

α -lipoic acid in the treatment of diabetic polyneuropathy

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Abstract

This article reviews the biochemical background as shows some preclinical and clinical evidence for the beneficial effects of the natural compound α -lipoic acid in the treatment of diabetic polyneuropathy. α -lipoic acid, which has been widely used for decades in Germany for this indication, may become an important treatment agent for this and other complications of diabetes.

1. Background

1.1 Introduction to diabetic polyneuropathy

Diabetes mellitus is one of the most rapidly growing health problems in the world. Diabetic polyneuropathy (DPN) is one of the most common long-term complications of diabetes.

All types of diabetic patients—insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), and secondary diabetic patients—can develop neuropathy. Its prevalence increases with the known duration of diabetes, and up to 50% of patients develop neuropathic symptoms within 25 years of the onset of diabetes 6.

DPN leads to serious disability and increased mortality. Patients with this syndrome show a general 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)8.

1.2 Diabetic peripheral neuropathy

Symptoms of DPN include numbness and often burning and sharply cutting pain, prickling sensations in the hands, feet, or legs. It involves sensory or motor neurons and may involve small or large nerve fibres, or both. The nerves to the feet are affected first because the damage is occurring along the entire length of the axons and the axons to the feet are the longest in the body, therefore the major associated morbidity is foot ulceration leading to limb loss 5.

Peripheral DPN can be further classified into large fibre and small fibre neuropathy. Large fibre neuropathy is characterised by painless paresthesia with impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. In advanced stage, sensory ataxia may occur. Large fibre neuropathy results in slowing of nerve conduction, impairment of quality of life, and activities of daily living. Small fibre neuropathy on the other hand is associated with pain, burning, and impairment of pain and temperature sensations. Nerve conduction studies are usually normal but quantitative sensory and autonomic tests are abnormal 1.

1.3 Diabetic autonomic neuropathy

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. Because of diversity of symptoms, autonomic DN often goes unnoticed by both the patient and the physician. Autonomic nerve involvement can occur as early as one year after the diagnosis of DM. Autonomic neuropathy has been reported to be present in up to 40% of Type 2 diabetic patients. Symptoms may include gastroparesis (a condition where the stomach is not emptying properly and characterized by nausea, vomiting, and abdominal distension), sexual dysfunction, low blood pressure when standing up (postural hypotension), and inability to sweat, as well as a variety of cardiac abnormalities. Diabetic autonomic neuropathy usually correlates with severity of somatic neuropathy such as orthostatic hypotension, resting tachycardia, and heart rate unresponsiveness to respiration 1.

2. Causes of diabetic polyneuropathy

The causes of neuropathy are not fully understood and are probably different for different varieties of diabetic neuropathy. Nerve damage is likely due to a combination of factors, among which two are considered to be the most important:

- a) metabolic factors, predominantly high blood glucose, but also long duration of diabetes, possibly low levels of insulin, and abnormal blood fat levels,
- b) neurovascular factors, leading to damage to the blood vessels that carry oxygen and nutrients to the nerves

2.1 Metabolic factors

Animal and in vitro experiments over the last 25 years have implicated four major pathways of glucose metabolism in the development of cellular dysfunction in diabetes. These include: 1) increased polyol pathway activity leading to sorbitol and fructose accumulation, NAD(P)H-redox imbalances, and changes in signal transduction; 2) nonenzymatic glycation of proteins yielding advanced glycation end-products (AGEs); 3) activation of PKC thereby initiating a cascade of stress responses, and 4) increased hexosamine pathway flux. Each pathway becomes perturbed as a direct or indirect consequence of hyperglycemia-mediated superoxide overproduction by the mitochondrial electron transport chain. Either inhibition of superoxide accumulation or euglycemia restores the metabolic and vascular imbalance and blocks both the initiation and progression of complications 4.

In the diabetic state, unchecked superoxide accumulation and resultant increases in polyol pathway activity, AGE accumulation, PKC activity, and hexosamine flux trigger a feed-forward system of progressive cellular dysfunction in cells with insulin-insensitive glucose transporters such as neurons 13. In the peripheral nerves, this confluence of metabolic and vascular disturbances leads to impaired neural function and loss of neurotrophic support, and long term, can mediate apoptosis of neurons and Schwann cells, the glial cells of the peripheral nervous system. Decreases in nerve growth factor (NGF), neurotrophin-3 (NT-3), ciliary neurotrophic factor, and IGF-I in nerves from animals with experimental diabetes are well documented and correlate with the presence of neuropathy 12.

2.2 Neurovascular factors

The vascular and neural complications of diabetes are closely related and intertwined. Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow. The first pathological change in the microvasculature is vasoconstriction. As the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy. Vasodilator agents (e.g., angiotensin-converting-enzyme inhibitors, α 1-antagonists) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Thus, microvascular dysfunction occurs early in diabetes, parallels the progression of neural dysfunction, and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy 16 .

2.3 Other causes

Other factors that have been proposed to contribute to DPN are: autoimmune factors that cause inflammation in nerves, mechanical injury to nerves, such as carpal tunnel syndrome,

inherited traits that increase susceptibility to nerve disease and lifestyle factors such as smoking or alcohol use.

3. Treatment of diabetic polyneuropathy

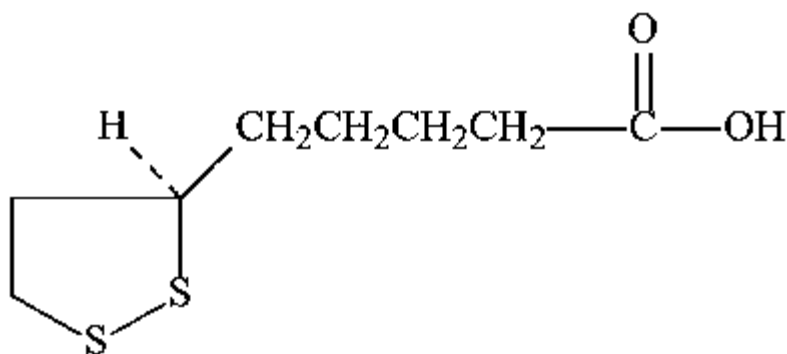
Although near-normoglycaemia is now generally accepted as the primary approach to prevention and treatment of diabetic complications, it is not achievable in many patients.

Based on the different pathogenetic mechanisms of DPN, several therapeutic approaches can be suggested. These treatments include the inhibition of the increased flux through the polyol pathway by aldose reductase inhibitors, administration of antioxidants to neutralize reactive oxygen species, improvement of reduced endoneurial blood flow and resulting hypoxia by vasodilating agents such as angiotensin-converting enzyme inhibitors, prostaglandin analogues, a PKC β inhibitor, C-peptide, neurotrophic support by administration of recombinant human NGF, inhibition of nonenzymatic glycation and formation of AGEs by AGE-inhibitors, and immunosuppressive-inflammatory treatment.

A very interesting compound is α -lipoic acid because it positively influences many of the proposed pathogenic principles of DPN. α -Lipoic acid was introduced in Germany as early as 1959 to treat acute poisoning, i.e. liver failure associated with ingestion of amanita phalloides, and shortly thereafter it was also prescribed to treat neuropathic complaints. α -lipoic acid has been licensed and used in Europe for treatment of symptomatic diabetic neuropathy for more than 20 years and we will attempt to describe the evidence for a beneficial effect of LA in DPN in the following chapters.

4. Lipoic acid

4.1 Chemical Structure of Alpha Lipoic Acid (ALA)



The chemical name for α -lipoic acid is 1,2-Dithiolane-3-pentanoic acid. α -lipoic acid contains two thiol (sulfur) groups, which may be oxidized or reduced (Fig. 1). The reduced form is known as dihydrolipoic acid (DHLA), while the oxidized form is known as LA. α -lipoic acid also contains an asymmetric carbon (marked with *), meaning there are two possible optical isomers that are mirror images of each other (R-LA and S-LA). Only the R-isomer is endogenously synthesized. α -lipoic acid supplements may contain either R-LA or a 50/50 (racemic) mixture of R-LA and S-LA.

4.2 Pharmacokinetics

Consumption of α -lipoic acid from foods has not yet been found to result in detectable increases of free α -lipoic acid in human plasma or cells. In contrast, high intravenous or oral doses of free α -lipoic acid (50 mg or more) result in significant but transient increases in free α -lipoic acid in plasma and cells. Exogenous racemic alpha-lipoic acid 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 hepatic extraction. In healthy volunteers following single oral and i.v. administration of 200 mg α -lipoic acid, the areas under curve (AUC) were 46.82 \pm 21.46 and 157.97 \pm 35.05 microg x min/ml for the oral and intravenous administration of 200 mg, respectively. The AUC following oral administration of 600 mg was 157.83 \pm 35.82 microg x min/ml. The difference in mean $t(1/2)$ for the oral and the i.v. dose was 25.3-32.7 min, respectively. The absolute bioavailability after the 200 mg dose was 29.1 \pm 10.3% 15.

4.3 Pharmacological properties of lipoic acid

α -lipoic acid, a naturally occurring disulfide compound, has long been known to be an essential cofactor for mitochondrial bioenergetic enzymes including pyruvate dehydrogenase and α -ketoglutarate dehydrogenase. Aside from its enzymatic role, *in vitro* and *in vivo* studies suggest α -lipoic acid also acts as a powerful micronutrient with diverse pharmacologic and antioxidant properties. α -lipoic acid is a vitamin-like substance that is often described as "nature's perfect antioxidant". First of all, α -lipoic acid is a very small molecule that is efficiently absorbed and easily crosses cell membranes. Unlike vitamin E, which is primarily fat-soluble, and vitamin C, which is water-soluble, α -lipoic acid can quench either water- or fat-soluble free radicals both inside and outside the cell. These diverse actions suggest that α -lipoic acid acts by multiple mechanisms both physiologically and pharmacologically, many of which are only now being explored. It has to be noted that the reduced form of α -lipoic acid DHLA, is the active compound providing nearly all the pharmacological benefits. However, α -lipoic acid can also be applied instead of DHLA because it will be reduced by the mitochondrial lipoamide dehydrogenase, which forms a part of the pyruvate dehydrogenase complex 2.

4.4 Antioxidant effect of α -lipoic acid (including its regenerating effect for other antioxidants)

α -lipoic acid 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. α -lipoic acid itself is not able to scavenge the superoxide radical, but the reduced form of α -lipoic acid, dihydrolipoic acid (DHLA), is able to scavenge superoxide and peroxy 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 (GSH). 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 α -lipoic acid is added to various types of animal and human cells in tissue culture, it causes a significant increase in cellular GSH levels 10.

4.5 Lipoic acid as an anti-inflammatory agent

Binding of ligands such as AGEs to the receptor for advanced glycation end products (RAGE) results in activation of the transcription factor nuclear factor kappa B (NF- κ B) and subsequent expression of NF- κ B-regulated cytokines. This pathway has been shown to be a relevant pathomechanism in diabetic polyneuropathies. 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. α -Lipoic acid can scavenge intracellular free radicals (acting as second messengers), downregulate pro-inflammatory redox-sensitive signal transduction processes including NF- κ B translocation, and thus attenuates the release of more free radicals and cytotoxic cytokines 17.

4.6 α -lipoic acid as a stimulator of glucose uptake and utilization (“insulinomimetic”)

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 α -lipoic acid'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 actually stimulate the regeneration of nerve fibers in animal models. Its ability to improve blood sugar metabolism is a result of its effects on glucose metabolism and an ability to increase insulin sensitivity in insulin-sensitive tissues such as liver and muscle 3.

5. α -lipoic in animal models of diabetic polyneuropathy

A variety of animal models of diabetic polyneuropathy – mostly the model of streptozotocin-induced diabetic neuropathy have been used to evaluate potential beneficial effects of α -lipoic acid.

In one study, the efficacy of α -lipoic 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. α -lipoic, in doses of 20, 50, and 100 mg/kg, was administered intraperitoneally five times per week after onset of diabetes. NBF in SDN was reduced by 50%; α -lipoic did not affect the NBF of normal nerves but improved that of SDN in a dose-dependent manner. After 1 month of treatment, α -lipoic supplemented rats (100 mg/kg) 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; it was improved in a dose-dependent manner in α -lipoic supplemented rats. The conduction velocity of the digital nerve was reduced in SDN and was significantly improved by α -lipoic 11

A further study reports highly selective effects of administration of α -lipoic acid to streptozotocin-injected diabetic rats. LA improved digital sensory but not sciatic-tibial motor nerve conductance velocity (NCV), corrected endoneurial 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 14.

It also been shown that pretreatment of diabetic rats with lipoic acid improves wound healing. Rats were made diabetic with streptozotocin (STZ) and treated systemically on alternative days with lipoic acid (100 mg/kg 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 α -lipoic acid-treated diabetic rats healed more rapidly than wounds in untreated diabetic rats. These findings suggest that prophylactic use of α -lipoic acid 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 9.

In another study, the effects of 2-week treatments with α -lipoic acid on endoneurial 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 endoneurial blood flow. α -lipoic acid 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 α -lipoic acid in lowering lipid and hemostatic risk factors for cardiovascular disease indicate potential additional antithrombotic and antiatherosclerotic actions that could be of benefit in human diabetes 7.

In summary, a plentitude of animal study based evidence points to a possible interference of α -lipoic acid with pathogenic principles of DPN.

5. Human studies

5.1 Effects of α -lipoic acid in patients with diabetic peripheral neuropathy

α -lipoic acid (which is often also called thioctic acid in Europe) 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, α -lipoic acid 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 α -lipoic acid 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-Lipoic Acid 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 18. The SYDNEY (Symptomatic Diabetic Neuropathy) Study was a monocenter trial including in-patients from a hospital in Moscow, Russia. 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 of α -lipoic acid (600mg 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 α -lipoic acid 19.

Primary analysis involved a comparison of the differences in TSS from baseline to the end of i.v. treatment between the groups treated with α -lipoic acid 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 α -lipoic acid 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 α -lipoic acid 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 α -lipoic acid 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 α -lipoic acid 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 α -lipoic acid after 3 weeks. The rates of adverse events did not differ between the groups 19.

The following conclusions were drawn from these trials: (i) short-term treatment for 3 weeks using intravenous thioctic acid 600 mg/day reduces the chief symptoms of diabetic polyneuropathy to 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 19.

5.2 Effects of α -lipoic acid in patients with diabetic autonomic neuropathy

There is also evidence for oral α -lipoic acid 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 α -lipoic acid showed statistically significant improvement compared to placebo and caused no significant side effects 20.

6. Conclusions

There is considerable preclinical and clinical evidence for the beneficial effects for α -lipoic acid as a safe and effective drug for the treatment of diabetic polyneuropathy. α -lipoic acid has been widely used for this indication in Germany for more than 30 years, and it may become an important treatment agent for this and other complications of diabetes worldwide in the near future.

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