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Combined efficacies of DL-α-lipoic acid and meso 2,3 dimercaptosuccinic acid against arsenic induced toxicity in antioxidant systems of rats

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Abstract

Health hazards caused by heavy metals have become a great concern to the population. Arsenic as an environmental agent is considered to be a toxic substance due to its carcinogenic potential in humans. Since arsenic compounds might exert their toxicity by the generation of reactive oxygen species, we have evaluated the effect of both DL-α-lipoic acid (LA) and meso 2,3 dimercapto succinic acid (DMSA) on the antioxidants and lipid peroxidation in arsenic treated rats. The objective of the study was to determine whether DL-α-lipoic acid and meso 2,3 dimercapto succinic acid could rehabitate antioxidant depletion and damage to biomolecules in protection against oxidative insults. A significant increase in the levels of reactive oxygen species formation and lipid peroxidation and decrease in the activities of antioxidant enzymes were observed in arsenic exposed rats. Supplementation of DL-α-lipoic acid and meso 2,3 dimercapto succinic acid to arsenic fed rats significantly increased the activities of superoxide dismutase, catalase, glutathione peroxidase with elevation in the levels of reduced glutathione, total sulfhydryl, ascorbic acid and α-tocopherol. In addition, significant decrease in the levels of reactive oxygen species formation and lipid peroxidation was also observed in our study. From our results, we conclude that DL-α-lipoic acid and meso 2,3 dimercapto succinic acid play a synergistic role in decreasing arsenic induced oxidative damage by elevating the antioxidant status in liver and kidney.

Keywords: Arsenic; Oxidative stress; Liver; Kidney; DL-α-Lipoic acid; DMSA

1. Introduction

Arsenic is one of the most important, current global environmental toxicants. It occurs mainly in nature, being present in minute quantities in the soil, the sea and

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in living matter. The contamination of arsenic in drinking water is a major health problem in certain areas including parts of Bangladesh, United States, Taiwan, Mexico, Japan and India where the arsenic concentration exceeds the WHO's drinking water provisional guidelines value 10 μg/L. Exposure of arsenic may cause many sever biochemical and pathological problems such as Blackfoot disease (Tseng et al., 1996), hypertension (Lai et al., 1994), diabetes mellitus (Chen et al., 1995) and cancers of liver, kidney, lung and bladder in humans (Hei and Filipic, 2004).

Arsenite, a trivalent form of arsenic [As(III)], forms strong complexes with thiols (Aposhian et al., 2004). It is reported that arsenic compounds exert its toxicity by the generation of reactive oxygen species during their metabolism in cells to cause tissue damage (Liu et al., 2001).

Arsenic is known to produce damage in the both liver and kidney tissues by enhancing peroxidation of membrane lipids (Ramos et al., 1995), which is a fatal process exclusively carried out by free radicals (Harris and Shi, 2003). Several studies have investigated possible relationship between lipid peroxidation (LPO) and cellular damage in both hepatic and renal tissues under various pathological conditions (Esterbauer et al., 1991). It has been recognized that arsenic exerts its toxic effects through several mechanisms, the most significant of which is the reversible reaction with sulfhydryl group's especially vicinal dithiols (Aposhian and Aposhian, 1989). The binding of arsenic to thiol containing amino acid residues in proteins has provided a mechanistic framework for envisioning interactions between proteins and arsenicals and for understanding the inhibition of the activities of enzymes by arsenical (Searle and Wilson, 1980).

Cell membranes are targets for oxidative damage produced by heavy metals (Leonard et al., 2004). Decomposition of membrane lipids is disastrous for living systems. The protection of cells against damage from oxygen and its metabolites can be accomplished through enzymatic and non-enzymatic means. Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and the non-enzymatic antioxidants namely ascorbic acid, α-tocopherol, reduced glutathione (GSH) and total sulfhydryl (TSH) scavenge free radicals and lipid peroxides and detoxify them (Dwivedi et al., 1984). Several reports have shown that lipid peroxidation is enhanced by disturbances such as depletion of cellular antioxidants (Cine and Moretti, 1995; Pompella et al., 1991).

Biological compounds with antioxidant properties contribute to the protection of cells and tissues against deleterious effects of ROS and other free radicals. α-Lipoic acid is a low molecular weight substance readily absorbed from the diet and is converted to dihydrolipoic acid (DHLA), which can be easily transported to many tissues. Recent studies show that α-lipoate and dihydrolipoic acid can act as potent antioxidants (Navarizzo et al., 2002). Dimercaptosuccinic acid, an antidote belonging to the mercapto family has vicinal dithiol moiety for the binding of arsenic and has been found as a potentially useful drug for the treatment of arsenic poisoning (Hantson et al., 2003; Flora et al., 2004). Yet, little is known about the combined effect of DL-α-lipoic acid (LA) and meso 2,3 dimercapto succinic acid (DMSA) on arsenic toxicity. Hence, the current study was designed to investigate the combined effects of these two compounds on antioxidant status during arsenic exposure in rat liver and kidney.

2. Materials and methods

Sodium arsenite, DL-α-lipoic acid, meso 2,3 dimercapto succinic acid, 2′,7′ dichlorofluorescein and were purchased from Sigma Chemical Company (St. Louis, USA). All other chemicals were of Analytical grade and were obtained from Sisco Research Laboratory, Bombay, India.

2.1. Experimental design

Male albino rats of Wistar strain weighing approximately 150 ± 10 g were obtained from King's Institute of Preventive Medicine, Chennai, and maintained in clean rooms. Animals were housed in spacious cages and were maintained at a temperature of 28 ± 1 °C, and under a 12-h light/12-h dark cycle. The animals were divided into five groups namely:

Group I	Rats received vehicles alone, served as control.
Group II	Rats received arsenic in the form of sodium arsenite in drinking water at a concentration of 100 ppm.