THE PROTECTIVE ROLE OF ALPHA LIPOIC ACID ON ORGAN DAMAGES INDUCED BY OXIDATIVE STRESS

S. Sharmilabanu* and N. Jayshree

1Institute of Pharmacology, Madras Medical College, Chennai - 600003.
2Professor of Pharmacology, Madras Medical college, Chennai- 600003.

ABSTRACT
Oxidative stress is known to play an important role and is considered to be the primary cause in the development of various disease conditions like cardiovascular diseases, cancer, diabetes mellitus, neurodegenerative diseases, inflammatory diseases as well as aging process in humans. Oxidative stress increases in the condition when there is an imbalance between the ROS (reactive oxygen species) production and anti-oxidant defense. Anti-oxidants may help in lowering the incidence of pathologies and protect the body from harmful alterations. Nowadays, numerous synthetic anti-oxidant supplements are also found in the market. Alpha lipoic acid (ALA) which is an natural anti-oxidant believed to have beneficial effect on oxidative stress parameters and meet all the criteria for an ideal anti-oxidant. The therapeutic action of ALA is based on its anti-oxidant properties. Current studies also support its use in the treatment of various diseases associated with oxidative stress. This review was undertaken to gather the most recent information regarding the protective role of ALA in organ damages induced by oxidative stress.

KEYWORDS: Oxidative stress, Alpha lipoic acid, Anti-oxidants, Reactive oxygen species.

INTRODUCTION
Oxidative stress is associated with a variety of pathological conditions including diabetes, atherosclerosis and cardiovascular diseases and neurodegenerative diseases. There are many factors associated with oxidative stress, which lead to the development of these diseases. One of the main factors is imbalance between the production of free radicals and the quenching effect of anti-oxidants. Excessive reactive oxygen species (ROS) production and weakened
Antioxidant mechanisms lead to the occurrence of oxidative stress and induction of apoptosis. ROS reacts with DNA, proteins, and lipids, resulting in the accumulation of products, the onset of degenerative processes and ultimately the development of many serious diseases and aging. Although aging is a natural process, it is accelerated by ROS production.

Oxidative stress is an imbalance between production of ROS present in cells and the ability of the body’s natural anti-oxidants to detoxify the reactive substances or repair the harm caused by them.\(^1\) Currently, antioxidants are used in order to reduce the production of ROS in cells and limit their harmful effects. One such effective antioxidant is Alpha lipoic acid (ALA).

LA is a natural antioxidant synthesized in the mitochondria of the liver and other tissues\(^2\), which plays a crucial role in metabolism. Its antioxidant properties were first discovered in the 1950s\(^1\) and later confirmed by subsequent studies.\(^3\)–\(^6\) Its strong reduction and low oxidation-reduction potential (−0.29 V) have made it the subject of many studies from various fields of medicine. It is currently regarded as one of the most potent cellular oxidation regulators.\(^7\) ALA is a remarkable compound that appears to have the property of both quenching of excess free radicals and interacting with other anti-oxidants and involved in the process of regenerating them. Considering the strong antioxidant properties of Alpha lipoic acid, the purpose of this review is to present the protective role of ALA on oxidative stress induced damage.

**ALPHA LIPOIC ACID**

\(\alpha\)-lipoic acid (ALA) [(5-1,2 dithiolan-3yl) pentanoic acid] was first isolated from bovine liver in 1951.\(^1\) Earlier, it was considered as vitamin and included in Vit B complex system. Later ALA was not considered to be a vitamin because of possible bio-synthesis in man (human) and plants. In humans, ALA is synthesized from fatty acids and cysteine but the quantity produced is very negligible (5-25nmol/g). Endogenously synthesized ALA is covalently bound to the amino group of lysine residues and functions as a co-factor for several important mitochondrial enzyme complexes. It is a dithiol compound that retains its protective functions both in oxidized and reduced form.
CHEMISTRY OF ALPHA LIPOIC ACID

Chemically it is a 6,8 dithiooctane acid containing eight carbon disulphide with chiral center and asymmetric carbon resulting in 2 possible isomers: R-LA and S-LA. Naturally occurring ALA is in R-form and the α-lipoic acid acid which is taken as dietary supplements to realize its reliable benefits. It is predominantly available as racemic mixture of R-LA and S-LA.[8] It is highly reactive because of tension of S-S-C bond in the heterocyclic circle. It is stable as solid, but it polymerizes when heated above its melting point(47.5°C) or under the influence of light. It is an amphipathic molecule that possesses both hydrophilic and hydrophobic properties and they do not exhibit any serious side effects. It interacts with other anti-oxidants and can regenerate them. For this reason, ALA is called as anti-oxidant of anti-oxidants.

MECHANISM OF ALPHA LIPOIC ACID

Alpha-lipoic acid acts by multiple mechanisms both physiologically and pharmacologically. Its role pharmacologically is to improve glycemic control and prevent polyneuropathy. Physiologically it acts as an antioxidant by directly terminating free radicals. It also chelates metal ions, increases cytosolic glutathione and vitamin C. The activity of the compound is mainly conferred by its presence of dithiolane ring (or) sulphhydryl groups. The compound exhibits its action based on following aspects.
METABOLISM OF ALPHA LIPOIC ACID
Alpha-lipoic acid is taken up by the cells where it is converted to DHLA by glutathione reductase, thioredoxin reductase (TrxR) and lactate dehydrogenase (LDH) and extensively metabolized by β-oxidation, in tissues. The metabolites of alpha-lipoic acid and DHLA are also suggested to play a significant role in the treatment of various pathological conditions.\[9\]

EFFECT OF ALA IN CHEMOTHERAPY INDUCED OXIDATIVE STRESS
Chemotherapy is a type of cancer treatment that uses drugs to kill cancer cells. Many chemotherapeutic agents are in use, among them Doxorubicin is an important anti-neoplastic agent which is been used in the treatment of a variety of human tumors but its usage is limited as it produces myocardiotoxicity as one of the major side effects.

Doxorubicin induced cardiotoxicity is mainly associated with overproduction of free radicals and disturbances in the mitochondrial metabolism. These free radical cause membrane and macromolecular damage that directly lead to myocardial damage. Alpha lipoic acid which is a unique anti-oxidant found to have beneficial effect in chemotherapy induced cardiotoxicity mediated by oxidative stress. In animal models of doxorubicin induced cardiotoxicity, administration of ALA reduced the oxidative stress and improved the anti-oxidant status.\[10\] The study confirmed that α- lipoic acid ameliorates the cardiotoxicity induced by doxorubicin using biochemical measures. It was found to decrease the serum creatinine kinase (CK) and lactate dehydrogenase (LDH). Furthermore it is been reported that α-lipoic acid administration prevented the rise of MDA levels as well as significant reduction of cardiac glutathione (GSH).
**EFFECT OF ALA ON OXIDATIVE STRESS INDUCED DIABETIC NEPHROPATHY**

Diabetic nephropathy is the major cause of renal failure and oxidative stress has an important role in its etiology and the formation of ROS is a direct consequence of hyperglycemia in which anti-oxidant treatment becomes potential therapy for diabetic nephropathy (DN). One such compound is ALA, that has gained considerable attention as an anti-oxidant for use in management of diabetic complications.

In Streptozocin (STZ) induced diabetic rat models prolonged supplementation of the diet with ALA has been associated with reduction of both hyperglycemia and diabetic renal injury. Effect of ALA in the improvement of hyperglycemic effect has been previously documented in both experimental diabetic rats and humans.\[^{11}\] Attenuation of renal damage induced due to oxidative stress by ALA is directly linked to its anti-oxidant activity. The unique anti-oxidant properties of ALA and its reduced form DHLA has been already reported in number of in-vitro and in-vivo experimental models.\[^{12, 13, 14}\] There are considerable evidences that oxidative stress has an important role in the pathogenesis of diabetic complications including nephropathy.\[^{15, 16}\] In experimental diabetic rat models, administration of ALA has been reported to attenuate nephropathy in association with reduced levels of oxidative stress markers\[^{17}\] which states that ALA supplementation prevents or delays the development of diabetic renal injury.

**EFFECT OF ALA ON LPS INDUCED OXIDATIVE STRESS IN HEART**

Lipopolysacchride (LPS) is a gram negative bacterial endotoxin and a major factor that contributes multiple organ failure including heart injury. Myocardial dysfunction in septic shock depends on presence of pro-inflammatory cytokines and ROS. Increased ROS production can result in myocyte hypertrophy, apoptosis and interstitial fibrosis which contribute to development of depressed cardiac function and progression of cardiac failure. Heart tissue is rich in PUFA and known for its high oxygen consumption. Therefore, it is more susceptible to oxidative stress than other tissues.\[^{18}\] In addition heart has comparatively the lowest level of anti-oxidant enzyme activity than majority of other tissues.

Biological compounds with anti-oxidant properties provide tissue protection against ROS induced by LPS. One such natural molecule known to prevent oxidative stress is ALA. It is considered as universal anti-oxidant that act in both lipid phase and aqueous phase.\[^{19, 20, 21}\]
In experimental models, administration of LPS lead to development of oxidative stress damage in heart tissue. There is also increase in the concentration of TBARS, lipid peroxidation indices, decrease in the concentration of GSH have also been reported. ALA counteracts the damage associated with LPS induced oxidative stress by inhibiting ROS production, restoring the reduced GSH levels and by scavenging of excess free radicals produced. Antioxidants such as ALA are widely regarded as attractive novel agents which can be employed to prevent oxidative stress. Several studies have reported that ALA administration effectively decreases the cardiac apoptosis.

EFFECT OF ALA IN OXIDATIVE STRESS INDUCED RE-EXPANSION PULMONARY ODEMA

Re-expansion pulmonary odema (RPE) is an iatrogenic disease that occurs during the treatment of pneumothorax (or) pleural effusion. It is usually developed due to removal of 2000ml (or) even more volume from the collapsed lungs, but the pathophysiology of RPE is not yet determined completely. In studies using animal models of RPE, it was found that oxidative stress also plays a vital role in the pathogenesis that was confirmed by increased levels of MDA (Malondialdehyde) which is an indirect marker for oxidative stress and remarkable depletion in the anti-oxidant enzyme status. Administration of ALA to the RPE induced animals significantly increased the anti-oxidant levels which indicate that ALA have a role in decreasing the oxidative stress associated with RPE and the ALA treatment contributes to preventing the development of experimental RPE in animal models by reducing oxidative stress. Many studies have confirmed that ALA can improve anti-oxidant enzyme levels by its capacity to regenerate the endogenous anti-oxidants. Finally, it can be concluded that ALA, by increasing the levels of natural anti-oxidants is found to have a protective effect on oxidative stress associated with re-expansion pulmonary odema.

CONCLUSION

Numerous investigations have provided abundant evidence that oxidative stress plays an important role in pathogenesis of many diseases. Studies indicate that antioxidants prevent development of oxidative stress induced diseases and may even improve the course of these diseases. LA is an ideal antioxidant that can provide protection against ROS-induced damage under conditions of elevated oxidative stress. It meets all the criteria for an ideal antioxidant, because it may reduce adverse effects of oxidative stress, has amphiphilic properties and does
not exhibit any serious side effects. It seems that lipoic acid is the most efficient drug of all antioxidants, which is confirmed by the following data.

- Lipoic acid is characterized by high reactivity towards free radicals and is capable of regeneration of vitamin C and E. In addition, it elevates tissue levels of GSH.
- Lipoic acid can be administered per orally since it is easily absorbed in the stomach. It crosses blood-brain barrier and does not show toxic actions at doses used for prophylactic and therapeutic purposes.
- Many experimental and clinical studies proved beneficial effect of lipoic acid in such diseases as diabetes, atherosclerosis and heart diseases, cataract, neurodegenerative diseases and liver diseases. However, involvement of lipoic acid in cell growth and differentiation requires further intense studies.

REFERENCES


