not sciatic-tibial motor nerve conductance velocity (NCV), corrected endoneural nutritive but not composite NBF, increased the mitochondrial oxidative state without correcting nerve energy depletion, and enhanced the accumulation of polyol pathway intermediates without worsening *myo*-inositol or taurine depletion (Stevens *et al.* 2000).

It also been shown that pretreatment of diabetic rats with LA improves wound healing. Rats were made diabetic with streptozotocin (STZ) and treated systemically on alternative days with LA (100 mg $kg^{-1}$ given via intraperitoneal injection) for 8 weeks. Untreated STZ-diabetic rats and non-diabetic rats served as control. At the end of the 8-week period, rats from all the three groups were subjected to abrasion wound formation. Skin wounds healed more rapidly in untreated non-diabetic rats than in the untreated diabetic rats. Wounds in LA-treated diabetic rats healed more rapidly than wounds in untreated diabetic rats. These findings suggest that prophylactic use of a-LA might be useful in preventing the development of non-healing skin ulcers from minor traumas in at-risk skin such as in the diabetic foot (Lateef *et al.* 2005).

In another study, the effects of 2-week treatments with LA on endoneural blood flow, nerve conduction parameters, lipids, coagulation, and endothelial factors, in rats with streptozotocin-induced diabetes were studied. Compared with their nondiabetic littermates, untreated diabetic rats had impaired sciatic motor and saphenous sensory nerve-conduction velocity, reduced endoneurial blood flow and increased serum triglycerides and cholesterol. Treatment effectively corrected the deficits in NCV and endoneural blood flow. LA was also associated with significant decreases in fibrinogen, factor VII, von Willebrand factor and triglycerides. Blood glucose and hematocrit levels were not significantly altered by treatments. These data suggest that the marked effects of LA in lowering lipid and hemostatic risk factors for cardiovascular disease indicate potential additional antithrombotic and anti-atherosclerotic actions that could be of benefit in human diabetes (Ford *et al.* 2001). In summary, a plenitude of animal study based evidence points to a possible interference of LA with pathogenic principles of DPN.

## POTENTIAL BENEFICIAL EFFECTS OF LA IN CELL CULTURE AND ANIMAL MODELS OF AD

### Protection of cultured neurons against toxicity of amyloid, iron and other neurotoxins by LA

Neurotoxicity of beta-amyloid (Aβ), the major component of the senile plaques, is contributes to neuronal degeneration in AD by stimulating formation of free radicals (Liu *et al.* 2007). Thus LA, which is able to cross the blood-brain barrier, would seem an ideal substance in the treatment of AD. Zhang *et al*. have investigated the potential effectiveness of racemic LA against cytotoxicity induced by Aβ (30 μM) and hydrogen peroxide (100 μM) in primary neurons of rat cerebral cortex and found that treatment with LA protected cortical neurons against cytotoxicity induced by both toxins (Zhang *et al.* 2001). In a similar study, Lovell et al investigated the effects of racemic LA and its reduced form, DHLA, in neurons (hippocampal cultures cultures) treated with Aβ (25-35 μM) and iron/hydrogen peroxide ($Fe/H_2O_2$). Pretreatment of neurons with LA significantly protected against Aβ and $Fe/H_2O_2$ toxicity, whereas concomitant treatment of cultures with LA and $Fe/H_2O_2$ potentiated the toxicity. In contrast, DHLA significantly protects against both Aβ and $Fe/H_2O_2$ mediated toxicity (Lovell *et al.* 2003).

In a further study, Müller and Krieglstein have tested whether pretreatment racemic LA can protect cultured neurons against injury caused by cyanide, glutamate, or iron ions. Neuroprotective effects were only significant, when the pretreatment with LA occurred for >24 h or from the day of plating onward prevented the degeneration of chick embryo telencephalic neurons. They authors conclude that neuroprotection occurs only after prolonged pretreatment with LA is probably due to the radical scavenger properties of endogenously formed DHLA (Muller and Krieglstein 1995). In summary, data from these studies suggest that pretreatment of neurons with LA before exposure to Aβ or $Fe/H_2O_2$ (or application of DHLA) significantly reduces oxidative stress and increases cell survival. Concomitant application of Aβ or $Fe/H_2O_2$ with LA can temporarily increase oxidative stress, because the reduction of LA by the pyruvate dehydrogenase complex consumes reducing equivalents and inhibits energy production. In a clinical setting, however, after the first dose of LA is given, the LA/DHLA equilibrium needs time to establish after an initial brief "prooxidant" period, and the beneficial effects of LA will continue thereafter.

### Protection of LA against age-related cognitive deficits in aging rats and mice

A protective effect of LA against cognitive deficits has been shown in a few studies in aged rats and mice. In one study, a diet supplemented with R-LA was fed to old rats to determine its efficacy in reversing the decline in metabolism seen with age. Young (3-5 months) and old (24-26 months) rats were fed a diet with or without R-LA (0.5% w/w) for 2 weeks. Ambulatory activity, a measure of general metabolic activity, was almost threefold lower in untreated old rats vs. controls, but this decline was reversed ($P<0.005$) in old rats fed R-LA (Hagen *et al.* 1999). In a combination treatment study, the effects on cognitive function, brain mitochondrial structure and biomarkers of oxidative damage were studied after feeding old rats a combination of acetyl-l-carnitine (ALCAR) [0.5 or 0.2% w/v in drinking water], and/or R-LA [0.2 or 0.1% w/w in diet]. Spatial memory was assessed by using the Morris water maze; temporal memory was tested by using the peak procedure (a time-discrimination procedure). Dietary supplementation with ALCAR and/or LA improved memory, the combination being the most effective for two different tests of spatial memory ($P<0.05$; $P<0.01$) and for temporal memory ($P<0.05$). The authors suggest that feeding ALCAR and LA to old rats improves performance on memory tasks by lowering oxidative damage and

improving mitochondrial function (Liu and Min 2002). Feeding the substrate ALCAR with LA restores the velocity of the reaction ($K_m$) for ALCAR transferase and mitochondrial function. The principle appears to be that, with age, increased oxidative damage to protein causes a deformation of structure of key enzymes with a consequent lessening of affinity (Km) for the enzyme substrate (Ames and Liu 2004). Activation of a key enzymatic reaction by LA follows a similar principle as the LA induced increase acetylcholine production by activation of choline acetyltransferase (Haugaard and Levin 2002). 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 and provides a good model for disorders with age-related cognitive impairment. In one study, the ability of LA (and also NAC) to reverse the cognitive deficits found in the SAMP8 mouse, was investigated. Chronic administration of LA improved cognition of 12-month-old SAMP8 mice in the T-maze footshock avoidance paradigm and the lever press appetitive task. Furthermore, treatment of 12-month-old SAMP8 mice with LA reversed all three indexes of oxidative stress. These results provide further support for a therapeutic role for LA in age and oxidative stress-mediated cognitive impairment including that of AD (Farr *et al.* 2003).

## CLINICAL TRIALS WITH LA

### Effects of LA in patients with diabetic peripheral neuropathy

LA has been used for nearly 30 years in Europe to treat diabetic neuropathy in human patients and is safe and well tolerated. In a reasonable number of studies, LA has been shown to significantly and rapidly reduce the frequency and severity of symptoms of the most common kind of diabetic neuropathy. So far, seven controlled randomized clinical trials of LA in patients with diabetic neuropathy have been completed using different study designs, durations of treatment, doses, sample sizes, and patient populations. Among those, the ALADIN I (Alpha-LA in Diabetic Neuropathy) and ALADIN III studies were multicenter trials including out-patients from 38 and 71 diabetes centers and general practitioners in Germany, respectively (Ziegler 2004). The SYDNEY (Symptomatic Diabetic Neuropathy) Study was a monocenter trial including in-patients from a hospital in Moscow, Russia (Ametov *et al.* 2003). The – unpublished – NATHAN (Neurological Assessment of Thioctic Acid in Neuropathy) II Study was a multicenter trial including out-patients from 33 diabetes centers in the USA, Canada, and Europe.

A comprehensive meta-analysis of these trials on the efficacy and safety LA (600 mg per day intravenously for 3 weeks) in diabetic patients with symptomatic polyneuropathy was performed recently. This meta-analysis included the largest sample of diabetic patients (n = 1258) ever to have been treated with a single drug or class of drugs to reduce neuropathic symptoms, and confirmed the favorable effects of LA.

Primary analysis involved a comparison of the differences in TSS from baseline to the end of iv treatment between the groups treated with LA or placebo. Secondary analyses included daily changes in TSS, responder rates (50% improvement in TSS), individual TSS components, Neuropathy Impairment Score (NIS), NIS of the lower limbs (NIS-LL), individual NIS-LL components, and the rates of adverse events. After 3 weeks the relative difference in favour of LA vs. placebo was 24.1% (13.5, 33.4) (geometric mean with 95% confidence interval) for TSS and 16.0% (5.7, 25.2) for NIS-LL. The responder rates were 52.7% in patients treated with LA and 36.9% in those on placebo. On a daily basis there was a continuous increase in the magnitude of TSS improvement in favour of LA vs. placebo, which was noted first after 8 days of treatment. Among the individual components of the TSS, pain, burning, and numbness decreased in favour of LA compared with placebo, while among the NIS-LL components pin-prick and touch-pressure sensation as well as ankle reflexes were improved in favour of LA after 3 weeks. The rates of adverse events did not differ between the groups. The following conclusions were be drawn from these trials: (i) short-term treatment for 3 weeks using intravenous LA (600 mg per day) reduces the chief symptoms of diabetic polyneuropathy by a clinically meaningful degree; (ii) this effect on neuropathic symptoms is accompanied by an improvement of neuropathic deficits, suggesting potential for the drug to favorably influence underlying neuropathy; (iii) oral treatment for 4–7 months tends to reduce neuropathic deficits and improve cardiac autonomic neuropathy; (iv) clinical and postmarketing surveillance studies have revealed a highly favorable safety profile of the drug (Ziegler *et al.* 2004).

The aim of the Sydney II study was to evaluate the effects of oral LA on positive sensory symptoms and neuropathic deficits in diabetic patients with distal symmetric polyneuropathy (DSP). In this multicenter, randomized, double-blind, placebo-controlled trial, 181 diabetic patients in Russia and Israel received once-daily oral doses of 600 mg (n = 45) (LA600), 1,200 mg (n = 47) (LA1200), and 1,800 mg (LA1800) of ALA (n = 46) or placebo (n = 43) for 5 weeks after a 1-week placebo run-in period. The primary outcome measure was the change from baseline of the Total Symptom Score (TSS), including stabbing pain, burning pain, paresthesia, and asleep numbness of the feet. Secondary end points included individual symptoms of TSS, Neuropathy Symptoms and Change (NSC) score, Neuropathy Impairment Score (NIS), and patients' global assessment of efficacy. Mean TSS did not differ significantly at baseline among the treatment groups and on average decreased by 4.9 points (51%) in ALA600, 4.5 (48%) in LA1200, and 4.7 (52%) in LA1800 compared with 2.9 points (32%) in the placebo group (all $P<0.05$ vs. placebo). The corresponding response rates (≥ 50% reduction in TSS) were 62, 50, 56, and 26%, respectively. Significant improvements favouring all three LA groups were also noted for stabbing and burning pain, the NSC score, and the patients' global assessment of efficacy. The NIS was numerically reduced. Safety analysis showed a dose-dependent increase in nausea, vomiting, and vertigo. Oral treatment with LA for 5 weeks improved neuropathic symptoms and deficits in patients with DSP. Although oral doses of 1200 and 1800 mg lead to a faster improvement – already significant after 3 weeks - in the TSS, 600 mg once daily appears to provide the optimum risk-to-benefit ratio (Ziegler *et al.* 2006).

There is also evidence for oral LA in autonomic neuropathy repairing damaged nerves that control organs such as the heart and digestive tract. The DEKAN (Deutsche Kardiale Autonome Neuropathie) study followed 73 people with diabetes who had symptoms caused by nerve damage affecting the heart. Treatment with 800 mg daily of oral LA showed statistically significant improvement compared to placebo and caused no significant side effects (Ziegler *et al.* 1997).

## CLINICAL TRIALS WITH LA IN AD

The first indication for a beneficial effect of LA in AD from an interesting case study. In 1997, a 74 year old patient presented herself at the Department of Medical Rehabilitation and Geriatrics at the Henriettenstiftung Hannover with signs of cognitive impairment. Diabetes mellitus and a mild form of polyneuropathy were her main concomitant diseases. With clinical criteria of DSM-III-R (category of mental disorder according to Diagnostic and Statistical Manual of Mental Disorders (DSM), deficits in the neuropsychological tests, a MRI without signs of ischemia and a typical SPECT showing a decreased bi-temporal and bi-parietal perfusion, early stage AD was diagnosed. A treatment with acetylcholinesterase inhibitors was initiated. The patient received 600 mg LA each day for treatment of her diabetic polyneuro-

pathy. Since 1997, several re-tests have been performed, which showed no substantial decline of the cognitive functions. Therefore, the diagnosis of mild AD was reevaluated several times, but the diagnostic features did not change and the neuropsychological tests showed an unusually slow progress of her cognitive impairment. At the present moment (2007), the patient is still able to live at home and to communicate with her environment satisfactorily.

These data inspired an open trial which was conducted by Prof. K. Hager at the Henriettenstiftung Hospital in Hannover. 600 mg LA (Thiocacid) was given daily to nine patients with AD and related dementias (receiving a standard treatment with acetylcholinesterase inhibitors) over an observation period of 337 ± 80 days. The cognitive performance of the patients before and after addition of LA to their standard medication was compared. Whereas a steady decrease in cognitive performance (a 2 point/year decrease in scores in the mini-mental state examination-MMSE-and a 4 point/year increase in the AD assessment scale, cognitive subscale – ADAScog – was observed before start of the LA regimen was observed, treatment with LA led to a stabilization of cognitive function, demonstrated by constant scores in two neuropsychological tests for nearly a year (Hager *et al.* 2001).

In a follow-up report, we have extended the analysis to 43 patients monitored over an observation period of up to 48 months. In patients with mild dementia (ADAS < 15), the disease progressed extremely slowly (ADAS: + 1.2 points/year, MMSE: - 0.6 points/year), in patients with moderate dementia at approximately twice the rate compared to our own control group and control groups from other published studies (Haxby *et al.* 1992; Ferris and Kluger 1997). However, the progression appears dramatically lower than data reported for untreated patients or patients on cholinesterase inhibitors in the second year of long-term studies, particularly in patients in early stages of AD. Despite the fact that this study was not double-blinded, placebo-controlled and randomized, our data suggest that treatment with LA might be a successful 'neuroprotective' therapy option for AD (Hager *et al.* 2007). However, a state-of-the-art phase II trial is needed urgently.

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