Protective effects of lipoic acid against oxidative stress induced by lead acetate and gamma-irradiation in the kidney and lung in albino rats

Rezk, R.G., & Abdel-Rahman, N.A.

Health Radiation Research Department and Radiation Biology Department, National Center for Radiation Research and Technology (NCRRT), Cairo, Egypt.

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ABSTRACT

Lipoic acid is widely used as antioxidant that protects tissues against a range of oxidative stress. The present study was designed to determine the protective effect of lipoic acid against oxidative organ damage induced by lead intoxication and/or gamma-irradiation. Rats were treated daily intraperitoneally (i.p.) with lipoic acid (200mg/kg/b.w) for 15 consecutive days before lead acetate injection (30mg/kg/b.w) i.p. for 5 days and/or whole body gamma-irradiation (3Gy). Animals were sacrificed on the 3rd day post the last treatment. Histological examination of kidney and lung tissues through light microscope showed that lead acetate injection and/or exposure to gamma radiation has provoked severe architectural damage in both tissues as necrotic lesions, atrophoid glomeruli and degenerated proximal and distal convoluted tubules, severe bronchiolitis fibrosis, decreased ciliated bronchioles and dilated and widened pulmonary artery. Histological damage was associated with significant biochemical changes as increase in lead, copper, iron, zinc and calcium levels in both kidney and lung tissues. Kidney and lung of rats treated with lipoic acid before lead intoxication and/or gamma-irradiation showed significant regenerated glomeruli structure, well-defined structure of proximal and distal convoluted tubules, regenerated ciliated bronchiole structure and improved pulmonary artery. Tissue regeneration was associated with significant decrease in Pb, Cu, Fe, Zn, and Ca levels in kidney and lung and prevented the accumulation of metals in these organs. It could be concluded that lipoic acid administration before lead and/or whole body gamma-irradiation might be capable to attenuate lead and/or gamma radiation induced organ injury and organ metals disruption.

INTRODUCTION

stress and resultant damages of lipids, proteins, and DNA. Lead is the common environmental heavy metal pollutant and have widespread distribution. Both natural and anthropogenic sources including mining, smelting, and other industrial processes are responsible for human and animal exposure(1). These pollutants many a times, are copollutants lead to concurrent exposure to living beings and resultant synergistic deleterious health effects(2). Several reports have indicated that lead can cause neurological, hematological, gastrointestinal, reproductive, circulating, and immunological pathologies, relative to the dose and the amount of lead exposure(3).

In vivo and in vitro studies suggest that lipid peroxidation is altered both in acute and chronic exposure to lead which harms proteins, cell membranes and DNA, among others. However, this damage could decline when antioxidants are supplied(4&(5). Jarrer and Mahmoud,(2000)(6) suggested that lead inclusion bodies may represent accumulation of both extracellular and intracellular materials as a result of cellular metabolic disturbance and/or alterations in nuclear membrane permeability. The formation of these intracellular inclusion bodies is a pathognomonic sign of chronic lead intoxication(7). Their accumulation is an early hallmark of lead intoxication nephropathy(8). On the
other hand, such inclusion bodies were shown to increase the incidence of renal adenocarcinoma\(^9\). Lead was predominantly localized in the renal proximal tubules, twice as much of the metal as the distal tubules\(^10\). Toxic effect of lead have been attributed to its capability to mimic calcium and alter calcium homeostasis\(^11\). Lead may ultimately perturb calcium-mediated functions or act by altering cell functions required for calcium homeostasis\(^12\). Crowe and Morgan,\(^{13}\) found that there is evidence for an interaction between lead and iron metabolism which could produce changes in lead and iron uptake by brain and other tissues. Iron deficiency was associated with increased intestinal absorption of lead as indicated by blood and kidney lead levels in rats exposed to dietary lead. Dekaney et al.,\(^{14}\) reported that intestinal absorptive cells transport nutritive metals such as copper, iron, and zinc. Cerklewski and Forbes,\(^{15}\), who revealed that simultaneous exposure of rat small intestine to zinc and lead reduced the amount of lead absorbed by that tissue. Radiation damage is largely caused by the overproduction of reactive oxygen species (ROS), including superoxide anion\(\text{O}_2^-\), hydroxyl radical\(\text{OH}\), and hydrogen peroxide\(\text{H}_2\text{O}_2\), that overwhelm the levels of antioxidants, resulting in oxidative stress. One of the most important consequences of oxidative stress is lipid peroxidation\(^16\). Exposure to ionizing radiation, chemical pollutants and dietary carcinogens can trigger free radical reactions in aerobic organisms and lead to formation of reactive oxygen species.

Deleterious reactions of these oxyradicals with biomolecules result in cellular DNA strand breaks, protein oxidation and lipid peroxidation\(^17\). According to\(^{18}\) hydroxyl radicals are extremely reactive and can attack any cell component and cause oxidative damage. These radicals can also lead to the formation of other reactive oxygen species (ROS)\(^19\). ROS can attack the polyunsaturated fatty acids of the cell membranes and induce lipid peroxidation\(^20\). Lipid peroxidation of cell membranes including mitochondrial membranes can in turn comprise cell integrity and function and affects its energy status, thereby causing further tissue injury\(^21\). These damages and subcellular metabolic changes may be acute and/or chronic and may or may not be fatal, depending on the extent of the radiation injury\(^22\). Bousvaros et al.,\(^{23}\) found that if the oxidative stress is sustained, it will progressively weaken the antioxidant defense system. According to\(^{24}\) lipoic acid has been widely studied as an agent that prevent and treat various diseases associated with oxidative disruption of mitochondrial function. Also\(^{25}\), reported that lipoic acid is highly effective in reversing oxidative stress arising from iron overload. Detsi et al.,\(^{26}\) found that lipoic acid is a potent antioxidant or anti-inflammatory agent for its ability to inhibit in vitro lipoxygenase as well as for its anti-inflammatory activity in vivo. According to\(^{27}\) reported that lipoic acid inhibit apoptosis of cell by means of its antioxidant activity. Lipoic acid is used in human cancer chemotherapy and chemopreventive agent\(^{28}\). This study has been conducted to investigate the protective role of lipoic acid on the structure of kidney and lung tissues and on Fe, Cu, Zn, Ca and Pb levels against the toxic effects of exposure to lead and/or whole body gamma-irradiation in albino rats.

**Material and methods:**

**Experimental animals**

All animal’s experimental procedure were performed in accordance with the Ethics Committee of the National Research Center and in accordance with the recommendation for the Proper Care and Use of Laboratory Animals (National Institute of Health guideline,\(^{1}\)1985. Forty eight male albino rats weighting (100-120gm) were used in this study. Animals were obtained from the animal farm of the Egyptian Organization for Vaccine and Biological Products. The animals were housed in cages and maintained under standered conditions of ventilation, and humidity. Food and water were available ad-libitum.
Gamma Radiation:

Irradiation was performed through the use of a Canadian Gamma Cell-40(137Cs) located at the National Center for Radiation Research and Technology (NCRRRT) in Nasr City Cairo, Egypt, at a dose rate of 1 Gy/1.5 min. Rats were whole body exposed to gamma radiation at a dose of 3 Gy delivered as one shot.

Treatment:

Lipoic acid was purchased from Sigma Chemical Company. The product is provided as concentrated exudates. Lipoic acid was administered to rats via intraperitoneal injection at a dose of 200 mg/kg bw.

Animals received lead via intraperitoneal injection of 30 mg/kg bw.(Johny et al., 2010) as 0.053 M lead acetate trihydrate(CH3COO)2 Pb3H2O) Karmakar et al., (1986).

Experimental design

Animals were categorized into 8 groups 6 rats each: 1) Control: Rats of this group were not treated with lipoic acid, lead, nor irradiated. 2) Lipoic acid: Rats were injected i.p with lipoic acid 200 mg/kg bw/day for 15 consecutive days, then sacrificed after 3 days. 3) Lead: Rats were injected i.p with lead acetate at 30 mg/kg bw/day for 5 days, then animals sacrificed after 3 days. 4) Irradiated: Rats were exposed to 3 Gy (as one shot dose) of whole body gamma-irradiation then sacrificed after 3 days. 5) Lead and irradiation: Rats received lead acetate for 5 consecutive days and on the 5th day, were exposed to 3 Gy gamma radiation then animals sacrificed after 3 days. 6) Lipoic acid + lead: Rats were injected i.p with lipoic acid (200 mg/kg bw/day for 15 consecutive days) followed by lead acetate injection i.p (30 mg/kg bw/day for 5 days) and then sacrificed after 3 days post the last treatment. 7) Lipoic acid + irradiation: Rats were injected i.p with lipoic acid 200 mg/kg bw/day for 15 consecutive days then exposed to 3 Gy whole body gamma radiation (one shot) and then sacrificed after 3 days of radiation exposure. 8) Lipoic acid + lead + irradiation: Rats were injected i.p with 200 mg/kg bw/day for 15 consecutive days followed by i.p. lead acetate injection (30 mg/kg bw/day) for 5 days and at the 5th day rats were exposed to a shot dose of 3 Gy gamma radiation. After 3 days of radiation exposure animals were sacrificed.

Experimental Parameters

Histological Preparation:

Animals were sacrificed 3 days after each treatment. Kidney and lung were immediately excised, fixed in buffered formal, processed routinely for paraffin embedding, then sectioned at 6 micrometers according to James (1976) and stained with the technique of Conn and Darrow (1960) using haematoxylin and eosin. Sections were examined by Olympus light microscope to detect the histological changes induced by any of the above treatments.

Biochemical analysis:

Tissues samples were prepared by washing throughout with deionized water. The weighed samples were digested in concentrated pure nitric acid (65%), (S.G. 1.42) and hydrogen peroxide in 5:1 (IAEA, 1980). Digested samples were carried out with acids at elevated temperature and pressure by using microwave sample preparation labstation MLS-1200 MEGA, Italy. Samples were converted to soluble matter in deionized water to appropriate concentration level. The studied elements were detected using standard curve method for each element (Kingestone and Jassie, 1988). Iron, copper, zinc, calcium and lead were estimated in kidney and lung. The selected elements were then
estimated quantitatively by using SOLAR system Unicam 939 Atomic Absorption Spectrometer equipped with a deuterium background corrections, fitted with GFTV accessory, a SOLAR GF 90 grafit furane and SOLAR FS90 plus, furnace auto sampler. The system was controlled by a SOLAR data station running the SOLAR advanced and Qc software packages. Hollow cathode lamps were used to determine the following elements, Fe,Cu,Zn,Ca and Pb. All solutions were prepared with ultra pure water. Value of concentration of the elements in each sample was calculated by the calibration curve method using standard stock solution(1000 Ug/ml) for each studied elements. All chemicals used were of A.R.grade.

Statistical analysis:

For statistical analysis mean and standard errors (X+SE) of data were calculated and compared by student “t” test

RESULTS

1.Histological observations:

Kidney sections of contol rats and lipoic acid treatment showed normal architecture of kidney as normal glomerulei,normal proximal convoluted tubules and distal convoluted tubules and normal capillaries.(Fig 1 a&b). Lead administered rats (30mg/kg/bw/day) for five days resulted in necrotic and fibrotic glomerulei, dilated , widened and degenerated proximal and distal convoluted tubules(Fig 1c). Whole body exposure of rats at 3Gy gamma-irradiation, applied as a single dose, resulted in loss of normal architecture of kidney (Fig1d), vacculated glomerulei, ruptured and ill-defined proximal and distal convoluted tubules.

Rats administered lead for five days 30mg/kg bw/day then exposed to whole body gamma radiation showed severe necrotic and disappearance of glomerulei, precipitation of lead around the proximal and distal convoluted tubulemembranes that became ill-defined structure(Fig 1e). Treatment of rats with lipoic acid 200mg/kg bw/day for 15 consecutive days before lead injection showed regenerated and ameliorated structure of glomerulei, improved structure of proximal convoluted tubules and well-defined structure of distal convoluted tubules(Fig 1f). Treatment of rats with lipoic acid 200mg/kg bw/day for 15 days before whole body exposure to radiation showed regenerated glomerulei, regenerated proximal and distal convoluted tubules (Fig 1g). Treatment of rats with lipoic acid 200mg/kg bw/day for 15 consecutive days before lead acetate injection and exposure to radiation resulted in mild regenerated glomerulei, mild amelioration of proximal and distal convoluted tubules(Fig 1h).

Microscopic examination of lung section of control rats and those treated with lipoic acid for 15 consecutive days showed that bronchioles are lined by simple columnar ciliated epithelial cells. The respiratory bronchioles continue on as long branching hallways (aleveolar ducts). The large door opened into the alveolar sacs and the small door opened into the alveoli. The delicate interalveolar walls were provided with extensive capillary network(Fig 1a,b). Rats injected with lead acetate, showed necrotic and ill-defined bronchioles, severe bronchiole fibrosis, sclerosis and necrotic, fibrotic respiratory potions(Fig 1c). In irradiated rats, ruptured and ill-defined shape of bronchioles, swelling and inflammatied bronchioles, haemorrhaged respiratoy portions of lung tissue were observed(Fig 1d).

Rats injected with lead acetate then exposed to radiation showed ruptured, swelling, inflammatied bronchioles with severe fibrosis and inflammatied, degenerated respiratoy portions, extremely dilated and widened, inflammatied pulmonary artery and haemorrhage (Fig1e). In rats treated with lipoic acid before lead injection, mild regeneration of bronchioles structure and mild amelioration of respiratory portions were observed (Fig1f). Treatment of rats with lipoic acid...
before irradiation showed regenerated bronchiole structure, ameliorated respiratory portions and mild regenerated pulmonary artery structure (Fig1g”). Treatment of rats with lipoic acid before lead injection and irradiation showed mild inflamed bronchiole, reduction in respiratory portions, fibrosis and mild improvement in pulmonary artery structure (Fig1h”).

2. Biochemical Results:

The results presented in table (1) showed significant increase of Fe, Cu, Pb and Ca of kidney tissue of rats group injected with lead acetate for 5 days and then sacrificed after 3 days. Whole body gamma irradiated rats exhibited a significant increase of Fe and Ca and there is no significant changes in Zn concentration with both lead injection or irradiated groups compared to control group. The injection of lipoic acid followed by exposure to gamma radiation showed significant increase of Fe, Ca, Pb and no significant change in Cu and Zn concentration of the kidney compared to control group (table 1). While, injection of lipoic acid 200 mg/kg bw/day for 15 days showed significant decrease in Fe, Cu and Ca concentration in kidney and no change of Zn and Pb compared to control group (table 1). Injection of lipoic acid before lead acetate injection showed in the kidney a significant increase of Ca and Pb, significant of Zn but no change of Fe and Cu concentration compared to control group (table 1). Injection of lipoic acid before exposure of rats to gamma rays resulted in a significant increase of Fe, Ca and Zn and no change in Cu and Pb concentration of the kidney compared to control group (table 1). Injection of lipoic acid before lead injection followed by gamma radiation exposure showed significant decrease of Fe, Zn, and increase of Ca and Pb concentration in kidney compared to control group (table 1). In rats injected with lead acetate for 5 days, the lung tissue showed a significant increase of Fe, decrease of Zn, no change in Cu, Ca and Pb concentration compared to control group (table 2). Upon injection of rats with lead followed by exposure to gamma rays the lung showed significant increase of Fe and Ca and a decrease in Zn with no change of Cu and Pb concentration compared to control group (table 2). While, injection of rats with lipoic acid showed significant decrease of lung Zn and Ca and no change of Fe, Cu and Pb concentration compared to control group (table 2). Injection of lipoic acid before lead injection showed significant increase of Fe and Pb, no change in Zn, Cu and a decrease in Ca concentration of the lung compared to control group (table 2). Upon injection of lipoic acid before radiation exposure lung showed a significant increase of Fe and no decrease of Cu, Zn and Pb compared to control group (table 2). Injection of rats treated with lipoic acid before lead injection followed by exposure to gamma radiation showed significant increase of lung tissue Fe and Pb, a decrease in Ca and no change in Cu and Zn concentration compared to control group (table 2).
Fig 1: photomicrograph of sections in kidney cortex of rats in different groups a) control b) lipoleic acid showing normal glomerulei (G), normal proximal convoluted tubules (pt) and normal distal convoluted tubules (dt). c) Lead administration showing: necrotic glomerulei, preecipitated lead in glomerulei, dilated & widened and degenerated proximal and distal convoluted tubules. d) Irradiation showing: dilated, vacculated glomeruler ruptured and ill-defined proximal and distal convoluted tubules. e) lead + irradiation showing: severe necrotic and disappearance of glomerulei, precipitation of lead around the proximal and distal tubules membranes that become ill-defined structure. f) lipoleic acid + lead: regenerated and ameliorated structure of glomerulei (G), improved structure of proximal convoluted tubules (pt) and well-defined structure of distal convoluted tubules (dt). g) lipolic acid + irradiation: regenerated glomerulei (G), regenerated proximal and distal convoluted tubules (pt) (dt). h) lipoleic acid + lead + irradiation showing: mild regeneration of glomerulei (G), mild amelioration of proximal and distal convoluted tubules (pt) (dt). (H&E) (x400).
Fig. 2 photomicrograph of sections in the lung of *a) control *b) lipoleic acid treated rats showing: normal architecture of lung, well–defined shape of bronchiole (b) and normal respiratory portions (r.p) of lungs and normal branch of the pulmonary artery (p.a). C*) lead administration showing: necrotic and fibrotic bronchiole (b) severe bronchiole fibrosis and necrotic and fibrotic respiratory portion (r.p). d*) irradiation showing: ruptured and destructed respiratory portion (r.p), swelling and inflammed bronchiole (b). e*) lead + irradiation showing: ruptured, swelling,
inflamed bronchiole (b) with severe fibrosis and inflamed , ruptured and degenerated respiratory portions , extremely dilated and widened and inflamed pulmonary artery (p.a ) and haemerrhage . f*) lipoelic acid + lead : mild regeneration of bronchiole (b) structure , and mild improvement of respiratory portions (r.p). g*) lipoelic acid + irradiation : regeneration of bronchiole (b) structure , ameliorated respiratory portions (r.p) and mild  regenerated pulmonary artery (p.a ) structure. . h*) mild inflamed bronchiole (b) , mild respiratory portions fibrosis (r.p) and mild improvement in pulmonary artery structure (p.a ) . ( H&E) (x400).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fe</th>
<th>Cu</th>
<th>Zn</th>
<th>Ca</th>
<th>Pb</th>
</tr>
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<tr>
<td>Control</td>
<td>90.14 + 6.7</td>
<td>5.48 + 0.38</td>
<td>21.25 + 3.10</td>
<td>67.47 + 3.41</td>
<td>3.77 + 0.08</td>
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<td>Pb% control</td>
<td>116.0 + 7.48*</td>
<td>8.88 + 0.508*</td>
<td>62.04%</td>
<td>22.92 + 2.32</td>
<td>7.85%</td>
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<tr>
<td>Irrad.% control</td>
<td>102.76 + 7.3*</td>
<td>9.12%</td>
<td>22.70 + 3.09</td>
<td>6.82%</td>
<td>156.6 + 5.62**</td>
</tr>
<tr>
<td>Pb+Irrad.% control</td>
<td>98.13 + 6.64*</td>
<td>6.75%</td>
<td>19.66 + 1.88</td>
<td>-7.48%</td>
<td>151.7 + 5.18**</td>
</tr>
<tr>
<td>Lipoic acid% control</td>
<td>79.27 + 4.99*</td>
<td>-12.05%</td>
<td>20.34 + 1.17</td>
<td>-4.28%</td>
<td>59.7 + 3.73*</td>
</tr>
<tr>
<td>Lipoic acid+Pb% control</td>
<td>87.62 + 6.85 -2.79%</td>
<td>5.80 + 0.549</td>
<td>14.69 + 0.97 -30.87%</td>
<td>164.5 + 6.41**</td>
<td>23.58 + 1.30***</td>
</tr>
<tr>
<td>Lipoic acid+Irrad.% control</td>
<td>98.88 + 5.66*</td>
<td>9.69%</td>
<td>5.58 + 0.778 1.82%</td>
<td>26.44 + 1.24 24.4%</td>
<td>178.5 + 7.79**</td>
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<tr>
<td>Lipoic acid+Pb+Irrad.% control</td>
<td>69.27 + 3.75 -23.15%</td>
<td>6.11 + 0.671 11.49%</td>
<td>18.79 + 1.59 -11.57%</td>
<td>84.10 + 4.21 24.64%</td>
<td>33.50 + 2.40***</td>
</tr>
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Each value represents the Mean + Standard Error (n=60)
P<0.01 : highly significant  P<0.001 : very highly significant.
### Table (2): Effect of lipoic acid administration and lead (Pb) on lung tissue and/or gamma radiation exposure in concentration levels iron, copper, zinc, calcium and lead.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fe</th>
<th>Cu</th>
<th>Zn</th>
<th>Ca</th>
<th>Pb</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>22.63+</td>
<td>5.07+0.95</td>
<td>112.3+9.46</td>
<td>199.8+11.90</td>
<td>2.89+0.19</td>
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<tr>
<td>Pb % control</td>
<td>35.49+</td>
<td>6.08+0.44</td>
<td>96.81+6.69</td>
<td>278.0+13.27</td>
<td>2.98+0.21</td>
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<tr>
<td></td>
<td>3.34**</td>
<td>19.92%</td>
<td>-13.79%</td>
<td>19.13%</td>
<td>3.11%</td>
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<td></td>
<td>56.82%</td>
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<td></td>
<td></td>
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<tr>
<td>Irrad. % control</td>
<td>27.16+</td>
<td>5.33+0.46</td>
<td>59.82+5.28</td>
<td>192.5+10.43</td>
<td>2.82+0.17</td>
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<td></td>
<td>1.79**</td>
<td>5.12%</td>
<td>-46.73%</td>
<td>-3.65%</td>
<td>-2.42%</td>
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<td></td>
<td>20.01%</td>
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<td></td>
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<tr>
<td>Pb+Irrad. % control</td>
<td>24.46+</td>
<td>5.16+0.20</td>
<td>57.15+4.83</td>
<td>282.74+13.0</td>
<td>3.01+1.10</td>
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<td>1.19*</td>
<td>1.77%</td>
<td>-49.10%</td>
<td>41.51%</td>
<td>4.15%</td>
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<td></td>
<td>8.08%</td>
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<td>Lipoic acid % control</td>
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<td>63.50+4.98</td>
<td>128.42+9.80</td>
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<td>0.79-2.91%</td>
<td>0.19%</td>
<td>-43.45%</td>
<td>-35.75%</td>
<td>-1.03%</td>
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<tr>
<td>Lipoic acid+Pb % control</td>
<td>31.31+</td>
<td>5.11+0.03</td>
<td>113.8+10.89</td>
<td>165.9+8.12</td>
<td>3.28+1.88</td>
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<tr>
<td></td>
<td>1.53*</td>
<td>0.78%</td>
<td>1.33%</td>
<td>16.96%</td>
<td>1.49%</td>
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<td></td>
<td>38.53%</td>
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<tr>
<td>Lipoic acid+Irrad. % control</td>
<td>26.16+</td>
<td>5.05+0.53</td>
<td>112.7+9.69</td>
<td>187.2+11.40</td>
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<td></td>
<td>1.4-0.39%</td>
<td>-0.39%</td>
<td>0.35%</td>
<td>-6.30%</td>
<td>2.76%</td>
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<tr>
<td>Lipoic acid+Pb+Irrad. % control</td>
<td>28.15+</td>
<td>5.11+0.61</td>
<td>114.7+1.105</td>
<td>114.8+8.88</td>
<td>3.32+1.19</td>
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<td></td>
<td>1.47*</td>
<td>0.78%</td>
<td>2.13%</td>
<td>-42.54%</td>
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<td></td>
<td>24.39%</td>
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</tbody>
</table>

Each value represents the Mean + Standard Error (n=6)

P>0.05 : not significant      P<0.05 : significant
P<0.01 : highly significant   P<0.001 : very highly significant

### DISSECTION

Lead is known to adversely affect many organs as kidney and lung because they are important targets\(^{(36)}\). In the present study lead acetate injection resulted in degenerated, vacuolated glomeruli, ruptured and ill-defined structure of proximal and distal tubules and the proximal tubular segment may
be the most likely renal target of chronic lead toxicity at least twice as much as of distal tubules. Graan et al., (1986)(38) postulated that it might be due to lead induced oxidative damage to the membranes by the accumulation of oxidant metabolites and by direct or indirect inhibition of antioxidant enzymes, reducing the total antioxidant protection of the cells, affecting membrane structure and function and altering physiological processes of organs and tissues(37). These damages are reflected in cellular structure changes and explain the close relationship between the morphological changes in kidney and lung and lead exposed animals.

Also, in present study lung tissue structure was affected by lead injection exposed as fibrotic bronchioles, destructed respiratory portions, hypertrophy of alveolar sacs, these features might result from lead oxidative stress. Lebd’Ko and Ryzhavskii,(2005)(38) postulated that they found a decrease in the ratio between the specific volume of alveolar lumens and interalveolar septa and hypertrophy of lymphoid tissue in the bronchiole wall and attributed this to activation of lipid peroxidation and decrease in antioxidant antiradical activity of lung. Fortoul et al.,(2004)(39) reported that lead mixed with cadmium resulted in increased number of nonciliated bronchiolar cells and an increased number of bundles of dividing cells. They also found that more cell damage was present in males, and correlated it with an increased loss of the nonciliated bronchiolar cells, more sloughing and necrosis due to oxidative stress induced by accumulation of lead in lung tissue which correlates with sex hormones.

Ionizing radiation produces harmful effects to the organisms and due to wide spread use of radiation in diagnosis therapy and industry, pharmacological intervention could be most potent strategy to protect humans or ameliorate the deleterious effect of ionizing radiation(40)&(41). Experimental studies on animals have shown that exposure to ionizing radiation induces oxidative stress in different tissues(42)&(43) as observed in the present study. The interaction of ionizing radiation with the biological systems result in the generation of ROS(44). ROS significantly affects the cellular membrane and induces peroxidation of the lipids, thereby producing damaging effects to the cells(45).

The present study showed that gamma rays (3Gy) given as one shot induced different histopathological lesions in the kidney of male rats. These lesions were represented mainly by collapsed glomeruli, degenerated renal convoluted tubules and the increase in the inflammatory cells as has been reported by(46). Previous histological studies of the effects of gamma-irradiation on the kidney structures of experimental animals have been documented. Some authors emphasized the presence of glomerular damage under the effect of irradiation(47).

In the present study damage of glomerular tuft was noticed with widening in urinary space of Bowman’ capsule, and finally ruptures in the late stages as a result of gamma-irradiation. This result was in agreement with the findings of(48)&(49) who indicated that, the structural changes have led to the concept that glomeruli appeared to be very radiosensitive, as after the clinically relevant dose of 6Gy in 3 fractions essentially all glomeruli were altered in the irradiated kidneys as compared to control. The lobulation and shrinkage in some glomerular tufts with rupture in Bowman’s capsule in the present study may be due to whole body gamma-irradiation in rats.

Also, in the present study the lungs of irradiated rats showed ruptured bronchioles, fibrosis, haemorrhage of respiratory portions with dilated and widened pulmonary artery. This might be due to the direct action of ionizing radiation and is in agreement with(50). Most damages of cells involve free radicals or more generally due to the reactive oxygen species(ROS). The activated oxygen species can damage the genetic material causing lipid peroxidation in cell membranes and inactive membrane bound enzymes(51). An excess of free radicals and accumulation of oxidative byproducts are associated with inflammatory process(52) responsible for the development of radiation sickness(53).
In parallel of histological studies on the effect of lead injection or/and gamma-irradiation biochemical parameters were studied. Certain metals such as Pb, Fe, Cu, Zn and Ca were measured in kidney and lung. Exposure to lead or/and gamma-irradiation as pollution factors, have caused damage to the balance and distribution of the trace metals in the studied organs. There is a great relationship between metals and its disruption in different organs after exposure to toxic metal lead or/and gamma radiation.

Lead levels in the studied organs (kidney and lung) exhibited the rates of lead retention under various stresses on the body, where the highest retention of lead was observed in kidney along the experimental time and the lowest retention was in the lung. Lead appears to accumulate wherever high levels of calcium are found, therefore the highest concentration of lead are found in the kidney (54) & (55). Lead intoxication induced a very high significant increase in lead in all organs studied especially in kidney (56). Lead appears within and among soft tissues where the highest concentration of lead seems to accumulate specially in those organs and tissues with the highest mitochondrial activity, these include the renal tubules (57) & (55). This comes in accordance with the highly significant increase in lead and calcium levels in kidney.

Lead administration resulted in increase of Zn, Cu, and Ca. The same group exhibited very high significance increase in lead levels in both kidney and lung (58). Lung showed a decrease in copper levels and an increase in Fe levels whereas in kidney, there is decrease in Fe levels which may lead to increase in copper levels.

In the present work, the increase in lung zinc meet very high significance increase in lung Fe. The role of lipoic acid (LA) as a natural antioxidant against lead or/and radiation revealed significant histological and biochemical changes in kidney and lung. The results obtained, in the present study, indicated that the pre lead injection or/and radiation exposure recorded significantly improved histological architecture after administration of LA. Using LA led to the formation of normal spherical nuclei, prevented pyknotic and necrotic nuclei features. This could be explained on the basis that exposure to radiation increase nuclear damage (60).

Hence, the recorded significant improvement revealed that LA is considered as an ideal therapeutic antioxidant because it is naturally existing, low molecular weight compound with very powerful antioxidant effect in both aqueous and lipid domains. This effect include free radical quenching (61) metal chelation (62) and regeneration of other antioxidants such as ascorbic acid, vitamin E and glutathione (63) and is effective in preventing or reducing damage caused by (ROS) (64). Because of its antioxidant properties, lipoic acid is used as therapeutic agent in many common disease like diabetes. This raises the possibility of using lipoic acid which can help against oxidative damage in other cases as exposure to trace elements (65) and/or ionizing radition (66). According to (66) LA as a potent antioxidant not only scavenges free radicals, but also raises the intracellular level of antioxidants by recycling them, and chelates heavy metals to prevent free radical generation. LA antioxidant role involves protecting cells from damage by preventing the destruction of lipids in cell membranes. Unlike other antioxidants LA is soluble in both water and fat because of these unique antioxidant functions, lipoic acid is known as the universal antioxidant (67).

It could be concluded that LA is an effective treatment for elements disturbance or radiation exposure, reducing indices of oxidative damage and normalizing ogran functions and teating many of diseases that will provide a fertile field for continued researches.
REFERENCES

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