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Review Article

The Potential of Alpha Lipoic Acid to Maintain Liver Function Tests in Xenobiotic-Induced Liver Toxicity: A Narrative Review

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ABSTRACT

Acute liver injury (ALI) is a life-threatening medical emergency which involves multiple organ systems. The synthetic, metabolic and excretory functions of the liver are severely impaired in ALI. ALI is defined as a rapid development of ALI with encephalopathy in patients who previously had normal liver functions. Drug-induced hepatotoxicity or drug-induced liver injury (DILI) is an acute or chronic response to a natural or manufactured compound. In the US, it is the leading cause of acute liver failure episodes (13-16%). The development of these disorders reflects complex pathological processes in which the oxidative stress caused by reactive oxygen species (ROS) and reactive nitrogen species (RNS) play pivotal roles. Alpha lipoic acid (ALA), which plays an essential role as an antioxidant has drawn considerable attention for use in managing liver disorders.

Keywords: Alpha lipoic acid, Hepatoprotective activity, Oxidative stress.

Introduction

Drug-induced hepatotoxicity or drug-induced liver injury (DILI) is an acute or chronic response to a natural or manufactured compound. The true incidence of DILI is not easy to determine as it is often underreported and there are various different diagnostic criteria applied. In the US and worldwide, DILI annual incidence in the general population is under 15-20 per 100,000. In the US, it is the leading cause of acute liver failure episodes (13-16%), yet it is paramount to note that it is still a much less common cause of acute liver injury overall.[1] The liver is constantly involved in biotransformation and this could lead to hepatotoxicity.[2, 3] Production of free radicals causes oxidative stress and this is the basis of drug-induced hepatotoxicity.[4]

Phytochemical compounds that protect the liver usually have a variety of activities, such as antioxidant, anti-inflammatory, immunomodulatory, and antiviral effects.[5] Alpha lipoic acid is a powerful antioxidant which has been previously found to have a wide range of health benefits including a protect effect on the liver. The present review is an up-to-date paper of current thinking regarding ALA and its use in providing antioxidant drug therapy on the potential role of ALA on xenobiotic-induced liver injury.

Chemistry of ALA

LA is also called thioctic acid and is chemically named 1,2-dithiolane-3-pentanoic acid (C8H14O2S2): with an oxidized (disulfide, LA) and a reduced (di-thiol: dihydro-lipoic acid, (Fig. 1) DHLA) form of LA.[6]

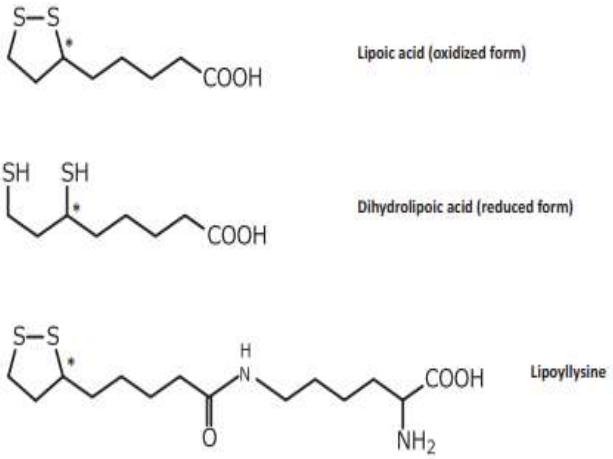

Figure 1: Chemical structures of lipoic acid (LA), dihydrolipoic acid (DHLA), and lipoyllysine (LA attached to biologic lysine residues);*, the structure contains a chiral center.

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Pharmacokinetics of α-Lipoic acid

ALA has a short half-life and bioavailability of about 30% due to certain mechanisms, including hepatic degradation, reduced solubility as well as instability in the stomach. However, this has been greatly improved through the use of various innovative formulations that directly increase ALA bioavailability.[7]

Recent applications of ALA in liver injury research

Cigarette smoking (CS) is common worldwide, in addition to many being exposed to secondhand smoking. cigarette smoke exposure leads to an increase in TNF‑α expression, MDA, AST, ALT and total bilirubin levels, which are associated with liver damage, and that ALA has a mild ameliorative effect on the liver damage induced by cigarette smoke. Studies using different ALA doses and routes of administration are needed to fully understand the healing effect of ALA against liver damage caused by CS.[8] a-LA has the capacity to secure the liver from the dangerous *in vivo* impacts of CCl4-actuated liver fibrosis.[9] ALA protects against schistosomiasis-induced liver fibrosis, which demonstrates that ALA is required for the maintenance of mitochondrial function by upregulating phosphorylation Dynamin-related protein 1(p-Drp1) expression to inhibit mitochondrial fission.[10] ALA ameliorates sodium valproate-induced liver injury in mice.[11] ALA ameliorates Imidacloprid-induced liver damage in albino rats.[12] The chronic exposure to chlorpyrifos (CPF) pesticide induces several human disorders including hepatotoxicity. The chronic exposure to chlorpyrifos (CPF) pesticide induces several human disorders including hepatotoxicity. ALA possess protective effects against CPF-induced liver injury through attenuation of apoptosis and oxidative stress. ALA showed significant antiapoptotic effects through downregulation of Bax and Caspase-3 expression levels.[13] Alpha lipoic acid also protects the liver in APAP-induced uremic albino male rats.[14]

ALA decreases the expression of pro-inflammatory IL-6 and increase of anti-inflammatory IL-10, and lower values of AST with the reduction of hepatic steatosis.[15] ALA protects the liver against amiodarone-induced hepatic injury.[16] ALA modulates TNF-*α* mediated 5-fluorouracil-induced hepatotoxicity in Wistar rats.[17]

The involvement of cell signaling pathways

ALA has hepatoprotective effects against methotrexate (MTX)-induced hepatic injury mediated by Nrf2/HO-1 pathway as well as anti-inflammatory and antiapoptotic properties.[18] α-LA activates Nrf2 signaling pathway, which upregulates the transcription of the enzymes for GSH synthesis and therefore GSH contents to alleviate cadmium-induced cytotoxicity in HepG2 cells.[19] ALA is able to protect CCl4-induced liver cirrhosis, an effect that may be associated with inactivation of the TGF-/Smad3 pathway and suppression of autophagy.[20] ALA mitigates acrylamide-induced hepatotoxicity in rats.[21] ALA downregulates the activation of NF-*κ* Signaling pathway and the pro-inflammatory cytokine TNF-α in 5-FU-induced hepatic damage in Wistar rats. It restores lipid peroxidation, liver destruction and antioxidants pointing strongly to the protective potential of ALA in 5-FU-induced hepatic damage in Wistar rats.[22,23]

Synergistic liver protective effects of ALA with other compounds

Pretreatment with anti-oxidative agents, namely ascorbic acid, ALA and silymarin, showed significant in vivo and in vitro influence in inhibiting the occurrence of hepatic injury induced by Acetaminophen (N-acetyl-p-aminophenol) APAP.[24] Acetaminophen-induced liver injury is mitigated by a combination of ALA and Thymoquinone (THQ), the most potent component of *Nigella sativa*.[25] Alpha-lipoic acid also protects against valproic acid–induced liver injury.[26] The combination of ALA, acetyl-L-carnitine (ALCAR), and coenzyme CoQ10 may provide an effective strategy in preventing anti-TB DILI.[27] ALA and silymarin treatment ameliorate thioacetamide (TAA)-induced oxidative damage,alterations in the liver function tests and liver histopathology in male albino rats.[28] Apocynin and α-LA in combination possess marked antifibrotic effects, and that NADPH oxidase (NOX) enzymes are partially involved in the pathogenesis of concanavalin (ConA)-induced liver fibrosis.[29] alpha-lipoic acid and royal jelly protect against CP-induced liver damage by their antioxidant effects. [30] Curcumin and ALA can be considered as promising natural therapies against liver injury, induced By N-(4-hydroxyphenyl) acetamide, NHPA, through their antioxidant and antifibrotic actions.[31] ALA and spirulina ameliorate aspartame-induced hepatic injury.[32] Biomarkers of cardiac,renal and hepatic damage are reduced by alpha lipoic acid and/or sesame oil (SO).They also restore antioxidant enzymes and reduce lipid peroxidation.[33] The abilities of SO and ALA to exert this protective effect is positively correlated with their abilities to suppress NO overproduction, maintain cellular antioxidant defense mechanisms and LPO. The harmful effects of diazinon can be prevented by sesame oil and or alpha lipoic acid because of their potent antioxidant abilities.They improve levels of GSH and the activities of GSH-Px, CAT and SOD in the heart,kidney and liver.They also lower NO and MDA levels,both of which support the hypothesis above.[34-38]

Nanoparticle-induced hepatic injury

ALA could be used as an applicable hepatoprotective agent against oxidative damage mediated by nano copper particle intoxication.[39] ALA also protects the liver against nano silver particle injury in male rats.[40]

Antioxidant properties of ALA

Alpha-lipoic acid (ALA) is a naturally occurring dithiol compound synthesized from octanoic acid in the mitochondrion and acts as a coenzyme for the mitochondrial respiratory enzymes.[41] ALA in many tissues is rapidly converted to its redox couple, dihydrolipoic acid (DHLA). Alpha lipoic acid is a short chain naturally occurring fatty acid which is needed for mitochondrial enzyme function.[42,43]. It occurs naturally in food and has improved functional capacity when given as a supplement.[44] Alpha lipoic acid helps in the regeneration of endogenous antioxidants like intracellular reduced glutathione (GSH) , vitamin E and vitamin C in order to scavenge free radicals.[45,46] ALA and DHLA can recirculate antioxidants and they can prevent free radical reaction.Their antioxidant properties are based on these.[47] Alpha lipoic acid has a wide range of benefits; the most important one is its role as an antioxidant which equals to that of coenzyme Q 10, vitamin C and vitamin E.[48] Free radicals such as lipid peroxides are effectively reduced by alpha lipoic acid because it is both fat and water soluble.[49] Diseases mediated by oxidative stress are treated effectively with alpha lipoic acid .[50] It is also able to reduce apoptosis in the liver because of its ability to reduce oxidative stress.[51] ALA and DHLA derivatives also have anti-inflammatory activities.[52] Alpha lipoic acid (ALA) is a cofactor of α-ketoacid dehydrogenase complexes and plays a fundamental role in fuel metabolism.[53] Alpha lipoic acid interacts with other antioxidants and thiols,changes cellular metabolic processes and also changes the redox status of cells.[54] It reduces the oxidized forms of other antioxidants, chelates metal ions. It is amphiphilic antioxidant that quenches reactive oxygen species. It can inhibit xenobiotic-induced liver toxicity as reported in adriamycin-induced hepatotoxicity in rats.[55] It also restored hepatic function in chloroquine intoxicated rats.[56] In addition, it ameliorated aflatoxin B1-induced excess production of lipid peroxides and maintained intracellular antioxidant status in the liver.[57] Furthermore, studies have reported synergistic activity with concurrent use of melatonin and alpha lipoic acid.[58] Production of free radicals leads to oxidative stress and this is the basis of drug- induced hepatotoxicity.[59]

Amelioration of lopinavir/ritonavir-induced liver damage by alpha lipoic acid in albino rats

The use of lopinavir/ritonavir can lead to elevated levels of aminotransferase in patients who already have liver disease. The drug could cause hepatic failure, hepatitis and even death.[60] Lopinavir/ritonavir also changes the morphology(histology) of the liver in laboratory animals treated with the drug.[61] Factors responsible for the induction of hepatotoxicity by treatment with lopinavir/ritonavir include oxidative stress which is as a result of mitochondria injury, depletion of antioxidants and free radical production in research using aminals.[62,63,64]

Melatonin and alpha lipoic acid decrease malondialdehyde (MDA), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) but superoxide dismutase (SOD), catalase(CAT) and glutathione (GSH) levels in rats. This is consistent with previous findings.[65] This is more noticeable in the rats treated simultaneously with melatonin and alpha lipoic acid. On the contrary,dose-dependent increases in serum AST, ALT, ALP and liver MDA levels with decreases in SOD, GSH and CAT levels are obtained in rats treated with LPV/r.[66] These findings are consistent with some reported observations.[67,68,69,70,71] AST, ALT and ALP are considered as markers of hepatocellular injury; therefore, increases in their levels in LPV/r treated rats are indicators of hepatocellular damage. This may be due to LPV/r-induced increase in the permeability of cell membrane resulting in the release of AST, ALT and ALP into the bloodstream.[72] When oxidative stress is induced in the liver by lopinavir/ritonavir, there is abnormal synthesis of liver enzymes such as alkaline phosphatase and aminotransferases. Lopinavir/ritonavir decreases CAT,GSH and SOD but increases MDA levels which is indicative of oxidative stress by the production of free radicals.[73,74,75] Generally, malondialdehyde is used as an index for lipid peroxidation, and lipid peroxidation is postulated as one of the mechanisms of free radical-induced tissue injury.[76] This means that lopinavir/ritonavir causes lipid peroxidation becauses it increases the levels of malondialdehyde. Membrane fluidity of liver cells can be modified by lipid peroxidation. This can then modify carrier mediated transport, activities of membrane bound enzymes and receptor binding, which could result in the leakage of certain intracellular enzymes.[77,78] Liver SOD,GSH and CAT were increased while serum AST,ALP,ALT and liver MDA were decreased in rats treated with individual dose of melanin and alpha lipoic acid. These observations are however more apparent in rats concurrently treated with melatonin and alpha lipoic acid. This agrees with a previous report on the inhibitory effect of melatonin on endotoxin - induced hepatotoxicity in rats.[79] Similarly it was reported the protective effects of melatonin and ALA on cadmium-induced oxidative damage in the liver of rats.[80] Attenuation of LPV/r-induced hepatotoxicity by melatonin and alpha lipoic acid pretreatments can be attributed to the inhibition of LPV/r-induced hepatic oxidative stress by these antioxidants.[81] Melatonin and alpha lipoic acid are said to stimulate the biosynthesis and regeneration of GSH,CAT and SOD and that is why there is increase in these antioxidants in rats supplemented with melatonin and alpha lipoic acid. Melatonin and its metabolites as well as alpha lipoic acid and its reduced form prevent oxidative stress by scavenging free radicals.[82,83,84,85] Alpha lipoic acid and melatonin can increase the activity of CAT,GSH and SOD thereby fostering more antioxidant activities.[86,87] Due to its small size and high lipophilic nature, melatonin can cross biological membranes easily and reach all compartments within the cell.[88] Thus protecting DNA, proteins and biological membrane lipids from the deleterious effects of free radicals.[89]

Melatonin has receptor-mediated local functions which also prevents oxidative stress (which can lead to cell death by necrosis and apoptosis) apart from its antioxidant and free radical scavenging roles.[90,91] In xenobiotic-induced hepatotoxicity, inflammation is said to play a pivotal role. Alpha lipoic acid and melatonin can inhibit oxidative stress-induced inflammatory cascade characterized by the production of inflammatory mediators.[92,93,94] Melatonin can modulate inflammatory cytokines and other mediators of inflammation which cause damage to the liver.[95] Melatonin prevents the infiltration and accumulation of neutrophils and the leakage of hepatic enzymes by preserving the integrity of hepatocyte membrane.[96,97,98] Synergistic anti-inflammatory and antioxidant activities is the reason behind enhanced effects seen with concurrent treatment of melatonin and alpha lipoic acid.[99]

Anti-inflammatory activity of ALA and Vitamin E

Lipopolysaccharides or endotoxins are released into the systemic circulation when bacteria die which can lead to hepatotoxicity.[100] Other direct mechanisms by which lipopolysaccarides cause hepatoxicity include activation of kupffer cells and other inflammatory cells. Most of the toxicities observed in LPS-induced injury has been attributed to toxic mediators produced by activated macrophages, including cytokines, such as tumor necrosis factor-α (TNF-α), interleukins (IL-1, IL-6, IL-8, and IL-12), other pro-inflammatory molecules, including platelet-activating factor, prostaglandins as well as reactive oxygen and nitrogen species (RONS), such as nitric oxide.[101] Pro-oxidant state can result from endotoxins [102]. This can lead to necrosis and apoptosis in the liver.[103] Moreover, LPS induces elevation in lipid peroxidation which is an index of oxidative stress that depends on both time and dose.[104] The reticulo-endothelial system especially kupffer cells of the liver mediate in the detoxification of endotoxins.[105]

Lipoic acid, vitamins C,E,A, non-enzymatic compounds such as glutathione(GSH),enzymatic antioxidants such as glutathione S-transferase (GST), glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT) are ways by which the body defends itself against the mediators of liver damage.[106] Therefore, antioxidants are vital substances which possess the ability to protect the body from damage caused by free radicals.[107] Vitamins are effective, easy and can be safely taken in large range of doses. These make them suitable for safeguarding tissues against oxidative stress.[108] Vitamin E is one of the most essential vitamins which is easily absorbed in the intestinal lumen because it is lipid soluble. Vitamin E can also inhibit free radical chain reactions.[109]

Hepatocyte damage, inflammatory reactions and steatosis are also present in laboratory animals treated with LPS.[110] Circulating LPS binds to Toll-like receptor- 4 (TLR- 4) on hepatic phagocytes and macrophages, leading to their stimulation and subsequently tend to release reactive oxygen species (ROS), reactive nitric species (RNS), as well as, pro-inflammatory cytokines, such as TNF-α and IL-6.[111] Additionally, LPS induces the migration of activated polymorphonuclear leukocytes (PMNs) into the liver, which constitutes another source of free radicals.[112] Markers of hepatic damage such as ALP, AST, and ALT are elevated with a single injection of LPS. These enzymes usually leak from the cytoplasm into circulation because of changes in membrane permeability.[113] This agrees with previous reports.[114,115] They previously reported that lipopolysaccharide damages the liver and increases serum amino transferase levels. Pretreatment with alpha lipoic acid ameliorates oxidative stress by reducing lipid peroxidation through scavenging free radicals. This reduces levels of ALP, AST, and ALT. This is also in agreement with previous reports.[116,117] Alpha lipoic acid also functions with other antioxidants such as vitamins E,C and glutathione to maintain the integrity of cell membranes.[118] Also, administration of vitamin E before LPS challenge results in a significant reduction in the serum aminotransferases levels as previously reported.[119-121] Vitamin E also has been reported to confer protection against such changes in formaldehyde and monosodium glutamate induced-hepatotoxicity and oxidative stress in rats.[122] Lipid peroxidation is an index of oxidative stress and LPS is said to facilitate it in tissues such as stomach, small intestine, brain, heart, and liver in rats.[123] Under conditions of oxidative stress, reactive oxygen and nitrogen species (RONS) attack the polyunsaturated fatty acids (PUFAs) of cell membranes causing destabilization, disintegration and alteration in membrane fluidity and permeability, all events which increase the rate of protein degradation and eventually leads to cell lysis.[124] MDA and other products from decomposed lipid hydroperoxides can interact with nucleic acids and protein leading to oxidative destruction of DNA and proteins.[125] MDA levels was decreased significantly by prophylactic administration of alpha lipoic acid in rats treated with LPS as previously reported.[126] ALA scavenges free radicals thereby reducing MDA levels. This effect can be explained on the basis that, ALA or its reduced form dihydrolipoic acid (DHLA) can prevent lipid peroxidation and protein damage via interaction with vitamin C and glutathione. Alpha lipoic acid is said to have a powerful antioxidant activity and as such can prevent protein oxidation and the generation of reactive oxygen species.[127] Catalase activity is also enhanced in rats treated with alpha lipoic acid. It was also reported that alpha lipoic acid increases catalase activity to promote antioxidant defense. Alpha lipoic acid also improves the hepatic redox by increasing GSH levels.[128] Both ALA and its derivate DHLA may act as extra-and intracellular redox couples and potent free radical scavengers. This may imply that ALA

prevents the oxidation of free or protein-bound thiols.[129] Alpha lipoic acid increases the GSH levels which also improves thiol status.[130] TNF-α and IL-6 levels are decreased by administration of alpha lipoic acid or vitamin E.[131,132] IL-10 is an anti- inflammatory cytokine that has been reported to down-regulate TNF-α, as well as other cytokines production, by suppressing their gene expression in an autocrine-like feedback loop.[133] The anti- inflammatory actions of IL-10 appear to require induction of the enzyme heme-oxygenase-1 (HO-1) through a map kinase pathway involving the p38 kinases. HO-1 is induced by IL-10 and is also induced by oxidative stress.[134] Alpha lipoic acid and vitamin E increase IL-10 levels. This means that the activation of the IL-10 feedback loop affects the inhibition of TNF-α formation. The anti-inflammatory effect of vitamin E may be indirectly related to inhibition of chemotaxis of neutrophils through inhibition of protein kinase C, 5-lipoxygenase, tyrosine-kinase and cyclooxygenase.[135] Increase in serum proinflammatory cytokines is prevented by alpha lipoic acid. Alpha lipoic acid has anti-inflammatory effects because it inhibits mediators of inflammation such IL-1 and TNF-α in LPS induced liver sepsis. The hepatoprotective activity of alpha lipoic acid is related to these mechanisms. These are by inhibition of proinflammatory cytokines and by inducing endogenous antioxidant activity.[136]

ALA ameliorates phenytoin–induced hepatotoxicity

Hepatotoxicity is one of the adverse effects of phenytoin.[137] Phenytoin induced hepatotoxicity is caused by oxidative stress.[138] Alpha lipoic acid is called "universal antioxidant" because it neutralizes free radicals in both lipid and aqueous media. ALA functions as both fat and water soluble antioxidant that easily crosses cell membranes, thereby it confers free radical protection to both interior and exterior cellular structures.Alpha lipoic acid has antioxidant activity in both oxidized and reduced states.[139] Alpha lipoic acid was initially used to treat hepatotoxicity induced by heavy metals, mushroom and alcohol. The antioxidant abilities of ALA and its role in glutathione recycling have encouraged its use in liver damage.Alpha lipoic acid was found to be more hepatoprotective than silymarin in chloroquine induced hepatotoxicity.[140] It was also previously concluded that oxidative stress is one of the mechanisms of phentoin induced hepatotoxicity.[141] Phentoin also depletes antioxidants such as SOD,catalase,GSH in liver and increased lipid peroxidation.[142,143,144,145]

ALA ameliorates hepatic injury in chloroquine-induced liver injury

Chloroquine induced hepatotoxicity is significantly mitigated by alpha lipoic acid. [146]

ALA ameliorates tamoxifen (TAM)-induced hepatic injury

Tamoxifen (TAM) induced hepatotoxicity is also mitigated by alpha lipoic acid. It was also suggested that ALA can be used in the prophylactic treatment of TAM-induced liver injury than its use as curative agent (post-TAM administration).[147] Thioacetamide (TAA) induced liver fibrosis is inhibited by co-administration with alpha lipoic acid in rats.[148] It was observed that the combination of both the antioxidants significantly decreased the TBARS level of the brain and liver and thereby attenuated oxidative stress, restored the δ-ALAD activity against arsenite induced toxicity.[149] Alpha lipoic acid also inhibits malathion induced toxicity.[150] Isoniazid and Rifampicin (INH- RIF) induced liver damage is also inhibited by alpha lipoic acid.[151] ALA restores total body weight of the rats and reduces the relative liver weight against changes brought about by treatment with phenytoin.[152]

Estradiol and -Lipoic Acid protect against liver damage in Rats

Elevated aminotransferase of even far greater than thrice the upper limit of the reference values might not lead to clinically significant liver damage.This is because of the enormous ability of the liver to restore vitality after damage as seen especially in drugs like tacrine and isoniazid.[153,154] Detoxification reactions metabolize xenobiotics resulting in increased substrate hydrophilicity for excretion. Lipid peroxidation is favoured by estrogen replacement.[155] Among the steroid sex hormones, 17-beta estradiol is the most effective antioxidant. A-lipoic acid has been used since early 1990s to prevent oxidative stress in lipophilic and hydrophilic media in form of food supplement. Another report showed that -lipoic acid could inhibit cytchrome P 450 reductase from hepatic microsomes through disulfide-thiol exchange between -lipoic acid and cytochrome P450 reductase.[156] It is well known that structure of nitric oxide synthase (NOS) is homologous to cytochrome 4 P450.[157] Therefore, it cannot be excluded that inhibition of hepatocyte NO synthesis by -lipoic acid is directly associated with reduced NOS activity due to the disulfide-thiol exchange between - lipoic acid and NOS. Estradiol treated rats show decreased ALP and a significant increase in MDA, creatinine and LDH levels. Estradiol restores biochemical parameters to the normal control in CCl treated rats. The mechanism by which estradiol induced its hepatoprotective properties may be due to the fact that estradiol induces the expression of heat-shock protein 70 (Hsp70), decreased NO, enhanced antioxidant enzyme activities, reduced neutrophil infiltration, and reduced lipid peroxidation.[158]

In ischemia, there is elevated levels of HSP70 which prevents hepatic and cardiac damage. It was reported that NO production in stressed cells could be modulated by the heat shock response (HSR); through repression of iNOS gene transcription after heat shock, Hsp70 and other heat- shock proteins may play a role in mediating iNOS inhibition.[159] Many pathways of apoptosis and stress-induced apoptosis can be prevented by the over expression of hsp70.[160] Increasing antioxidant levels in hepatocytes cells is another mechanism by which estradiol carries out hepatoprotective activity.[161] For example MDA level is decreased and SOD level is increased by estradiol in CCl treated rats.These results suggested that estradiol treatment could also increase antioxidative bioactive molecule expression in liver after CCl4 intoxication and attenuate neutrophil infiltration and ROS injury in liver or other tissues.[162] There is improvement in biomarkers of liver damage which is consistent with previous scientific report about the role of alpha lipoic acid against oxidative stress and hepatotoxicity.[163]

Conclusion

ALA is able to protect cells and tissues from ROS and free radicals due to its antioxidant properties. The LA/DHLA couple has been called the "universal antioxidant." Furthermore, many studies have reported that LA can regulate the transcription of genes associated with antioxidant and anti-inflammatory pathways.LA has been shown to possess a number of beneficial effects both in the prevention and in the treatment of hepatotoxicity in several experimental conditions and clinical trials. In the future, a combination of currently used pharmaceuticals, together with natural antioxidants such as LA, could be taken into account in the design of both in the prevention and in the treatment of hepatotoxicity and other liver diseases.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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