Review Article

Diabetic Neuropathy and Use of Alpha-Lipoic Acid in Diabetic Neuropathy

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ABSTRACT

Diabetes is a chronic metabolic disease results from chronic hyperglycaemia, with a high prevalence worldwide. It is one of the most common non-communicable diseases and a leading public health concern. Chronic hyperglycaemia results from insufficient insulin production (type 1 diabetes, formerly called insulin-dependent diabetes) or insulin resistance (type 2 diabetes, formerly non-insulin dependent diabetes). Diabetic neuropathy due to nerve damage caused by uncontrolled hyperglycaemia is a common and serious complication strongly associated with diabetes mellitus. There is accumulating evidence suggesting that free radical mediated oxidative stress is implicated in the pathogenesis of diabetic neuropathy by inducing neurovascular defects that result in endoneurial hypoxia and subsequent nerve dysfunction. Alpha-lipoic acid (ALA) is a naturally occurring substance, essential for function of different enzymes that take part in mitochondria & oxidative metabolism. It is believed that ALA or its reduced form dihydrolipoic acid (DHLA) have many biochemical functions acting as biological anti-oxidant, as metal chelator, reducers of oxidized form of other agents such as vitamin-E, C and modulator of the signalling transduction of several pathways (insulin). ALA acts as a scavenger of ROS and has antioxidant properties that could block the oxidative stress-inflammation pathways activated in diabetic neuropathy. The therapeutic properties of ALA might include the ability to restore glucose availability and increase insulin-stimulated glucose transport. It could therefore be useful both in prevention and treatment of diabetic neuropathy.

Keywords: Diabetes, Diabetic neuropathy, oxidative stress, anti-oxidant, Alpha-lipoic acid (ALA), dihydrolipoic acid (DHLA), scavenging free radicals.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder that continues to be a major worldwide health issue. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action and is associated with chronic hyperglycaemia and disturbances of carbohydrate, lipid, and protein metabolism.[1]

Types

Diabetes mellitus is mainly divided into two types.

1) Type-1 Diabetes mellitus.

2) Type-2 Diabetes mellitus.

Type-1 DM: It is also called Insulin dependent diabetes mellitus or juvenile diabetes. It is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency.[2]

Type-2 DM: It is also called Non-Insulin dependent diabetes mellitus. It is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic-beta cell failure.[3]

Diabetes affects 382 million people worldwide and its prevalence is expected to increase to 592 million by the year 2035.[4, 5]

Diabetic peripheral neuropathy (DPN) and diabetic autonomic neuropathy (DAN) are the most common micro vascular disorders of diabetes mellitus [6], which leads to considerable morbidity and a decreased quality of life.[7,8,9] Diabetes mellitus is strongly associated with increased oxidative stress, which could be a consequence of either increased production of free radicals or reduced anti-oxidant defense.[10]

DIABETIC NEUROPATHY

Diabetic neuropathy due to nerve damage caused by uncontrolled hyperglycaemia is a common and serious complication strongly associated with diabetes.[11]

Diabetic neuropathy presents a major public health problem. It is defined by signs and symptoms of peripheral nerve dysfunction in diabetic patients, in whom other causes of neuropathy have been excluded.

Diabetic neuropathy includes a number of syndromes, depending upon the classes of nerve fibres involved.[12] The involved neurons may be afferent (sensory), efferent (motor), or both.

There are four types of diabetic neuropathy:

1. Peripheral neuropathy (also called diabetic nerve pain and distal polyneuropathy)

2. Proximal neuropathy (also called diabetic amyotrophy)

3. Autonomic neuropathy

4. Focal neuropathy (also called mononeuropathy)

1. Peripheral neuropathy: It is the most common form of neuropathy. It affects nerves that leading to your extremities i.e., to your feet, legs, hands, and arms.

2. Proximal neuropathy: It specifically affects the muscles in the upper part of your leg(s), buttocks, and hips.

3.Autonomic neuropathy: It can affect so many of your body's systems (Autonomic nerves) that control your heart, bladder, lungs, stomach, intestines etc.

4.Focal neuropathy: It affects one specific nerve. It can also be called mononeuropathy. It mostly affects nerves in the head (especially ones that go to the eyes). It can also affect the torso and legs.[13]

PATHOGENISIS OF DIABETIC NEUROPATHY

Chronic hyperglycaemia is believed to play a key role in the pathogenesis of diabetic neuropathy via oxidative stress generated in different pathways.

- Enhanced flux through polyol pathway.
- Glucose auto-oxidation and accumulation of advanced glycation end products (AGEs).[14]
- Hexosamine pathway.
- Increased protein kinase-c activation.
- Mitochondrial dysfunction.[15]

Diabetic peripheral neuropathy (DPN) pathophysiology can be mainly explained as neural dysfunction caused by the interplay of decreased blood flow to nerves as a result of hyperglycaemia and increased oxidative stress, which induces local inflammatory reactions through reactive oxygen species.

Good glycaemic control reduces the risk of developing DPN, but glycaemic control is not always achievable and is usually not sufficient to halt the DPN progression.[16]

Oxidative stress

Oxidative stress occurs in a cellular system when the production of free radical moieties exceeds the antioxidant capacity of that system.[17]

Diabetes increases the formation of reactive oxygen species (ROS). This ROS affect the vascular endothelium, damaging cells and altering specific functions. Nitric oxide (NO) is an important target for ROS.

Superoxide from variety of sources can react with nitric oxide (NO) produced by vascular endothelium or nitrergic nerves, to form peroxynitrate (ONO2-), which would reduce endothelium dependent relation and nitrergic neurotransmission.

Thus, for peripheral neuropathy, increasing vasodilation to restore vasa nervorum perfusion is a primary concern by giving anti-oxidants.[18]

Polyol pathway

Hyperglycaemia results in elevated intracellular glucose in nerves, leading to saturation of the normal glycolytic pathway.

Extra glucose increases the polyol pathway and that produces sorbitol and fructose.[19] This pathway has long been thought to be an important in diabetic complications, particularly for neuropathy.[18]

Increased flux through polyol pathway mediated by aldose reductase and sorbitol dehydrogenase, leading to accumulation of sorbitol in nerve fibres and reduces the levels of myo-inositol. The latter reduction is associated with reduced NA+- K+- ATPase activity.[12]

This results in reduction in the axon capacity to propagate the membrane action potential and diminished capacity of nerve regeneration. The excessive activation of polyol pathway depletes cytosolic NADPH and subsequently Glutathione (GSH).[20]

Formation of advanced glycation end products (Ages)

Glucose at elevated concentrations undergoes non enzymatic reaction with amino group of proteins [17] and lipids to form reactive di-carbonyl intermediates by auto-oxidation, which further reacts to form a variety of advanced glycation end products (AGEs).[18]

Accumulation of AGEs exerts their damaging effect by binding to specific receptors on the surface of neurons (RAGE- Receptor for advanced glycation end products).[12]

Long-term inflammatory responses upregulate RAGE and stimulate nuclear factor kappa B. The damages induced by AGEs results in diminished neutropic support, impaired nerve blood flow, disrupted neuronal integrity, and impair repair mechanisms.[19]

Increased generation of ROS and AGEs in diabetes have marked neurovascular effects which contribute to degeneration of neurons. [18]

Hexosamine pathway

In the process of glucose metabolism, nearly 3% of total sugar gets involved in the hexosamine pathway by means of fructose-6-phosphate.[21]

Fructose-6-phosphate is diverted from glycolysis to form glucosamine-6-phosphate under the action of glutamine-6-alanine aminotransferase, which inturn converts into uridine diphosphate - (UDP-) N-acetyl glucosamine (UDP-GlcNAc).[15]

Hyperglycaemic conditions create additional flux through hexosamine pathway that ultimately results in an increased activation of Sp1, a transcription factor implicated in diabetic complications.

Increased PKC activation

Hyperglycaemia stimulates the formation of diacylglycerol, which then activates PKC.

The PKC is an important element in function of nerves and pathogenesis of diabetic neuropathy. Activation of PKC initiates an intracellular signalling cascade such as overexpression of NF-Kappa B, TGF-beta and also decreases the endothelial nitric oxide synthase.

PKC triggers stress genes that phosphorylate transcription factors and thus alter the balance if gene expression result in oxidative stress.[19]

Mitochondrial dysfunction

Mitochondria are intrinsically associated with ROS production; its normal function is altered by hyperglycaemia.

Hyperglycaemia generates ROS coupled with hyperpolarization of the mitochondrial membrane potential (MMP), followed by mitochondrial membrane depolarization, which is temporally related to an increase in ADP: ATP ratio and an absolute decrease in ATP levels.

This in turn is coupled with cytochrome *c* release from the intermitochondrial membrane space and cleavage of caspases, resulting in dorsal root ganglion apoptosis.[15] (In diabetes, dorsal root ganglion neurons are exposed to increase concentrations of glucose).

PATHOGENISIS OF DIABETIC NEUROPATHY

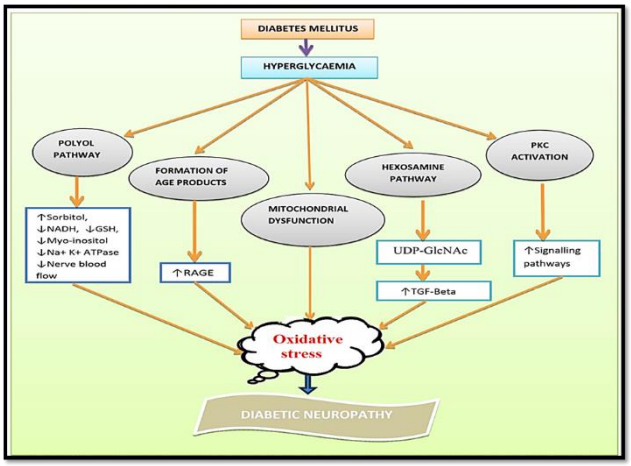


Figure 1: Pathogenesis of Diabetic Neuropathy

SYMPTOMS OF DIABETIC NEUROPATHY

Depending upon the affected nerve, symptoms of diabetic neuropathy can range from pain and numbness in your legs and feet to problems with your digestive system, urinary system, blood vessels, heart etc.

Peripheral neuropathy

- Numbness (reduced ability to feel pain or changes in temperature)
- Sharp pains / cramps
- Tingling or burning sensation
- Muscle weakness
- Loss of reflexes, especially in the ankle
- Increased sensitivity to touch
- Loss of balance and coordination
- Serious foot problems, such as ulcers, infections, and bone and joint pain.

Autonomic neuropathy

- Bladder problems, including urinary tract infections or urinary retention or incontinence
- Constipation, uncontrolled diarrhoea or both
- Difficulty swallowing
- Problems controlling body temperature
- Increased or decreased sweating
- Erectile dysfunction
- Slow stomach emptying (gastro paresis), causing nausea, vomiting, bloating and loss of appetite
- Sharp drops in blood pressure after sitting or standing that may cause you to faint or feel lightheaded etc.

Diabetic amyotrophy

- Severe pain in a hip and thigh or buttock
- Eventual weak and shrinking thigh muscles
- Difficulty rising from a sitting position
- Abdominal swelling, if the abdomen is affected
- Weight loss.

Diabetic Mononeuropathy

- Pain in the shin or foot, lower back or pelvis, front of thigh, Chest or abdomen.
- Aching behind one eye
- Double vision
- Difficulty in focusing
- Paralysis on one side of your face (Bell's palsy).[22,23]

TREATMENT OF DIABETIC NEUROPATHY

The goal of treating diabetic neuropathy is to prevent further tissue damage and relieve discomfort.

The first step is to bring blood sugar levels under control by diet and anti-diabetic medication. Another important part of treatment involves taking special care of the feet by wearing proper fitting shoes and routinely checking the feet or cuts and infections.[24]

Treatment of diabetic neuropathy is divided into two groups:

i) Symptomatic treatment

ii) Treatment for nerve regeneration[25]

i) Symptomatic treatment

a) Tricyclic drugs (Anti-depressants): Amitriptyline, Imipramine.

b) Anti convulsants : Gabapentin, pregabalin

c) Opioids : Tramadol, oxycodone

d) Others: Capsaicin topical cream, Duloxetine,lidocaine patches etc.[26]

ii) **Treatment for nerve regeneration**

The agents used for nerve regeneration are known as neurotrophic factors. The neurotrophic factor is defined as a naturally occurring protein that is released by target tissues of responsive neurons, binds to specific receptors and is retrogradely transported to the cell body where it regulates gene expression through the actions of second messenger systems.

Examples: Epidermal growth factor (EGF), Transforming growth factor (TGF) – αTGF - β1, TGF - β2.[25]

USE OF ALPHA LIPOIC ACID IN DIABETIC NEUROPATHY

Since oxidative stress is enhanced in diabetic patients with neuropathy, a pharmacologic strategy aimed at overcoming the deficit of antioxidant agents should provide significant relief from complications for neuropathic patients.

The ideal treatment should prevent or arrest the progressive loss of nerve functionality and improve symptoms with minimal side effects.

ALA is a powerful antioxidant and several studies – including the SYDNEY2 trial – have demonstrated an improvement in neuropathic symptoms and deficits. Results of a meta-analysis provided evidence that treatment with ALA 600mg/day over 5 weeks is safe and significantly improves both neuropathic symptomatology and neuropathic deficits to a clinically meaningful degree in diabetic patients with symptomatic polyneuropathy.[7]

In one study, seventy-four patients with type-2 diabetes were given either a placebo, or ALA. When compared to the placebo group, those receiving the ALA had significantly greater insulin-sensitivity and improvement in insulin stimulated glucose disposal. The researchers logically concluded, "The results suggest that oral administration of alpha-lipoic acid can improve insulin sensitivity in patients with type2 diabetes".[27]

A three week multi centre randomized controlled trail (ALADIN Study) demonstrate that treatment with ALA over 3 weeks using a dose of 600mg per day reduces the symptoms of diabetic neuropathy patients

ALA has been approved for treatment of diabetic neuropathies in Germany. [8,14]

ALPHA-LIPOIC ACID (Lipoic acid)

Alpha-lipoic acid (ALA), also known as thioctic acid and 1, 2-dithiolane-3-pentanoic acid (C8H14O2S2), is a naturally occurring substance existing in almost all types of prokaryotic and eukaryotic cells.[28] It acts as a coenzyme for several important enzymes in almost all tissues of the body.[29]

It was incidentally discovered by Snell et al in 1937 as a potato extract required for bacterial growth. The agent was latter characterized by Reed and colleagues in 1951.[14]

ALA has amphiphilic property i.e., it exhibits both hydrophilic and hydrophobic properties.[30] It is a small molecule, soluble in both water and fat.[27] So it is widely distributed in plants and animals in cellular membranes and cytosol.[31]

ALA is a necessary cofactor for mitochondrial α-ketoacid dehydrogenases, and thus serves a critical role in mitochondrial energy metabolism. [32]

It has the ability to scavenge free radicals.[29,33] Therefore ALA/DHLA (reduced form) couple has been called the "UNIVERSAL ANTI-OXIDANT". [31]

This antioxidant effect has been clearly shown to reduce lipid peroxidation, improve endoneurial blood flow and glucose uptake, correct deficits in neuropeptides, enhance the activity of endogenous protective superoxide dismutase and catalyse and prevent apoptosis.[33]

ALA diminishes increased oxidative stress in diabetic patients and useful to treat diabetic neuropathy.[34]

Structure

Alpha-Lipoic acid (1, 2-dithiolane-3-pentanoic acid) is an eight carbon disulphide that contains a single chiral center[35], that is denoted by Asterisk.[36]

It has two enantiomeric forms (optical isomers)

1. R-isomer

2. S-isomer

Only R-isomer is essential as a co factor in biological systems.[32]

This R-isomer exerts a neuroprotective and neurotropic function that is essential for restoring the physiological, biochemical processes altered by oxidative damage and, consequently, for overcoming certain symptoms typical of peripheral neuropathy.[37]

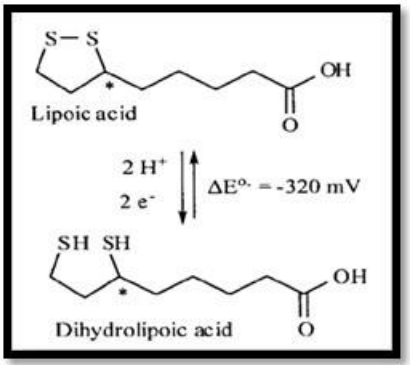


Figure 2

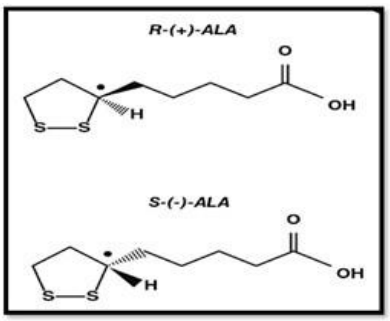


Figure 3

Synthesis

ALA can be synthesized through enzymatic reactions in plants and animals' mitochondria from octanoic acid cysteine (as sulphur donor). Mammalian cells can synthesize ALA through the action of mitochondria lipoic acid synthase.[37]

Normally alpha-lipoic acid is present in very small amounts (5-25 nmol/g) in mammalian tissues, in bound form with enzyme.[29]

Sources

Dietary sources – It is found in wide variety of foods from animals and plants. Mostly seen in muscle meats, heart, kidney, liver, and to a lesser degree of fruits and vegetables such as Broccoli, carrots, beets, tomatoes.[35,38, 39]

Action of Alpha- Lipoic Acid in Diabetic Neuropathy

In general, antioxidants provide a preventive measure against the hazards of oxidative stress with their ability to neutralize, balance and sponge up free radicals by coupling with unpaired electrons.[27]

Alpha-lipoic acid acts by multiple mechanisms both physiologically and pharmacologically -

Physiologically – acts as an antioxidant (direct and indirect), terminates free radicals.

Pharmacologically – improves glycaemic control, polyneuropathy.[29]

The mechanisms of the rapid improvement in both neuropathic symptoms and deficits may be related to an improvement in nerve blood flow mediated by the antioxidant action of ALA and also improvement in endoneural glucose uptake metabolism and nerve conduction.[40]

1. Direct Anti-Oxidant

Alpha lipoic acid (ALA) has been shown to prevent or even reverse hyperglycaemia- induced nerve dysfunction by reducing free-radical-mediated oxidative stress.[7]

ALA is a unique [27] potent free radical scavenger (it binds to free radicals), that is absorbed from the diet, transported into cells[39] probably via several systems such as medium chain fatty acid transporter, a Na^+ dependent vitamin transport system, and an H^+-linked monocarboxylate transporter for intestinal uptake[31] and reduced to dihydrolipoic acid (DHLA), which has greater free radical binding activity than ALA.[39]

The cellular reduction of ALA to DHLA is accomplished by NAD (P) H-driven enzymes, thioredoxin reductase, lipoamide dehydrogenase, and glutathione reductase.[31]

Alpha-lipoic acid (ALA) – Oxidized

↓

Dihydrolipoic acid (DHLA) – Reduced

The chemical reactivity of ALA is mainly due to its dithiolane ring.[32] The thiol groups of ALA & DHLA make them capable of scavenging a variety of reactive oxygen species and reactive nitrogen species.[36]

The oxidized (ALA) and reduced (DHLA) forms create a potent redox couple that has a standard reduction potential of −0.32 V. This makes DHLA one of the most potent naturally occurring antioxidants.

2. Glycemic Control

ALA is also known to give positive results in glycaemic control, and also neuropathies associated with diabetes. Excessive oxidative stress in endothelial cells has been shown to ameliorate proinflammatory cytokine levels and to mediate the degradation of insulin receptors via MAPK cascades.[35]

ALA stimulates glucose uptake upon translocation and regulation of the intrinsic activity of glucose transporters, an effect that might be mediated by p38 mitogen-activated protein kinase (p38MAPKs) and activation of some kinases such as insulin receptor substrate 1 (IRS1), phosphatidylinositide 3-kinase (PI3K) and protein kinase B (Akt).

ALA may acts as mild oxidant by transiently forming mixed disulphides with sulfhydryls on insulin receptors leading to activation of insulin receptors and ultimately results in uptake of glucose by cells.[36]

3. Regeneration of Endogenous Anti-Oxidants (ALA as Indirect antioxidant)

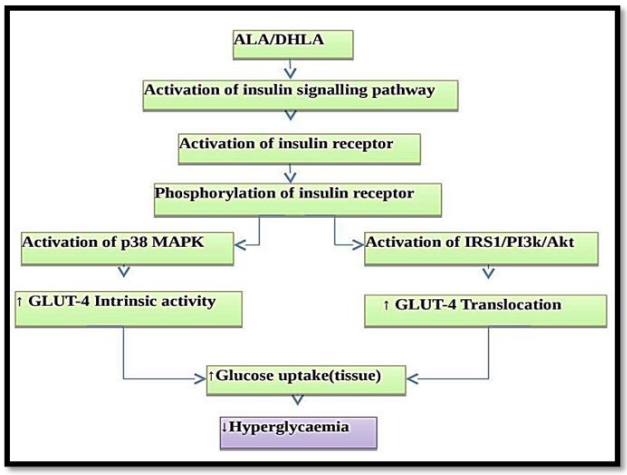


Figure 4: ALA as Indirect antioxidant

ALA may act indirectly to maintain cellular anti-oxidants status by either inducing the uptake or enhancing the synthesis of endogenous low molecular weight anti-oxidants or antioxidant enzymes.[32]

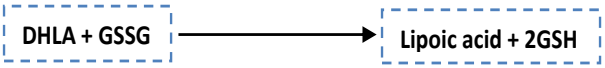
a) GSH system (Glutathione)

The GSH system is the most important cellular defense mechanism as a ROS scavenger regulating the intracellular redox state.[28]

Glutathione is one of the most important low molecular weight cellular antioxidants, buffering the thiol redox state.[1] Glutathione is a sulphur tripeptide containing glutamate, cysteine and glycine.[38]

ALA increases the levels of GSH either by regenerating their active forms from GSSG (Glutathione disulphide) or increasing their synthesis.

1) The DHLA/ALA redox couple has a reduction potential of -0.32, making it a powerful reductant. It has the capacity to regenerate a number of oxidized anti-oxidants to their active anti-oxidant forms.[36]



2) Alpha-lipoic acid can significantly increase the cellular capacity of GSH synthesis by inducing nuclear factor erythroid 2-related factor 2 (Nrf-2)-mediated antioxidant gene expression.

Release and activation of Nrf2 takes place and subsequently it localizes in the nucleus, where it binds the ARE gene (Antioxidant Response Element), enhancing the synthesis of GCL (Glutamate-cysteine ligase) and ultimately results in increased GSH synthesis.[31]

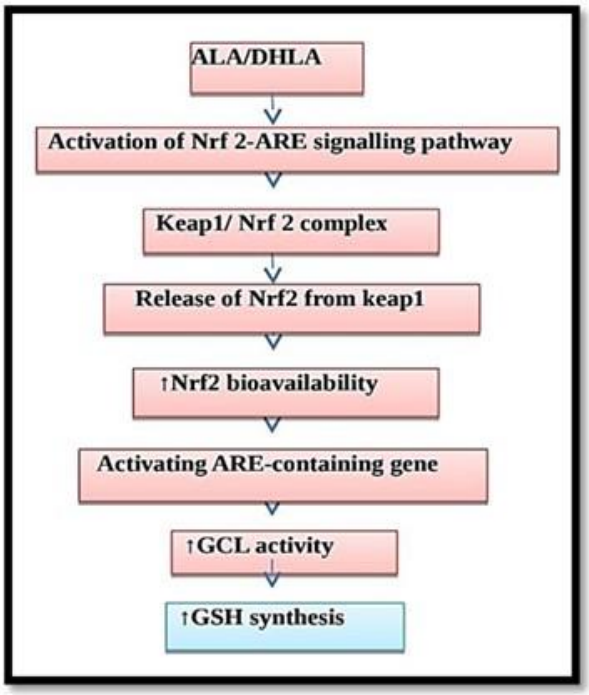


Figure 5: GSH synthesis

b) Regeneration of Vit-E, C.

DHLA has the ability of reducing the oxidized forms of other antioxidants such as vitamin C and E.[1]

There are also strong indications that DHLA regenerates alpha-tocopherol, possibly by directly interacting with tocopheroxy radical or, more likely, through indirectly reducing dehydroascorbate, which then reduces tocopherol. [36]

Chelation of Metal Ions (ALA as Indirect antioxidant)

LA/DHLA are considered as chelator compounds because they chelate divalent transient metal ions both in vivo and in vitro, but by different mechanisms of action.

Because of the presence of 2 thiol groups, LA and DHLA both have metal-chelating properties. In fact, LA is a potent chelator of divalent metal ions in vitro, and forms stable complexes with Mn2+, Cu2+, Fe2+, and Zn2+.

In addition to being direct reactive oxygen species scavengers, both LA and DHLA chelate redox-active metals *in vitro* and *in vivo*. It has been demonstrated that LA had a profound dose-dependent inhibitory effect upon Cu2+-catalyzed ascorbic acid oxidation.[31]

OTHER ACTIONS

1. Anti-inflammatory agent (Inhibition of Nuclear factor – kappa B)

Elevated levels of oxidative stress play an important role in chronic inflammation.

Oxidative stress-associated inflammation is thought to provoke early vascular events.

These events require the activation of NF-kappaB, a transcription factor that induces expression of many genes involved in inflammation and endothelial cell migration.

LA has been studied for its antioxidant properties in cytokine induced inflammation; it is also widely known as an inhibitor of NF-kappaB.[32]

2. Modulation of Adenosine monophosphate protein kinase (AMPK)

ALA has some important functions in the activity and expression of 5'adenosine monophosphate-activated protein kinase (AMPK) in peripheral tissues and in brain (hypothalamus).

ALA is able to modulate the activity of AMPK in the brain by metabolic stresses that inhibit ATP production such as ischemia, hypoxia, and glucose deprivation as well as by oxidative stress.[38]

DOSING OF ALA IN DIABETIC NEUROPATHY

ALA is efficacious in ameliorating neuropathic symptoms like pain, burning, numbness etc.[33]

Treatment with ALA administered intravenously or orally for several weeks or months improves neuropathic symptoms and defects.[34]

Dose : Oral → 600 - 1800mg/day,

IV → 600mg/day.

Dietary bioavailability studies show that an oral ALA dose is rapidly absorbed from the gastrointestinal tract and appreciably increases plasma ALA levels.[36]

It is recommended that ALA be taken 30 min before or 2 hours after eating.[39]

ADVERSE EFFECTS OF ALA

Adverse events related to the administration of ALA were described mainly in clinical trials. The majority of the events are less toxic and are dose dependent.

Adverse effects include nausea, vomiting, abdominal discomfort and diarrhoea. [38]

Rare effects include dizziness, vertigo, non-specific psychiatric complaints, sleep disturbances.[39]

OTHER USES OF ALA

- Brain diseases and cognitive dysfunction
- Obesity
- Non-alcoholic fatty liver disease
- Burning mouth syndrome
- Cardiovascular diseases and vascular dysfunction
- Cancer
- Glaucoma
- Osteoporosis
- Diabetic nephropathy, retinopathy etc.[38, 40]

CONCLUSION

Hyperglycaemia, resulting from defective insulin secretion, insulin resistance, or both is characteristics of diabetes mellitus (DM) as a metabolic disease. Diabetic neuropathy due to nerve damage caused by uncontrolled hyperglycaemia is a common and serious complication strongly associated with diabetes mellitus. Since oxidative stress is enhanced in diabetic patients with neuropathy, a pharmacologic strategy aimed at overcoming the deficit of antioxidant agents should provide significant relief from complications for neuropathic patients. Alpha-lipoic acid (ALA) has been widely prescribed drug for treatment and prevention of diabetic complications since it affects the main pathogenesis links. ALA and its reduced form DHLA have many biological functions in different intracellular systems resulting in a wide range of actions such as antioxidant protection, chelation of metal ion, regeneration of other anti-oxidants such as glutathione, vitamin –E, C and also act in multiple signalling transduction pathways like insulin, nuclear factor kappa-B. The ALA/DHLA has been called the universal anti-oxidant. The mechanisms of the rapid improvement in both neuropathic symptoms and deficits may be related to an improvement in nerve blood flow mediated by the antioxidant action of ALA and also improvement in endoneural glucose uptake metabolism and nerve conduction. Treatment with ALA 600 mg IV daily for 3 weeks represents a well-tolerated and effective therapy for diabetic neuropathy. Similarly, an oral dose of 600 mg daily administered for up to 5 weeks could offer benefits in symptoms and signs without significant side effects. It could therefore be useful both in prevention and treatment of diabetic neuropathy.

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