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Investigation of Oxidative Effect of Aluminium in Albino Rats

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Abstract

Oxidative stress is associated with increased production of oxidizing species (from reactive oxygen species or transition metals) or a significant decrease in the effectiveness of antioxidant defense. Aluminum toxicity was investigated using antioxidant status in serum of male Wistar albino rats. Antioxidants studied in this work include superoxide dismutase (SOD) and glutathione S- transferase (GST). The results show that specific activities of SOD and GST significantly increased ($P<0.05$) and decreased ($P<0.05$) in the test animals given 0.38, 3.8, and 38 mg/kg body weight as compared to the control after days 7 and 14 respectively. The results suggest that aluminum intoxication mobilizes antioxidants indicating possible oxidative stress.

Keywords: Aluminum, Antioxidant; Toxicity; Oxidative stress;

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1. Introduction

Aluminum is an inorganic element found in group three of the periodic table. It is ubiquitous being the third prevalent element and abundant metal in the earth's surface mainly in combined form- silicates, oxides, hydroxides, halogens, and other elements in the soil, rocks clays, and gems [1].

Aluminum finds use in a variety of applications perhaps because it is light weight and cheap, combines easily with other elements and corrosion-free [2]. Aluminum is widely used in Food industries as a packaging foil, drying agent (e.g. sodium silico-aluminate- a fine powder), used to dry cocoa, salt and other products and flocculating agents in most municipal water supply [3 and 4], food additives and colourings as well as toothpaste [5]. In pharmaceutical industries and medicine, aluminum is used as an antacids (anti-diarrheal agents) containing significant amounts of aluminum as aluminum hydroxide ($Al(OH)_3$, buffered aspirin compounds, vaccines phosphate binders, antiperspirant to inhibit sweating, deodorants, lip-stick, skin creams, tooth paste, vaginal douches, baby wipes, etc. [6- 8]. These domestic and and industrial application of aluminum may increase its burden to humans via food, water and drugs. Bone is the main tissue for aluminum burden causing bone disease [9] and skeletal system disease [10]. Other target tissues include the brain, kidneys and liver causing anemia [11]. Signs and symptoms of aluminum intoxication are colic, dementia, esophagities, gastro enteritis, kidney and liver damage [12-15]. Aluminum transverses across the membrane and enters into the blood circulation where it binds to the serum proteins, particularly transferrin [16]. Aluminum transferrin (Al-tf) complex is taken up by cells through transferrin receptors akin to iron absorption [17]. In the cells majority of aluminum binds to the nuclei, mitochondrial and cytosolic compartments [18]. Aluminum accumulates in the mammalian tissues such as the kidneys causing nephrotoxicity [19-20], liver causing cholestasis [21] accumulation of aluminum in the cell organelles could disrupt many biochemical processes [22-24]. Despite the ample clinical and

experimental data available, the mechanisms of aluminum toxicity remain largely unknown [25]. *In vitro* and *in vivo* experimental studies have shown the formation of reactive oxygen species in the potential neurotoxic effect of aluminum, particularly in Alzheimer's disease [26-27]. Antioxidants are key elements, which the body's defence system employs to neutralize the activities of these free radicals. Antioxidants work primarily by donating an electron to the free radical, there by stabilizing it. The antioxidants themselves do not become free radicals by donating electron because they are stable in either form [28]. In other words antioxidants are free radical scavengers. Inside the cells, antioxidant defense is provided by specific enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. Outside the cells, in the blood plasma, synovial fluids found in the joints, cerebro-spinal fluid and other fluids of the body. Oxidative stress is associated with increased production of oxidizing species (from reactive oxygen species or transition metals) or a significant decrease in the effectiveness of antioxidant defenses, such as glutathione.

In this study, antioxidants such as superoxide dismutase (SOD), and glutathione S-transferase (GST) were investigated. Monitoring these endogeneous enzymes as biomarkers of oxidative stress during aluminum intoxication becomes very necessary and this is the essence of this study.

2. Materials and Methods

Male Wistar albino rats, twenty-four in number used were bought from the animal house of the Faculty of Veterinary Medicine, University of Nigeria, Nsukka. The rats aged between 8-10 weeks with body weight range of 150-205g. The aluminum in form of aluminum chloride ($AlCl_3$) was the toxicant administered daily to the experimental animals at different doses: 0.38, 3.8, and 38 mg/kg body weight while the control animals were administered normal saline (0.2ml). All Chemicals used in this study were of analytical grade and were obtained from reputable companies (Merck, Germany; BDH Chemicals Ltd, Proole, England and May and Baker Ltd England). Four separate metabolic cages of six rats each were housed and distributed randomly with each rat differentially marked and acclimatized for five days. The Institutional Animal Ethics Committee approved the study before the experiment and certified all experimental protocols. The four groups were labeled I, II, III, and IV. Groups II, III and IV were the experimental/test groups given 0.38, 3.8, and 38 mg/kg body weight whereas group I, is the control animals which received normal saline (0.2 ml) for 7 and 14 days respectively. The normal saline served as the vehicle used in dissolving the toxicant.The route of administration was oral by means of gastric intubation. All animals were fed with commercial feed (grower's mash) and water *ad libitum* for fourteen (14) days. The experiment was replicated twice and their results were pooled together. Blood was collected from each group i.e. control and the three test groups on the days 7 and 14 respectively through the median cantus vein in the eyes of the rats with the aid of a capillary tube and transferred into plastic test tubes. This was later centrifuged at 2000xg in separate test tubes to obtain the serum. The animals were later sacrificed. Specific activities of GST and SOD were assayed according to the methods of [29 & 30] respectively. Protein determination was assayed by the method of [31].

2.1 Statistical Analysis

Significant differences were assessed by one-way analysis of variance (ANOVA) while differences between treatment groups were calculated using student's independent t- test at acceptance level of $P<0.05$.

3. Results and Discussion

The specific SOD activity of aluminum-treated rats are shown in Table 1a below.

The specific activity of superoxide dismutase (SOD) (units / mg protein) was significantly higher ($p<0.05$) in all the aluminum-treated groups compared to the control after seven and fourteen days. Specific SOD activity increased significantly ($P < 0.05$) after fourteen days compared to seven days in all the test animals.

The GST levels in the sera of the aluminum-treated rats are shown in Table 1b. The results show non-significant decrease ($p>0.05$) in GST level between the control and aluminum-treated rats given 0.38mg/kg and 3.8 mg/kg $AlCl_3$ after seven days of exposure. The test group given 38mg/kg $AlCl_3$ showed a significant decrease in GST level when compared to the control and the

test group given 0.38 mg/kg. After fourteen days of aluminum exposure, the GST levels were significantly lower ($p<0.05$) in the test groups given 3.8mg/kg and 38mg/kg than that of the control group. The test group given 0.38mk/kg showed none significant decrease ($p>0.05$) in GST activity level with the control group while within the test groups, there was a significant decrease in GST level in test groups given 38mg /kg and 0.38mg/kg $AlCl_3$ respectively. Glutathione S-transferease activity decreased after fourteen days compared to seven days in all the test animals but were not statistically significant ($P > 0.05$).

Table 1a: Total serum protein and sod activity

7 DAYS / GROUPS	Total serum protein (mg / ml)	Superoxide dismutase (SOD) Activity (Units /ml)	Specific activity (Unit/mg protein)
Control	0.96 ± 0.03	0.48 ± 0.03	0.53 ± 0.05
0.38mg /kg	^{B}0.95 ± 0.05	0.51 ± 0.02	^{A}0.59 ± 0.01*
3.8mg /kg	0.92 ± 0.04	0.62 ± 0.02	^{B}.071 ± 0.02*
38mg/kg	^{A} 0.86 ± 0.05*	0.78 ± 0.03	^{C}1.04 ± 0.02*

14 DAYS / GROUPS	Total serum protein (mg/ ml)	Superoxide dismutase (SOD)Activity(Units/ml)	Specific activity (unit/mg protein)
Control	0.92 ± 0.01	0.33 ± 0.01	0.38 ± 0.01
0.38mg /kg	^{A} 0.89 ± 0.02*	0.81 ± 0.02	^{A} 1.15 ± 0.15*
3.8mg /kg	^{B}0.79 ± 0.04*	0.98 ± 0.04	^{B}1.42 ± 0.27*
38mg/kg	^{C}0.59 ± 0.05*	1.36 ± 0.04	^{C}2.51 ± 0.30*

(A, B) and (A, B, C) significant different ($p<0.05$) within the test groups

Table 1b: Serum glutathione levels (Units/L)

GROUPS /DAYS	CONTROL	0.38mg/kg	3.8mg/kg	38mg/kg
7	14.39±1078	^{A}14.15±1..86	12.56±2.14	^{B}10.32±1..48*
14	17.20±1.64	^{A}14..50 ±1.77	12.10 ±2.05*	^{B}9.89±3.48*

(A,B) significantly different ($p<0.05$) within test groups

* Significantly Different Between The Control And Test Groups

Antioxidant systems are normally induced in living aerobic organisms to counter the effect of oxidative stress [32]. Oxidative stress creates an imbalance between reactive oxygen species and biological system's ability to readily detoxify the reactive intermediates which results in cellular damage. This imbalance in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cells'macromolecules including proteins, lipids, and DNA. In addition, some reactive oxidative species act as cellular messengers in redox signaling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling and by extension compromise the integrity of the cell membrane.

In humans, oxidative stress is thought to be involved in the development of cancer [33], Parkinson's disease, Alzheimer's disease [34], atherosclerosis, heart failure [35], myocardial infarction [36-37], fragile X syndrome [38], Sickle Cell Disease [39], lichen planus [40], vitiligo [41], autism [42] and chronic fatigue syndrome[43]. However, reactive oxygen species can be beneficial, as they are used by the immune system as a way to attack and kill pathogens [44]. Short-term oxidative stress may also be important in prevention of aging by induction of a process named mitohormesis [45]. From this study, results show that SOD activity increased significantly ($p<0.05$) in all the aluminum treated groups, while, GST activity decreased significantly ($p<0.05$) for the test groups when compared to the control group after the seventh and fourteenth days of treatment respectively. Glutathione S- transferases (GSTs) consist of a family of multifunctional enzymes that detoxify endobiotic and xenobiotic compounds by covalent linking of glutathione to hydrophobic substrates. They are also ubiquitous and play a key role in cellular detoxification. They protect cells against toxicants by conjugating them to glutathione, thereby neutralizing their electrophilic sites, and rendering the products more water-soluble. These enzymes constitute a defense system independently, cooperatively, or synergistically [46]. These enzymes (SOD, GST, catalase, GSH-peroxidase) tend to be in higher concentration in locations where reactive oxygen species (ROS) damage is more likely and potentially more damaging [47]. Data from this work indicate that SOD activity increased with increased concentration of the toxicant while GST activity decreased with increased concentration, suggesting oxidative stress. The increase in SOD activity may be attributed to an induction of the enzyme in the presence of reactive metabolites probably the toxicant (aluminum), suggestive of tissue damage. This result is in line with the observation of [47], who reported that SOD activity tend to be in higher concentration in locations where ROS damage was more likely and potentially more damaging. The result also agrees with an the earlier work done by [48], who reported an increase in SOD activity in erythrocytes of alcoholic patients. In another study by [49] reported contrary result in SOD activity in aluminum exposed rats fed with selenium supplements. The reduction in GST

activity observed in this study was time and concentration dependent. Work done by [50] reported that GST depletion occurred in experimental rats exposed to heavy metal (e.g. mercury). The pro-oxidant potential of mercury, they observed was due in part to the depletion of antioxidants, particularly GSH. This may be applicable to the rats exposed to aluminum compounds. It has been reported elsewhere that oxidative stress is a contributing factor in aluminum toxicity [51-52]. Similarly, that aluminum interferes with iron ions, particularly with trivalent iron ions which participate in oxido-reduction have been reported in the work of [53], hence resulting in increased production of free radicals. Aluminum builds a complex with oxygen [54]. Since GST and SOD systems are essential for cellular detoxification of many toxic xenobiotics [55], monitoring these endogenous enzymes as biomarkers during aluminum exposure becomes very crucial. In normal tissue, there is a balance between the production and scavenging of reactive oxygen metabolites (ROMs). According to [56], oxidative stress occurs when the rate of cellular antioxidant depletion exceeds the rate of replacement. The consequence of such is tissue damage and may lead to cell death [57].

4. Conclusion

The study suggests that aluminum intoxication may predispose biological organisms to oxidative stress as evidenced in the mobilization of antioxidants. This probably occurs in locations where ROS damage was more likely and potentially more damaging.

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