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Heavy Metals (Cadmium and Arsenic) Bioaccumulation and Their Impact on Antioxidant Status in Liver and Kidney of Male Albino Rats

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ABSTRACT

Cadmium and arsenic are the most common environmental toxicants that pose adverse impact on human health upon their entry. Cadmium and arsenic are not metabolized or excreted easily and hence gets bioaccumulated in different organs leading to an escalation in their concentration promoting suppression of antioxidants status and causes organ damage. The present study was designed to evaluate the toxicity of cadmium and arsenic both individually and in combination in the liver and kidney of male albino rats. Wistar strain male albino rats were treated with cadmium as cadmium chloride ($CdCl_2$) at a dose of 22.5 mg/kg body weight ($1/10^{th}$ LD50 / 96 h) and arsenic as sodium arsenate (Na_3AsO_4) at a dose of 42 mg/kg body weight ($1/10^{th}$ LD50 / 96 h) for a time interval of 30 days. The rats were sacrificed after a specific time interval, Cd bioaccumulation and oxidative stress enzymes were calculated in liver and kidney. The present study results suggest that Cd was more toxic to kidney and As was more toxic to liver, but combined treatment might have showed antagonistic effects to each other. It suggests that combined administration might promote MT protein synthesis that helps in the production of antioxidants and depletes toxicity levels.

1. Introduction

Cadmium and arsenic are present in the air, food, and water in alarming amount and widespread environmental contaminants with no indispensable biological function. Organisms are more prone to exposure of different toxicants especially in the areas of metallurgical works, which results in the development of oxidative stress and pose negative impact on human health [1]. Heavy metals accumulation occurs predominantly in the liver and kidneys, and its toxic effects depends on dose & duration of exposure [2]. The bioaccumulation of the toxic heavy metals in the organism's body poses an impact on human health, leading to an extensive range of diseased conditions like mental disorder, damage the lungs, liver, kidney (chronic renal failure), testis (male infertility) and long-term exposure might promote nucleic acids damage, mutations in DNA, disruptions in endocrine and reproductive systems subsequently leading to cancer. Bioaccumulation depends on species, body size, age, dose, as well as pH, salinity, and dissolved organic matter [3].

Free radical generation occurs frequently to maintain proper cellular function. Protection of cells and body system against ROS, animal cells are well equipped with a highly complex intrinsic defence mechanism known as antioxidant defence mechanism. Hence it is essential to eliminate free radicals from the body by production of antioxidants. Arsenic and cadmium forms free radicals and promotes oxidative stress in organism promoting kidney impairment and immunologic disorders. Heavy metals get accumulated in tissues and reacts with enzyme active sites leading to inhibition of enzyme activity [4]. Enzymatic activities get altered by showing impact on biological micro environment that is required for enzyme action. MDA accumulation is an indicator of lipid peroxidation that impairs membrane structure and function. SOD protects cells against toxic effects of superoxide anions, CAT catalyzes hydrogen peroxide reduction and protects the tissues from highly reactive hydroxyl radicals. GSH is potential reducing agent that detoxifies heavy metals and reduces peroxides or be conjugated with electrophilic compounds. GPx indicate the protection of tissues from the secondary effects of peroxides and reduces hydrogen peroxide to water [5]. Glutathione – S – transferase (GST) shows cellular defence mechanism against reactive oxygen species and crucial enzyme that regulate stress-induced signalling pathways.

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2. Experimental Methods

2.1 Chemicals

Cadmium as cadmium chloride ($CdCl_2$) and arsenic as sodium arsenate (Na_3AsO_4) are purchased from Merck (Dormstadt, Germany). All other chemicals used in the present study were obtained from the standard chemical companies like Sigma Chemical Co. (St Louis, MO, USA) and SD Fine Chemicals, India. The chemical molecules used in the present study are of the maximum purity.

2.2 Animals

Three months-old adult Wistar strain male albino rats weighing about 180 ± 20 g were preferred for present study. The rats were purchased from Sri Venkateswara Traders, Bangalore, Karnataka, India and maintained in stainless steel meshed cages at 23 ± 2 °C and relative humidity of 50 ± 20% in 12:12 h light:dark cycle. Rats were fed with standard rat chow purchased from Sai Durga Feeds and Foods, Bangalore, India and drinking water were given at *ad libitum*. The rats were acclimatized under laboratory conditions for about 10 days prior to experimentation. The protocol and animal use has been approved by the Institutional Animal Ethics Committee, (Resol. No. 58/2012/(i)/a/CPCSEA/IAEC/ SVU/AUR – CS), Sri Venkateswara University, Tirupati, Andhra Pradesh, India.

2.3 Experimental Design

Rats were acclimatized and partitioned into two groups, namely control and experimental. Control rats are treated as Group 1 and received only deionized water without Cd and As treatment. The experimental rats were divided into three groups (Group 2-4). Group 2 were intoxicated with Cd as $CdCl_2$ at a dose of 22.5 mg/kg body weight ($1/10^{th}$ LD50/96 h) for a time interval of 30 days (d). Group 3 were intoxicated with As as Na_3AsO_4 at dose of 42 mg/kg body weight ($1/10^{th}$ LD50/96 h) for a time interval of 30d and Group 4 were treated with Cd (22.5 mg/kg body weight) and As (42 mg/kg body weight) in combination for a time interval of 30 days (d).

2.4 Isolation of Tissues

After specific time intervals, the control and experimental rats were sacrificed, liver and kidney tissues were quickly isolated and stored under ice cold conditions. The tissues were kept in deep freezer at –80 °C and

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used for analysis of bioaccumulation levels and oxidative stress enzymes; viz. cadmium accumulation [6], arsenic accumulation [7], lipid peroxidation (LPO) [8], superoxide dismutase (SOD) [9], catalase (CAT) [10], glutathione – S – transferase (GST) [11], glutathione peroxidase (GPx) [12] and glutathione (GSH) [13].

3. Results and Discussion

In the present study cadmium and arsenic bioaccumulation levels were measured in liver and kidney and suggested that cadmium bioaccumulated more in kidney and arsenic bioaccumulated more in liver, but in combined administration of Cd and As there is less bioaccumulation when compared to individual supplementation of Cd and As.

Table 1 Cadmium and Arsenic Bioaccumulation levels in the test tissues – liver and kidney

S. No.	Tissue	Control	Cadmium	Arsenic	Cadmium + Arsenic
1	Liver	1.52±0.121	26.62±1.141[a]	35.43±1.559[a]	20.84±1.85[a]
		PDC	+1651.315	+2230.921	+1271.052
2	Kidney	2.84±0.541	42.58±2.968[a]	32.86±1.940[a]	23.95±1.95[a]
		PDC	+1399.295	+1057.042	+743.309

Mean± SD of the six individual observations + and – percent increase and decrease respectively over control. All values are at level of significance p<0.001

Evidences show that when metals are administered orally and subcutaneously, more was deposited in the liver than in the kidneys [14]. There is a gradual mobilization of these metals from the liver to the kidney upon exposure. Higher Cd and As uptake was more in the kidney when compared to other organs [2, 15]. Arsenic content in the liver is higher than that of muscles might be due to the reason that muscle does not have direct contact with the arsenic and the muscle is not involved actively in detoxification [16, 17]. Cd and As were found to accumulate more in the kidney than in the liver. Cd content was found to be more in kidney when compared to muscle [18]. When compared to single doses (As 10 mg/kg, Cd 2.6 mg/kg, and As 10 mg/kg + Cd 2.6 mg/kg) the mixture As + Cd was not much toxic than individual metal [19].

Table 2 Alterations in the activity levels of selected oxidative stress enzymes in the liver of Cadmium and Arsenic treated rats

S.No.	Parameter	Control	Cadmium	Arsenic	Cadmium + Arsenic
1	LPO	40.18±1.956	69.35±3.948[a]	79.78±2.171[a]	65.38±2.191[a]
		PDC	+72.59	+98.55	+62.71
2	CAT	31.45±1.237	19.93±1.723[a]	15.14±1.383[a]	25.07±1.412[b]
		PDC	-56.47	-51.86	-20.28
3	SOD	54.94±2.323	38.31±2.131[a]	32.21±1.760[a]	46.74±3.477[b]
		PDC	-30.26	-41.37	-14.92
4	GST	68.82±3.640	46.00±1.414[a]	39.31±2.621[a]	52.01±3.905[a]
		PDC	-33.15	-42.87	-24.42
5	GPx	19.93±1.640	12.67±1.348[a]	8.12±0.778[a]	14.19±1.365[a]
		PDC	-36.42	-59.25	-28.80
6	GSH	10.89±1.044	5.11±0.396[a]	3.54±0.258[a]	7.49±0.737[a]
		PDC	-53.07	-67.49	-31.22

Mean± SD of the six individual observations; + and – percent increase and decrease respectively over control. a- indicates the level of significance P<0.001; b- indicates the level of significance P<0.01.

The LPO activity showed maximum increment in liver of arsenic treated rats and in kidney of cadmium treated rats. Cd induced oxidative stress increased superoxide anion radical and hydrogen peroxides, singlet oxygen molecules generation under toxic insult. Most of the antioxidant enzymes become inactive by Cd and As exposure which results in the enormous creation of ROS and also due to damaging the antioxidant defence status in animal. Another reason for this is due to direct binding of the Cd and As to enzyme active sites hence the active site is occupied by Cd making it unavailable for the other substrates rendering them unavailable to fit at active site of enzyme [20, 21]. Hence the antioxidants system is disrupted in the organism showing profound impact on organisms health.

The SOD and CAT play an important role in quenching H_2O_2 radicals. SOD is the first line defence against ROS that dismutase O_2^- to H_2O_2, but it is highly toxic to the cell and hence need to be eliminated further by the action of catalase enzymes. The excessive increase in H_2O_2 was hence decreased by the activity of CAT [22] under normal conditions. Decreased SOD and CAT activity indicates that elevated production of superoxide radical anions and insufficient NADPH requirement, which is required for the activation of CAT from its inactivated form. Essential cofactor such as Zn or Cu displacement or binding to thiol groups of the enzyme also inhibits activity of some enzymes like SOD.

Table 3 Alterations in the activity levels of selected oxidative stress enzymes in the kidney of cadmium and arsenic treated rats

S.No.	Parameter	Control	Cadmium	Arsenic	Cadmium+Arsenic
1	LPO	54.35±2.189	83.43±5.49[a]	72.48±2.171[a]	66.7±3.464[b]
		PDC	+53.50	+33.35	+12.23
2	CAT	45.79±3.566	21.45±1.395[a]	25.18±2.085[a]	32.03±1.383[a]
		PDC	-31.79	-45.00	-30.05
3	SOD	65.38±2.191	31.45±1.237[a]	43.45±2.303[a]	52.43±2.264[b]
		PDC	-51.89	-33.54	-19.80
4	GST	73.48±4.704	47.73±1.838[a]	54.88±3.455[a]	65.12±4.432[b]
		PDC	-35.043	-25.31	-11.37
5	GPx	25.04±2.110	13.22±1.275[a]	17.18±1.514[a]	21.19±1.387[b]
		PDC	-55.19	-31.38	-15.37
6	GSH	14.35±1259	6.08±0.026[a]	9.12±0.796[a]	11.29±1.026[b]
		PDC	-57.63	-36.44	-21.32

Mean± SD of the six individual observations; + and – percent increase and decrease respectively over control. a- indicates the level of significance P<0.001; b- indicates the level of significance P<0.01.

By decrease in the GST activity under toxic stress, H_2O_2 production within the cell is increased and subsequently promotes cellular damage. Cd and As stress declined the GST activity in the liver, kidney and testis of toxicity induced rat group in present study. The depletion of GST due to cadmium exposure in the present study may be due to oxidative stress induced by cadmium and arsenic thus compromising the cellular defence mechanism against such stress.

The GSH depletion recorded might be attributed GSH oxidation due to ROS and depleted sulfhydryl group of cysteine moiety in GSH due to its high affinity for cadmium and arsenic forming Cd/As-GSH complex. Declined GSH levels might also showed impact on histopathology. The differences in GSH levels indicate that mixture of Cd+As is less toxic that individual supplementation of Cd and As. Cd and As toxicity increased the risk of renal injury [23].

GPx showed prime defense against Cd toxicity and GPx dependent mechanism shows liver protective effects from metal toxicity, GPx molecules might be consumed during heavy metal toxicity. GPx indicate the protection of tissues from the secondary effects of peroxides and reduces hydrogen peroxide to water is disrupted under the toxicity of cadmium and arsenic.

Cd and As combined treatment caused antagonistic effects and might induce metallothionein synthesis. Arsenic might have been bounded to metallothionein induced in the liver due to the presence of cadmium. Metallothionein is capable of binding to arsenic, and so reduce the amount of arsenic available for toxicity. Metallothionein prevented acute cadmium-induced hepatotoxicity and cell death [24].

Cadmium and arsenic are prominent toxic metals with antagonistic effects on liver and kidney upon exposure [2, 25]. Cd and As affects phosphatases activity and might promote organs damage by enhancing free radicals production. As + Cd in combination behaved as arsenic and caused induction of lipid peroxidation and behaved as cadmium in the induction of metallothionein. As + Cd mixture toxicity cannot be prophesied from the toxic mechanisms of single components [19, 26].

4. Conclusion

Cadmium given diet was more toxic to the kidney promoting nephrotoxicity, while the arsenic given diet was more toxic to the liver promoting hepatotoxicity and the combination of As + Cd cannot be predicted by examining the effects of the individual components in a mixture. It may indicates that both the metals cadmium and arsenic are antagonistic to each other when they are consumed together and might induce Metallothionein synthesis that helps in the production of antioxidants and depletes toxicity levels under combined administration of cadmium and arsenic.

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