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The Role of Reduced Glutathione on the Activity of Adenosine Deaminase, Antioxidative System, and Aluminum and Zinc Levels in Experimental Aluminum Toxicity

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Abstract

Aluminum (Al) is one of the most abundant element in the world. But aluminum exposure and accumulation causes serious diseases, related with free radicals. Reduced glutathione (GSH) is a tripeptide with intracellular antioxidant effects. This study aimed to investigate the role of GSH on adenosine deaminase (ADA), antioxidant system, and aluminum and zinc (Zn) levels in acute aluminum toxicity. In this study, Sprague–Dawley rats ($n=32$) were used. The rats were divided into four equal groups ($n=8$). Group I received 0.5 mL intraperitoneal injection of 0.9% saline solution (NaCI), Group II received single-dose $AlCI_3$, Group III was given GSH for seven days, and Group IV was given $AlCI_3$ single dose, and at the same time, 100 mg/kg GSH was given for seven days. At the end of the trial, blood samples were collected by cardiac puncture. Serum total antioxidant status (TAS) and Zn levels were lower in the aluminum-administered group than the control group. In contrast, plasma total oxidant status (TOS) and aluminum concentrations and ADA activity were found higher in the aluminum-administered group than in the control group. Unlike the other groups, group GSH administrated with aluminum was similar to the control group. As a result, GSH administration has a regulatory effect on ADA activity, antioxidant system, and Zn levels in experimental aluminum toxicity. In addition, GSH may reduce the oxidant capacity increased by Al administration and may have a tolerant role on the accumulated serum Al levels. But long-term experimental Al toxicity studies are needed to reach a firm conclusion.

Keywords Aluminum · Zinc · Antioxidative system · Adenosine deaminase

Introduction

Aluminum (Al) is the third most common and widely used element in the world. It has been reported that it causes many health problems and toxic effects in living organisms due to its extensive use in foods, cosmetics, and industry [1, 2]. Exposure to aluminum in low concentrations are genotoxic. And short-term exposure to aluminum may effect brain. Demyelination occurs especially at the beginning of the exposure. Aluminum is known for its neurotoxic and neurodegenerative effects also [3, 4]. This element takes a role in the formation of superoxide radicals and the Fenton reaction in the body; therefore, it is defined as a pro-oxidant substance [5–7]. Related with its role on oxidative stress, recently, there are many studies investigating the aluminum's effects on antioxidant system. Free radicals damage macromolecules such as DNA, lipids, and proteins due to their excessive reactivity. And molecules, destroying or reducing the effects of free radicals, are defined

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as antioxidants [8, 9]. The thiol system is very important in the oxidant/antioxidant balance. Particularly, they constantly interact with two-electron oxidants. Dynamic thiol balance is controlled by thioredoxins (Trx), glutathione (GSH), and cysteine (Cys) [10].

GSH is a hydrophilic and highly concentrated intracellular tripeptide [11]. With the presence of cysteine precursors, GSH is synthesized by two-step ATP-bound reaction in all cells, especially in the liver. GSH can control its synthesis by a negative feedback mechanism [12, 13]. With the presense of toxic oxygen products and free radicals, GSH is oxidized to glutathione disulfide (GSSH) by non-enzymatic reactions [14]. One of the GSH component is cysteine. Cysteine plays role in the detoxification of oxidative molecules which occurs during natural metabolic processes of the metabolism [15]. Oral intake is sufficient for GSH production. Because of its essential role in many redox reactions, GSH is constantly oxidized, and this situation causes a decrease in GSH levels. Therefore, the need for GSH may depend on physiological processes. Particularly, low blood GSH levels may related with irregular diets, exposure to oxidants, usage of drugs, and toxicity [16].

Adenosine deaminase (ADA) is a metabolic enzyme produced in all cells and is mainly involved in purine metabolism and the immune system [17]. ADA catalyzes the convertion of adenosine and 2′-deoxyadenosine to inosine and 2′-deoxyinosine, respectively, by deamination reactions. ADA also catalyzes the deamination of methylated adenosines. Adenosine, the substrate of ADA, is an anti-inflammatory molecule involved in regulation of the immune system. The increase in the activity of ADA is also effective in elevation of the inflammation markers (26–28). The increase in adenosine, 2′-deoxyadenosine, and dATP levels due to ADA deficiency causes immunosuppressive effect [18, 19]. In addition, ADA deficiency also causes accumulation in 2′-deoxyadenosine and this leads to inhibition in S-adenosyl-L-homocysteine (SAH) hydroxylase activity. SAH hydroxylase is vital in methylation for the formation of lymphocytes. 2′-Deoxyadenosine is also an essential component of the DNA molecule. As a result of the increase in the level of 2′-deoxyadenosine, intracellular phosphorylation increases and this causes an increase in the dATP levels. Accumulation of dATP inhibits the dATP ribonucleotide reductase activity, and this situation disrupts DNA synthesis, repair, or replication [20, 21].

Especially under metabolic stress, adenosine is one of the extracellular purines involved in the signaling step of processes such as immunity and inflammation [22]. In case of the increased immune response, ADA levels may increase up to 100 times in inflammatory and hypoxia cases such as immunodeficiency syndromes, atherosclerosis, cancer, infectious diseases, diabetes, obesity, and autocoid adenosine production [23, 24]. Increase in the amount of adenosine elevates ADA activation rapidly. Related with the elevation in ADA activity, ADA is considered as a marker of oxidative stress [25]. Due to the excessive decrease in ADA activity, increased adenosine levels may have toxic effects and limit the activation of immune response, by decreasing the production of B and T lymphocytes. It has been shown in many studies that ADA activity increases due to ROS increase in oxidative stress, but in the presence of antioxidant molecules, a decrease in ADA activityhas been determined [26, 27]. Related with this information, we aimed to investigate the effect of reduced glutathione on adenosine deaminase activity, antioxidative system, and aluminum and zinc levels in experimental aluminum toxicity.

Materials and Methods

In the study, 32 Sprague–Dawley rats (200–230 g) were divided into four equal groups ($n = 8$) at 2–3 months of age from The Animal Breeding Laboratories of The Experimental Research and Application Center (Elazığ, Turkey). Before the experimental procedure, permission for the use of laboratory animals was obtained from Kafkas University Animal Experimentation Ethics Board (KAU-HADYEK 2017–034). Animals were kept at room temperature (25 °C) and relative humidity (50–55%) in a 12-h light and dark cycle. Animals were fed a regular pelleted diet (Bayramoğlu-Erzurum), and drinking water was provided ad libitum.

Experimental Design

Rats were treated as follows:

Group I: served as control and received 0.5 mL intraperitoneal injection of 0.9% saline solution (NaCI) for seven days.

Group II: $AlCI_3$-treated (1/100 LD50) (34 mg/kg, in sterile 0.9% saline buffer, pH 4.5) intraperitoneal injection for seven-day acute toxicity. $AlCI_3$ was dissolved in 0.9% saline [28].

Group III: reduced glutathione (100 mg/kg) was dissolved in 0.9 saline and given intraperitoneally for seven days.

Group IV: $AlCI_3$ was dissolved in 0.9% saline and treated $AlCI_3$ (1/100 LD50) (34 mg/kg) intraperitoneal injection for seven days. At the same time, 100 mg/kg GSH (Merck) was given intraperitoneally for seven days.

At the end of the experimental period of 7 days, blood samples were collected by cardiac puncture. The serum were separated by centrifugation at 3000 rpm for 10 min and stored − 45 °C until analysis. Aluminum and zinc levels in the serum were assayed by ICP-MS (CPMS Nexion 300X) [29, 30]. The serum TAS and TOS were determined colorimetrically (PowerWave XS, BioTek, Instruments, USA) with a commercial kit (Rel Assay Diagnostic, Gaziantep, Turkey). Serum ADA activity was assayed by a colorimetric method.

Determination of ADA Activity in Serum

Serum ADA activity was assayed by a colorimetric method described by Giusti and Galanti [31]. It is based on the measurement of ammonia in a Berthelot reaction. Ammonia is generated when ADA reacts with adenosine (substrate). The chemical definition of one unit of total ADA is the amount of ADA necessary to release one µmol of ammonia per minute from the substrate under standard experimental conditions. The ADA activities of the groups were expressed as U/L.

Determination of Aluminum and Zinc Levels in Serum by ICP-MS

All glassware, containers, tubes, and pipette tips must be soaked in 10% TraceMetal Grade HNO_3 for at least 24 h. Then, they were washed with double distilled water several times before use. Metal-free (Al ≤ 1 ng/g) labware was used in all sample processing and analysis procedures to prevent possible Al contamination.

Standards and Chemicals

Al and rhodium (Rh) reference standard solutions and tuning solutions were purchased from Agilent Technologies (CA, USA). High-purity (99.999%) argon gas used for ICP–MS analysis was obtained from HABAŞ (Antalya, Turkey). Ultrapure water (18.2 M × cm) was produced via ELGA DI Polishing System (High Wycombe, UK). HNO_3 (TraceMetal Grade) was purchased from Sigma.

Calibration Standards and Quality Controls

For comparative analysis of the trace element concentrations of Zn and Al in serum, a serial dilution of the control samples and calibration in decreasing amounts (10, 50, 100, 200, 450, 700, and 1000 ng/mL) as calibration standards had been prepared via diluting the stock solution. The calibration standards were designed daily in the surrogate matrix.

We selected Zn 66 and Al 27 as the isotope of our targeted analytes. The matrix-matched protocol was used to eliminate mass matrix interference. The surrogate matrix used in this study was 2% (v/v) HNO_3 solution prepared in ultrapure H_2O. The kinetic energy discrimination mode was used for Al to eliminate polyatomic ion interference to prevent pollution with atmospheric particulates, sample preparation and dilution of standards were performed under a clean hood.

Sample Preparation for ICP–MS Analysis

Before analysis, 50 µL of the blood samples were placed in metal-free plastic containers pre-cleaned with 2% (v/v) HNO_3 for digesting with 8-mL 65% HNO_3 and 1-mL 30% H_2O_2 in a microwave oven (MilestoneStard-D) in two steps. The samples were heated to 180 °C for 10 min in the first step *n*. Following this, the heating was continued for another 15 min at 180 °C [29]. After digestion, they were placed in the autosampler for analysis. Inductively coupled plasma masss spectrometery, an ICP-MS Nexion 300X system equipped with software, was used to determine Zn and Al in blood samples [30]. The operational parameters of ICP-MS are listed in Table 1.

Sample uptake tubing was 0.38 mm id (green/orange). The PVC drain tubing was 1.30 mm id (gray, gray), and the autosampler tubes were metal-free conical tubes, all of which were prewashed with 2% (v/v) HNO_3 for sterilization. The ICP–MS was operated via RF power of 1600 W with helium flow of 4.5 L min^{-1} in the gas cell. The nebulizer flow rate, the auxiliary gas flow rate, and the plasma gas flow rate were 0.98, 1.2, and 15 L min^{-1}, respectively. The integration time was 0.1 s per point to obtain one point per mass. The autosampler was also equipped with a programmable rinse function. The assay was blindly run in triplicate for each sample, and the mean of three readings was used for further statistical analyses.

Determination of TAS and TOS in Serum by Commercially

Serum total antioxidant and total oxidant status levels were measured by commercially available test kits (Rel Assay Diagnostics, Turkey). The TAS levels were measured by a novel method based on automated colorimetric measurement developed by Erel (2004). In this method, results are expressed as µmol Trolox Eq/L [32].

In the serum samples, TOS levels were measured by a novel method based on automated colorimetric measurement developed by Erel (2005). The assay is calibrated with hydrogen peroxide (H_2O_2), and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (µmol H_2O_2 Eq/L) [33].

Statistical Analysis

The data obtained from the analyses were expressed as mean ± SEM. Statistical analyses of data were performed using SPSS 16.0. Data were initially tested for normality by

Table 1 ICP-MS operating parameters

Parameter	Value
Plasma conditions	1600 W
Plasma gas flow	15 L min^{-1}
Carrier gas flow	0.75 L min^{-1}
Dilution gas flow	1 L min^{-1}
He gas flow	4.5 L min^{-1}

the Kolmogorov–Smirnov test. Then, the data were tested with ANOVA, followed by Tukey's post hoc test. p values less than 0.05 ($p < 0.05$) were considered statistically significant.

Results

At the end of the seven-day experimental period, plasma TOS concentration in the aluminum-given group was significantly ($p < 0.05$) higher than in the control and other experimental groups. In contrast to the data on TOS concentration, plasma TAS concentration in the aluminum-given group was found significantly ($p < 0.001$) lower than in the control and other experimental groups.

Serum ADA activity in the aluminum-given group was significantly higher ($p < 0.05$) than in the control and reduced glutathione-given groups. At the same time, no statistical difference was found in the aluminum + reduced glutathione-given group.

The highest serum Al level was detected in the group given Al and the group given Al + GSH compared with the control group. The aluminum levels detected in the group given reduced glutathione were found statistically ($p < 0.001$) lower when compared to the control group. Serum zinc concentration in the aluminum-treated group was found significantly ($p < 0.05$) lower than in the control group and other experimental groups (Table 2).

Discussion and Conclusion

It has been observed in many studies that heavy metal accumulation increases ROS production in many tissues and disrupts the oxidative balance. Today, Al exposure is almost impossible to avoid, so it is crucial to minimize the damage caused by Al. The use of molecules with antioxidant properties is considered an effective method to eliminate oxidative stress [34–36].

Our study aimed to investigate the effect of reduced glutathione on adenosine deaminase activity, antioxidative system, and aluminum and zinc levels in experimental aluminum toxicity. Exposure to Al causes an increase in mitochondrial activity and deterioration of outer membrane permeability. This increases the number of cytochromes in the extracellular region and the activation of signaling pathways such as caspase-3 and phosphoinositide-3 kinase (PI3K). As a result, an increase in ROS and oxidized GSH can be observed [37]. Indeed, Orihuela et al. (2005) showed that thiobarbituric acid (TBARS), which is an essential indicator of lipid peroxidation, were increased and GSH levels were decreased in at the end of oral administration of aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$) [38]. Similar with the previous studies, in another study, the authors have found a significant decrease in SOD, CAT, GPx, GR activity, and GSH amount and an increase in TBARS levels after the oral administration of $AlCl_3$ for 30 days [38, 39].

Nowadays, it is impossible to avoid Al exposure. Usage of antioxidants is considered an effective method in reducing the damage caused by Al. Antioxidant substances such as curcumin, selenium, and vitamin E are reduced due to aluminum toxicity [40–42]. Administration of GSH itself or its esters such as N-acetyl cysteine increases the antioxidant capacity and the amount of GSH in body. However, the results may be depend on the GSH application ways to living organisms. In the study in which oral GSH administration is preferred, a difference can be observed in the total amount of GSH. This is thought to be due to its degradation by intestinal and hepatic γ-glutamyltransferase [11, 43, 44].

Measurement of total antioxidant capacity (TAC) in samples gives cumulative information about oxidative stress. It can help us infer by obtaining a cumulative value instead of the sum of the measurements of many enzymatic or non-enzymatic (such as GSH and vitamin E and C) and antioxidant parameters such as superoxide dismutase (SOD), catalase, glutathione peroxidase, and glutathione reductase. TAC measurement is considered an important criteria especially in the evaluation of antioxidant-rich supplement's effects [45, 46]. In experimental studies, it has been reported that

Table 2 Aluminum, zinc, TAC, TOC levels, and ADA activity in experimental groups

Parameters	Group I	Group II	Group III	Group IV	p values
Aluminum (PPM)	0.58 ± 0.09^{bc}	2.82 ± 0.195^{a}	0.46 ± 0.061^{c}	0.87 ± 0.010^{b}	0.000
Zinc (PPM)	0.91 ± 0.051^{a}	0.41 ± 0.083^{b}	0.91 ± 0.135^{a}	0.64 ± 0.12^{ba}	0.003
TAC (mmol Trolox Eq/L)	1.10 ± 0.053^{a}	0.79 ± 0.081^{b}	1.13 ± 0.084^{a}	1.10 ± 0.084^{a}	0.015
TOC (μmol H_2O_2 Eq/L)	12.35 ± 0.76^{b}	19.01 ± 1.35^{a}	10.48 ± 1.46^{b}	13.32 ± 0.71^{b}	0.000
ADA (U/L)	10.33 ± 0.72^{b}	15.78 ± 1.81^{a}	10.20 ± 0.79^{b}	12.83 ± 1.75^{ab}	0.015

Group I: control; Group II: aluminum; Group III: reduced gluathione; Group IV: aluminum + reduced gluathione

[a.b]The groups in the same line labeled different letters are statistically significant

glutathione supplementation increases the TAC levels [47, 48]. Also, it has been reported that foods rich in sulphurous amino acids increase GSH expression and the activity of antioxidant enzymes such as superoxide dismutase and catalase [49].

In the study, while the TAC levels of the GSH-administrated group were found to be higher than the control group, TAC levels of aluminum-administrated group were found lower when compared with the control group. Moreover, TAC levels of GSH administrated with aluminum group were found higher than the control and aluminum-administrated groups in the study. These results are proving the efficacy of GSH on antioxidant defense against Al toxicity. Parameters such as malondialdehyde (MDA), 8-hydroxy-2′-deoxyguanosine (8-OH-dG), lipid peroxides, isoprostane, and total oxidant capacity (TOC) give information about the oxidative damage on the body [50]. It has been reported that GSH supplementation has a lowering effect on serum oxidant markers; therefore, it may be effective in the regulation of oxidative stress [51–53]. In our study, the TOC levels were found high in the aluminum-administrated group; however, while the TOC levels of the GSH administrated with aluminum group were found to be statistically low, our results show that GSH has a significant effect on heavy metal toxicity.

Another result obtained from our study is a decrease in Al levels in rats treated with glutathione. This result can be related with the chemical properties of GSH. It has been shown in previous studies that GSH forms complexes with Al(III) compounds [54]. When the structure coordination chemistry of GSH is examined, its two carbonyl ends (glutamyl–COOH group and glycyl–COOH group) are suitable sites for Al binding and have high affinity [55, 56]. Therefore, when we evaluated the data we obtained and previous studies, we concluded that GSH forms complexes by binding with Al.

Studies investigating the effect of heavy metals on ADA activity are limited. Senger et al. showed that mercury chloride ($HgCl_2$) has an inhibitory effect on ADA activity in zebrafish [67]. Low concentrations of + 2 precious metal ions such as cadmium (Cd^{+2}) and cobalt (Co^{+2}) show a robust inhibitory effect on ADA activity. It was noted that calcium (Ca^{+2}) and iron (Fe^{+2}) ions showed weak inhibition [57]. In a study investigating the effect of Al toxicity on ADA activity, it has been reported that ADA activity increases during Al toxicity [58, 68]. It has been shown that plants with antioxidant effects such as turmeric and ginger, which are polyphenolic foods significantly reduce the ADA activity [59]. But, in other a study in which rabbits were given GSH supplementation, it was reported that GSH supplementation did not cause any change in ADA activity [53]. In our study, when compared with the control group, ADA activity was found high in the aluminum-administered group, but there was no difference in the GSH-administrated group. The data we obtained from the study are similar with the previous studies showing that ADA activity is positively correlated with increased oxidative stress.

Essential elements (including zinc, copper, calcium, and iron) are present in blood and tissues in small amounts. Zinc is intimately involved in protein, RNA, and DNA syntheses. The mechanism of aluminum-induced toxicity and zinc levels in sera has not yet been defined. There we were investigating the possible changes in zinc levels when exposed to Al. In the study, the zinc levels were found statistically lower in the aluminum group [60]. Röllin et al. reported that the amount of Al increased in the blood of the workers working in the factory where Al was processed, but the amount of Zn in the serum did not change. They also mentioned that this may be related with dose [61]. However, in another study conducted in China, it was reported that the Zn levels of the workers in the Al factory decreased [62].

In a study investigating the effects of Zn supplementation against chronic Al toxicity in rats, the authors noted that aluminum increases the formation of Fe^{+2} ions, causing free radical formation, and can also attack the double-layered cell membrane to form free fatty acids, and Zn supplementation reverses this situation. For this reason, its excessive use and the decrease in the level of antioxidant proteins containing Zn can be evaluated as inevitable [63]. In another study, it was stated that there is competition with Al and Fe + 2 for binding to proteins and that Al attacks iron-binding proteins and releases Fe + 2 ions. Considering the oxidative effects of free Fe + ions, it is quite reasonable to reduce the level of Zn due to its antioxidant properties [64, 65]. There is no satisfactory explanation for the decrease in serum concentrations of zinc associated with Al exposure. It was speculated that high plasma Al binds to essential elements, especially copper and zinc, inducing metallothionein also [66, 69]. According to the results we obtained from the study, the Zn levels were found low in the Al-administered group. This indicates an inverse relationship between Al and Zn concentrations.

As a result, additional GSH administration in experimental aluminum toxicity has a regulatory effect on adenosine deaminase activity, antioxidative system, and Zn levels. In addition, GSH may reduce the oxidant capacity induced by Al administration and may have a tolerant role on the accumulated serum Al level. But, long-term experimental Al toxicity studies are needed to reach a firm conclusion.

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Author Contribution O.A, E.A, K.Y.D, and C.A. conceived the original idea and build. O.A, D.K, T.T.Z, and C.G. supervised the research. Experiments were performed by O.A, K.YD, T.K, R.E. D E.A, and C.G. All authors read and approved the final manuscript written by O.A, E.A, and D.K. There are no conflicts to declare. Also all authors checked and approved the final manuscript.

Data Availability All data are available in the article. It can also be requested from the corresponding author.

Declarations

Ethics Approval The study protocol was approved Kafkas University Animal Experimentation Ethics Board (KAU-HADYEK 2017-034).

Competing Interests The authors declared that they have no conflict of interest.

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