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Effect of Zinc, Selenium and their Combination on Cadmium- Induced Oxidative Stress in Rat Kidney-A Molecular Study

Safaa I. Khater, Hamad A. ELsaadawy, Shrouk A. El-Basyoni*
Biochemistry Department**,** Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt

Abstract

Cadmium (Cd) is considered as a very toxic heavy metal which transfers to the body through many routes as food, water and air. Zinc (Zn) and selenium (Se) have a great role in alleviation of Cd toxicity in kidneys. This study aimed to look into the interaction between Cd, Zn, Se and their effects on gene expression of the antioxidant enzymes in the kidneys of rats. Fifty male adult albino rats were divided into five groups (n=10) that received orally the following doses daily for one month: Group I: control group received normal saline, Group II: received 2mg/kg BW $CdCl_2$, Group III: was administered 2mg/kg $CdCl_2$ and 2mg/kg $ZnCl_2$, Group IV: received 2 mg/kg $CdCl_2$ and 0.23 mg/kg Na_2Seo_3, and Group V: received 2 mg/kg $CdCl_2$, 2 mg/kg $ZnCl_2$ and 0.23 mg/kg Na_2Seo_3). The gene expression levels of SOD1, CAT, GPx, HSP70 and MT1 were assessed in the kidneys; treatment with Cd lowered the expression of antioxidant enzymes (SOD1, CAT, and GPx) and increased the expression level of HSP70 and MT1. Only partial ameliorative effects on the oxidative stress caused by Cd in the kidney have been observed with Se or Zn supplementation during exposure to Cd, while the co-treated with Se and Zn revealed better protection against the observed oxidative stress in kidney.

Keywords: Zinc, Selenium, Cadmium, Oxidative Stress, Gene Expression, Metallothionine

Introduction

World Health Organization recorded that cadmium (Cd) is a very dangerous for public health [1]. Cd enters in the soil, ground and drinking water via agricultural and industrial activities. Cd has high soluble nature and Plants absorb its compounds easily from soil resulting in accumulation in human and animal feed [2]. So, humans can easily expose to Cd through the diet [3]. Vegetables and cereals contain the highest amount of Cd present in the diet [4]. Smoking, occupational exposure and house dust are also other sources of Cd exposure [5]. Cd induces oxidative stress and causes damage to the cell through; competition with redox-active metals, depletion of antioxidant metabolites, exhaustion of antioxidant enzymes and interfering with electron transport chain which lead to damage of mitochondria and cell apoptosis [6].

Enzymatic and non-enzymatic defense mechanisms are involved together in protection of cells from oxidative stress caused by Cd [7]. The enzymatic antioxidants include superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and esterase [8], and non-enzymatic include molecules such as glutathione (GSH) and trace metals such as selenium and zinc [9].

Zinc is an essential metal involved in treatment of harmful effect caused by heavy metals specially Cd. Zinc has the same chemical and physical properties of Cd, so it competes with Cd in the enzyme binding sites [10]. Zinc also induces the metallothionein (MT) synthesis, which helps to detoxify Cd by binding it [11]. Moreover, recent studies suggested that intake of zinc can ameliorate Cd induced oxidative stress [12], due to zinc is a cofactor of copper zinc- superoxide dismutase enzyme.

Selenium (Se) plays an important role in the intra-cellular antioxidant system as a structural component of the selenoprotein enzymes, including glutathione peroxidase. The selenoprotein enzymes catalyze the reduction of hydro peroxidases to less toxic products, thereby protecting cells against oxidative stress [13]. Many studies approved that treatment with selenium during Cd exposure decreased the harmful effect of cadmium toxicity in kidney and other organs. Selenium contributes to the antioxidant defense system as a cofactor of the glutathione peroxidase (GPx) enzyme, which has a significant role in alleviation of Cd toxicity and improving the antioxidant capacity of the host [14]. Selenium

***Corresponding author email: (dr_chrry54@yahoo.com), Biochemistry Department, Faculty of Veterinary Medicine, Zagazig University, 44511, Egypt.**

also can enhance cadmium detoxification through forming inactive complex with cadmium and so help to eliminate it [15]. The aim of this study was to evaluate the interaction between Cd, Zn and Se and their effects on gene expression of the antioxidant enzymes in the kidneys of rats

Material and Methods

Animal Management

Each group of rats was housed in separate cage. The room of the experiment was maintained at temperature 24 ± 3 °C and relative humidity at 70% and a 12 h light/12 h dark cycle was applied. The animals were given a standard laboratory pellet feed and purified drinking *ad libitum*. Oral dosing was done by number of gauge oral feeding needle.

Chemicals

Cadmium chloride (CdCl2) was purchased from Merck (Darmstadt, Germany), a vial of sterilized cadmium chloride powder contains 100 gm. of cadmium chloride active ingredient. Zinc chloride (ZnCl2) was obtained from Sigma Aldrich. (St. Louis, MO, USA), a vial of sterilized zinc chloride powder contains 500 gm. of zinc chloride active ingredient. Sodium selenite (Na2Seo3) was purchased from Basingstoke Hampshire, England; a vial of sterilized sodium selenite powder contains 100 gm of sodium selenite active ingredient.

Animal Selection and Grouping

Fifty male adult albino rats were used in the experimental investigation of this study. All experimental animals after acclimatization for two weeks before treatment, were divided into five groups (n=10): Group I: control group received normal saline, Group II: received($CdCl_2$), at a dose level of (2mg/kg), Group III: received($CdCl_2$) and ($ZnCl_2$), at a dose level of (2 mg/kg &2 mg/kg) respectively , Group IV: received($CdCl_2$) and (Na_2Seo_3),at a dose level of (2 mg/kg & 0.23 mg/kg) respectively and Group V: received ($CdCl_2$), ($ZnCl_2$) and (Na_2Seo_3),at a dose level of (2 mg/kg &2 mg/kg &0.23 mg/kg) respectively. Intra-gastric tubes were used for the treatment of all animals daily for one month. Then the animals were killed and kidney tissues were collected for biochemical and molecular analysis.

Sampling

Immediately after sacrifying, kidney tissue was taken divided into two parts, one for homogenization and estimation levels tissue residue in kidney, and the other was wrapped in aluminum foil and put immediately in liquid nitrogen container to make snap-freezing of tissue and minimize the action of endogenous RNase, for real time-PCR analysis and estimation of gene expression levels of selected genes in kidney tissues.

Determination of the tissue residue of Cd, Zn and Se

The samples were prepared according to Nasr *et al.*, [16]. Briefly, one gram of rat kidney tissues was transferred to a clean screw capped glass bottle and digested with 10 ml of digesting solution (nitric acid/ per chloric acid 4:1) for 4 hours at room temperature, followed by heating at 40-45°C for one hour in water bath, then temperature raised to 75°C until the end of digestion. After cooling at room temperature, the digest was diluted to 20ml with deionized water and filtered through 0.45µm Whatman filter paper. The filtrate was kept in refrigerator till analysis. For the preparation of the blank solution, 10 ml solution of nitric/ per chloric acid (4:1) were put in a screw capped glass bottle and exposed to the same previous procedure [16]. Quantitative determination of cadmium, zinc, and selenium residues was conducted by using thermo Jarrell Ash Atomic Absorption Spectrophotometer, in Central Laboratory of Faculty of Veterinary Medicine, Zagazig University. The concentrations of metal (ppm) in the examined samples were calculated according the following equation:

Concentration of metal in samples= AXB÷W, where A= metal concentration (ppm) in the prepared samples from the digital scale reading of Atomic Absorption Spectrophotometer, B= the final volume of the prepared samples, W= weight of samples in gram.

Molecular analysis

The total RNA was extracted from kidney tissue by using RNeasy Mini Kits (Qiagen, Cat. No. 74104), following the manufacturer instructions. The extracted RNA was quantified and qualified by using Nano Drop®

ND-1000 Spectrophotometer, Nano Drop Technologies, Wilmington, Delaware USA. The purity of RNA was checked and ranged between 1.8 and 2.1, demonstrating good quality of the RNA. First strand cDNA was synthesized using Revert Aid TM H Minus (Fermentas, life science, Pittsburgh, PA, USA), according to manufacturer instructions. One µl of total cDNA was mixed with 12.5 µl of 2x SYBR_ Green PCR mix with ROX from Bio-Rad, 5.5 µl of D.D water and 0.5 µl of each forward and reverse primers for the measured genes. The normalization assessed by using β-actin gene as a control. Primer sequences of rat SOD1, CAT, GPx, HSP70 and β-actin were obtained from the published sequences of [17], and for MT1 from the published sequences of [18]. (Table1). According to Livak and Schmittgen [19] the ($2^{-\Delta\Delta ct}$) method was used to calculate fold change for quantification of mRNA levels.

Table 1: Primers sequences for qRT-PCR

Gene	Oligonucleotide sequence	Annealing temperature	Number of cycle
SOD1	F 5'- ACACAAGGCTGTACCACTGC -3' R 5'- CCACATTGCCCAGGTCTCC -3'	58.5	40
CAT	F5'- TGCCGTCCGATTCTCCACAG -3' R 5'- TCCCACGAGGTCCCAGTTAC -3'	58.5	40
GSH-Px	F 5'- GTCCACCGTGTATGCCTTCTCC-3' R 5'- TCTCCTGATGTCCGAACTGATTGC -3'	58.5	40
HSP70	F 5'- ATCTCCTGGCTGGACTCTAACA -3' R 5'- CACCCATCTGTCTCCTAGATCA -3'	58.5	40
MT1	F 5'- GCGTCACCACGACTTCAAC -3' R 5'- GTCACATCAGGCACAGCAC -3'	60	40
ß-actin	F 5'- ACTATCGGCAATGAGCGGTTCC -3' R5'- CTGTGTTGGCATAGAGGTCTTTACG 3'	58.5	40

Results and Discussion

Tissue residue

Cadmium concentration in kidney tissues

Our results come in agreement with Zabulyte *et al*., [20] who confirmed that, the highest levels of Cd accumulation in rats found in kidney and Cd can induce multiple renal injuries. Data presented in Table (2) showed that there was a significant increase ($p<.05$) in the concentration of kidney cadmium in the (Cd), (Cd and Zn), (Cd and Se) and (Cd, Zn and Se) treated groups in comparison to control group, this result come with the result obtained by Štajn *et al*., [21]. But we found that, there was a significant decrease in Cd level in kidney tissues in groups III and V treated with Zn and combined Zn & Se, than that treated with Cd only, this may be due to that, Zn and Se act as antagonist to Cd, Brzóska and Moniuszko-Jakoniuk [22] mentioned that, Cd can interact with zinc and selenium during absorption, distribution, and excretion. Cd also interferes with functions of these elements. The antagonistic effect between Zn and Cd has approved that, Cd is an antimetabolite of Zn.

Zinc concentration in kidney tissues

As shown in Table (2) the concentration of zinc in kidney tissues was significantly decreased ($p<.05$) in (Cd) treated group in comparison to control group because of the similarity between zinc and cadmium in their chemical and physical characters so they compete at the active site of the enzyme as suggested by [23]. While, the conc. of zinc is significantly increased ($p<.05$) in (Cd and Zn), (Cd and Se) and (Cd, Zn and Se) treated groups in comparison to Cd treated group. The last result is in the same respect with other authors [22] who suggested that the exposure to Cd can modify Zn homeostasis by inducing the transport of Zn to target organs such as liver and kidneys.

Selenium concentration in kidney tissues

As shown in Table (2), there was a significant decrease ($p<.05$) in kidney Se concentration in Cd treated group in comparison to control group this may be due to Cd exerts its harmful effect by a

displacement of redox-active metals [6]. While, the concentration of Se in kidney was significantly increased in Se treated groups (Cd and Se) and (Cd, Zn and Se) in comparison to Cd treated group. Accordingly, the increased concentration of Se in kidneys may be explained by forming Cd-Se protein complexes [24, 25]. The accumulation of both Se and Cd were increased in kidney after exposure to both elements and thus indicate that Se ameliorated the toxic effects of Cd and enhanced the accumulation of Cd and Se in kidney [26].

Table 2: Means ± S.E. Cadmium, zinc and selenium concentration (µg\g) in kidney tissues

(µg\g)	Control	Cd	Cd&Zn	Cd&Se	Cd&Zn&Se
Cadmium	0.55 ± 0.01^{c}	5.31 ± 0.21^{a}	4.13 ± 0.11^{b}	4.94 ± 0.09^{a}	0.50 ± 0.04^{c}
Zinc	26.1 ± 0.1^{b}	17.71 ± 0.23^{d}	29 ± 0.49^{a}	20.73 ± 0.23^{c}	27.2 ± 1.21^{ab}
Selenium	0.193 ± 0.002^{ab}	0.173 ± 0.003^{b}	0.175 ± 0.002^{b}	0.208 ± 0.009^{a}	0.214 ± 0.01^{a}

Molecular biological analysis

Superoxide dismutase expression in kidney tissues

Results showed in Table (3) revealed that SOD1 mRNA expression level in kidney decreased significantly in Cd treated group in comparison to control one, the inhibition of CuZnSOD expression is due to the competition between Cd and Zn in the enzyme binding sites as mentioned by Uchida *et al*., [27] and Hussain *et al*., [28]. Available data indicated that Cd has the ability to compete at the site of Zn in the Cu Zn SOD molecule, resulting in inactive complex [29]. While the level of expression increased significantly in kidney of Zn treated groups (Cd&Zn) and (Cd&Zn&Se), and thus confirmed that Zn acts as Cd antagonist and antioxidant against Cd induced oxidative stress [30, 31]. However, Se did not increase CuZn SOD expression in our finding; different results were reported before [32].

Glutathione peroxidase expression in kidney tissues

Data presented in Table (3) showed that there was down regulation in the GPx gene expression in the kidneys of Cd treated group in comparison to control group, this result has been explained before [33] as Se is a cofactor of GPx enzyme, and this decrease in GPx expression may be due to depletion of Se by Cd. Other authors [34] mentioned that a chemical complex may be formed between Cd and Se at the active site of the enzyme, in addition to the competition for sulfur containing amino acids by Cd-metallothionein and GPx [35]. While there was up regulation in the GPx gene expression in the kidney of Se treated groups (Cd&Se) and (Cd&Zn&Se). This up regulation of GPx gene expression in Se treated groups may be attributed to increase the bioavailability of Se after co-treatment with sodium selenite and so increased GPx activity, as suggested before [36]. There was up regulation in the GPx gene expression in the kidney Zn treated groups (Cd&Zn) and (Cd&Zn&Se), because zinc affects regulation of glutathione (GSH) synthesis [37].

Catalase expression in kidney tissues

Results showed in Table (3) revealed that there was significant decrease in catalase gene expression in the kidney of Cd treated group in comparison to control group, in agreement with our result, Jurczuk *et al*., [38] suggested that iron is an essential component of catalase enzyme and Cd decrease the level of iron in kidney. While there was a significant increase in catalase gene expression in kidney of Zn treated groups (Cd&Zn), and (Cd&Zn&Se) in comparison to Cd treated group, and these results are in the same line with Khan *et al.*, [39], but it remained at the control value in kidney of Se treated groups.

Table 3: Fold change of relative gene expression of antioxidant enzymes in kidney tissues

Fold change	control	Cd	Cd&Zn	Cd&Se	Cd&Zn&Se
SOD1	1.11±0.02[b]	0.311±0.01[c]	1.91±0.02[a]	0.942±0.06[b]	2.03±0.07[a]
GPX1	1.07±0.02[b]	0.42±0.01[c]	0.863±0.05[b]	1.03±0.08[b]	2.05±0.04[a]
CAT	1.05±0.05[a]	0.343±0.07[b]	0.932±0.03[a]	1.19±0.06[a]	1.23±0.08[a]

Heat shock protien70 expression in kidney tissues

Data presented in Table (4) showed that there was up regulation in HSP_{70} gene expression in the kidney of Cd treated group in comparison to control group. Accordingly, Giffard *et al.*, [40] and Han *et al.*, [41] suggested that HSP70 is induced by a variety of different stressors, including heat, hypoxia, reactive oxygen species and toxic compounds, this may explain increasing the level of HSP_{70} in the kidney of rats which exposed to cadmium, while there was down regulation in HSP_{70} gene expression in the kidney of the group which given (Cd&Zn&Se) in comparison to Cd treated group. Agreement with our result, it is well documented also that Se [36] or Zn [42] can ameliorate the harmful effects of Cd induced oxidative stress in different tissues.

Metallothionien expression in kidney tissues

Data presented in Table (4) showed that there was up regulation in MT1 gene expression in the kidneys of Cd treated group in comparison to control group, which comes in the same line of some authors [43] who suggested that Body defense system is extensively activated during cd exposure and normal cell releases metallothionein (MT), which help in elimination of metals because it contain high amount of cystiene. Also there was up regulation in MT1 gene expression of the group treated with zinc as mentioned by others [44] these studies mentioned the similar ability of Zn as inducer of MT expression in kidney. The activation of MT transcription factor was increased in the presence of high amount of zinc [15]. The obtained results in our experiment suggested that the combination between Se and Zn is more powerful than that of either Se or Zn alone in revealed Cd toxicity in kidney which agree with other finding of many authors [45-47] who mentioned that the treatment with selenium as sodium selenite in combination with another microelement as zinc can provide better protection against cadmium toxicity.

Table 4: Fold change of relative gene expression of heat shock protein$_{70}$ (HSP_{70}) and metallothionine (MT1) in kidney tissue

Group	HSP_{70}	MT1
control	1.07±0.02[b]	1.05±.03[c]
Cd	2.032±0.06[a]	2.02±.o5[a]
Cd&Zn	1.51±0.03[b]	2.13±.09 [a]
Cd&Se	1.63±0.05[ab]	1.64±.02[ab]
Cd&Zn&Se	1.46±0.07[b]	1.41±.04[b]

Conclusion

The present study showed that the accumulation of Cd in rat kidneys after dietary intake of Cd markedly altered the gene expression of antioxidant enzymes as (SOD, CAT and GSH-Px) and some proteins as (HSP_{70} and MT1). The obtained results showed that the dietary intake of Se decreased the oxidative stress caused by Cd in rat kidney. Se can alter the distribution of Cd in tissues and help detoxification of Cd by forming Cd-Se complexes. Zn treatment also can ameliorate Cd induced oxidative stress in the kidney. Zn itself act as an antioxidant and helps in MT synthesis which is very important in Cd detoxification. Zinc and selenium ameliorate the activity of the antioxidant enzymes as (GSH-Px, SOD and CAT) and decrease HSP70 gene expression. Moreover,

our results showed that the combination between zinc and selenium treatment has a significant role in amelioration of Cd induced oxidative stress in kidney of rat than either Se or Zn alone.

Conflict of interest

The authors declare no conflict of interest.

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الملخص العربي

تأتير الزنك والسيلينيوم والدمج بينهما على الاجهاد التأكسدى الناتج من التعرض للكادميوم فى كلى الفئران- دراسة جزيئية

صفاء خاطر، حمد السعداوي و شروق البسيوني

قسم الكيمياء الحيوية-كلية الطب البيطري- جامعة الزقازيق

يعتبر الكادميوم واحدا من اكثر ملوثات البيئة سمية حيث ينتقل خلال كثيرا من السلاسل الغذائية. ويعتبر الزنك والسيلينيوم مضادات لسمية الكادميوم. وقد صممت هذه الدراسة لتبين التأثير المضاد للزنك والسيلينيوم على الاجهاد التاكسدى الناتج من التعرض للكادميوم فى كلى الفئران وذلك عن طريق دراسة التعبير الجينى لبعض الانزيمات المضادة للاكسدة فى كلى الفئران. وقد استخدم فى هذه الدراسة خمسون فئرا قسمت لخمس مجموعات وهى: المجموعة الاولى (الضابطة) قد جرعت يوميا بمحلول ملحى, المجموعة الثانية قد جرعت يوميا عن طريق الفم ب(٢مجم/كجم) من كلوريد الكادميوم, المجموعة الثالثة وقد جرعت يوميا ب(٢مجم/كجم)من كلوريد الكادميوم و(٢مجم/كجم) من كلوريد الزنك, المجموعة الرابعة وقد جرعت يوميا ب(٢مجم/كجم) من كلوريد الكادميوم و(23.مجم/كجم) من سيلينات الصوديوم, المجموعة الخامسة قد جرعت يوميا ب (٢مجم/كجم)من كلوريد الكادميوم و(٢مجم/كجم) من الزنك و(23.مجم/كجم) من سيلينات الصوديوم لمدة شهر. وقد اظهرت النتائج ان التعرض لكلوريد الكادميوم يؤدى الى نقص فى التعبير الجينى للانزيمات المضادة للاكسدة فى الكلية (السوبر اكسيد ديسميوتاز, كتالاز, الجلوتاثيون بيرواكسيداز) وزيادة فى التعبير الجينى لكل من بروتين الصدمة ٧٠ والميتالوثيونين. ويقل هذا التأثير الضار للكادميوم والاجهاد التأكسدى الناتج عنه فى كلى الفئران عند استخدام كل من الزنك والسيليونيوم على حده, ولكن الدمج بينهما يؤدى الى تحسن ملحوظ وحماية عالية للنسيج الكلوى ضد الاجهاد التاكسدى الناجم عن الكادميوم.