

In vivo Interaction Between Cadmium and Essential Trace Elements Copper and Zinc in Rats

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Abstract : The complex in vivo interaction between Cd, a toxic metal and essential trace elements, mainly Zn and Cu, has not been elucidated yet. The objective being the elucidation of this interrelationship, Cd was subcutaneously administered as CdCl₂ (1 mg/kg/day) for 5 consecutive days to Swiss albino male rats (n=10). After 5 days, the rats were decapitated. Cd, Zn and Cu levels were estimated in hepatic, renal, cardiac and skeletal muscle specimens. Cd was found to be significantly elevated in all tissues (p< 0.001). Zn was increased in hepatic and renal tissues (p< 0.001 and p< 0.05) compared to

the controls. Cu was also significantly increased in these tissues. Myocardial and skeletal muscle tissues also manifested a significant increase in Cu and Zn in this group.

It is concluded that Cd administration alters the Zn and Cu status in vivo. However, the mechanism underlying the interactions between toxic and essential elements should be further investigated.

Key Words: Cadmium, copper, zinc, metallothionein. The abbreviations used are: Cd, cadmium; Cu, copper; Zn, zinc; MT, metallothionein.

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Introduction

Cadmium (Cd) is a toxic metal with sterilizing, teratogenic and carcinogenic effects (1). Cd exposure due to industrial pollution or cigarette smoke is an important risk factor for public health which may lead to cardiovascular diseases or cancer. Cd has no known functions in the metabolism of eukaryotes. It is shown that Cd is an inhibitor of the enzymes with sulphhydryl groups and disrupts the pathways for the oxidative metabolism (2). The complex interrelationships between Cd and some essential elements have not been elucidated. In vitro studies suggest that there is competition for transport mechanisms between Cd and some essential trace elements, mainly zinc (Zn) and copper (Cu) (3).

This study was undertaken to investigate the effect of Cd on the in vivo distribution of Cu and Zn in hepatic, renal, cardiac and skeletal muscle tissues at levels that lead to organ dysfunction.

Materials and Methods

Swiss albino male rats 6 months-1 year of age, weighing 150-200 g, were used in the study. The study group (n=10) received 1 mg/kg/day Cd subcutaneously as

CdCl₂ for five consecutive days while saline was injected into the control group (n=10). The administration of Cd was designed, taking into consideration the dose levels responsible for kidney damage (4,5). At the end of the fifth day, the rats were decapitated and hepatic, renal and cardiac tissue samples along with skeletal muscle from sartorius and femoris muscles were obtained.

The tissue samples were washed with saline and then left to dry in an oven at 65°C until they reached a stable weight. After being weighed, the tissue samples were wet digested in an acid mixture of HNO₃: H₂SO₄: HClO₄ (3:1:1; v/v) and brought to 10 ml of volume with bidistilled-deionized water. All samples were stored at -20°C until analysis. Cu and Zn concentrations were measured with an inductively coupled plasma atomic emission spectrometer (ICP-AES JY-24, Jobin Yvon).

Cd analysis was performed using a graphite furnace atomic absorption spectrometer (Perkin Elmer 2380).

The statistical analysis was performed with the SPSS for Windows 6.1 (SPSS, Inc). In order to examine the relationship between Zn and Cu levels and injection of Cd, descriptive statistics, Mann-Whitney U test and Pearson correlation were applied.

Results

In the Cd administered group, Cd levels were found to be significantly increased ($p < 0.001$) in all the tissues, the highest accumulation being observed in the liver (Table 1).

Table 1. Cadmium concentrations in the tissues of the control and cadmium injected rats ($\mu\text{g/g}$).

Cd ($\mu\text{g/g}$)	Control (n=10)		Cadmium (n=10)	
	Mean	SD	Mean	SD
Hepatic tissue	0.10	0.02	292.78	65.46
Renal Tissue	0.20	0.05	167.10	33.04
Cardiac tissue	0.27	0.07	10.39	2.29
Muscle tissue	0.23	0.10	2.33	0.95

Zn was increased significantly in hepatic and also in renal tissues ($p < 0.001$ and $p < 0.05$, respectively) in the Cd-injected group compared to the controls (Table 2). It was also noted that in hepatic tissue, Cd was significantly correlated to Zn ($r = 0.937$) in the Cd group.

Cu was also significantly increased in both hepatic and renal tissues due to Cd injection ($p < 0.05$), yet the increase was more prominent for renal tissue (Table 2). In hepatic tissue, Cu manifested a positive correlation with Cd content ($r = 0.675$) in the Cd group, while no correlation was observed between Cu and Cd contents of renal tissue in either the control or the cadmium groups.

In both the myocardial and skeletal muscle tissues, a significant increase was observed for Cu ($p < 0.05$ and $p < 0.001$, respectively) and Zn ($p < 0.05$ for both tissues) in

the Cd injected group (Table 2). Additionally, in cardiac tissue, a significant correlation existed between Cd and Cu ($r = 0.839$) in this group.

Discussion

Along with many harmful metabolic effects, Cd may disrupt the distribution of essential elements. As there are no known specific uptake mechanisms for Cd, its accumulation may occur through processes that exist for essential elements (3,6).

In this study, Cd exposure gave rise to a significant increase in Zn and Cu in hepatic tissue, both being parallel to Cd. It is postulated that the hepatotoxic effect of Cd is due to its binding to sulphhydryl groups and the interaction with sulphhydryl groups affecting the transport of Zn and Cu (6).

It should be stressed that the increase in Zn in hepatic tissue was more prominent and the correlation of Zn with Cd was higher in comparison to Cu. Blazka et al. (6) suggest that the majority of Cd uptake occurs by a process associated with Zn transport.

According to our findings, the interaction between Cd and Zn is more outstanding for hepatic tissue, implying that the Zn metabolism follows a different route in the liver compared to that in the kidney. In concordance, Sato et al. (7) reported that although Cd administration resulted in Zn accumulation in both the liver and kidney, the increase in hepatic Zn content was more outstanding in Cd-treated rats. On the other hand, Cu showed a much more prominent increase in renal tissue.

In contrast to the significant correlation between Cd and both Zn and Cu in hepatic tissue, no correlation was noted between Cd and these essential elements in renal

	Zn ($\mu\text{g/g}$)				Cu ($\mu\text{g/g}$)			
	Control (n=10)		Control (n=10)		Control (n=10)		Control (n=10)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hepatic tissue	86.05	10.98	223.92	51.16	10.42	1.34	14.23	2.41
Renal tissue	58.08	4.86	97.69	17.19	12.84	0.43	46.20	7.22
Cardiac tissue	63.69	6.38	87.99	13.72	19.02	2.66	24.75	4.62
Muscle tissue	22.31	11.34	60.59	13.73	1.61	0.81	4.24	0.88

Table 2. Zinc and copper concentrations in the tissues of the control and cadmium injected rats ($\mu\text{g/g}$).

tissue. Thus it may be stated that the mechanisms for cellular uptake and accumulation related to these elements are different in hepatic and renal tissues. Metallothionein, a low molecular weight protein with a high cysteine content and a high affinity for Zn, Cd and Cu, is suggested to play an important role in the concentration of these elements in the liver and kidney (8). The similarities and the differences in the biochemical behavior of Zn, Cd and Cu toward metallothionein may help to elucidate the distribution pattern of these elements.

Besides hepatic and renal tissues, this study also shows the interaction between Cd, Zn and Cu in cardiac

and skeletal muscle tissues. Thus, our results clearly indicate that Cd administration affects the distribution of Zn and Cu in the organism. These interactions may be explained by clarifying the role of metallothionein as well as other transport molecules in the transport and storage of Cd.

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