Cadmium: Hypertension Induction and Lead Mobilization

Hubert L. Walker, PhD, and Henry A. Moses, PhD
Nashville, Tennessee

In recent years interest has increased in the study of the metabolism of cadmium because of its presence in the environment as a toxic agent. Having no known essential bodily functions and possibly altering the action of various other trace metals, eg, lead and zinc, cadmium has been suspect as a causative factor in certain pathological alterations, such as hypertension. A study of this association was undertaken by the authors.

Female Sprague-Dawley rats were fed laboratory chow and given cadmium nitrate ad libitum. Systolic pressure was monitored and weights were recorded at weekly intervals. Cadmium and lead were determined in kidney and liver tissues of the sacrificed animals by using a trace metal analyzer and by atomic absorption spectrophotometer. After 36 weeks on the experimental regimen, the cadmium-treated animals had higher systolic pressures than the control group (155 ± 10 mmHg compared to 96 ± 5 mmHg). Increased levels of cadmium reflective of the cadmium consumed were found to occur in liver and kidney tissues. The urinary excretion of delta-aminolevulenic acid by the experimental animals was higher than that of the control animals. This suggests that the supplemented cadmium induced lead to leave the kidney and become metabolically active.

Cadmium is one of several nonessential trace elements to which everyone is exposed through diet and environment. Interest in the metabolism of cadmium has increased in recent years, especially since its presence as an environmental agent has been associated with hypertension in susceptible human population groups.[1]

Studies indicate that cadmium (Cd) accumulates in human tissues with age[2] and there appears to be a correlation between this and the incidence of certain chronic diseases, such as emphysema, lung cancer, chronic bronchitis, and arterial hypertension.[3]

It has been known for some time that cadmium has no known essential biological function. Cd was first reported to show toxic effects by Stockhusen and Trucinski in the late 19th century. In separate reports each of these researchers described incidences of gastrointestinal disturbances and certain other disorders prevalent in Swedish foundry workers exposed to fumes containing cadmium.[4]

Early studies in 1920 demonstrated that human toxicity to cadmium resulted from industrial exposure.[5] Tipton in 1952, through a spectrographic study of trace elements in human tissue, found that Cd has a tendency to concentrate in the kidney.[6] Since that time, considerable work has been done dealing with Cd and its effect upon human[7] and animal[8] tissues, as well as its relationship to other trace metals, both essential and nonessential.

Schroeder was able to produce a replica of human hypertension in rats by including small doses of cadmium in their diet.[3] Perry found that Cd, in addition to increasing blood pressure, increases the apparent renin activity in peripheral blood.[9] Morgan, on the other hand, carried out research on tissue concentration in man and found no support for the hypothesis that Cd concentrations may be related to hypertension.[10]

Studies by Schroeder and Lerner indicate that human subjects exhibiting hypertension have considerably more Cd in certain tissues, the kidney in particular, than do normal persons.[3,11] Whether this association with the kidneys relates to pathogenesis remains unknown.

The studies here presented were undertaken to investigate the relationship between Cd metabolism and hypertension, and to determine if oral Cd has an effect on the metabolism of another toxic metal, lead (Pb).

Materials and Methods

Twenty-five female Sprague-Dawley rats approximately four months old were divided into three groups. Group 1, the controls, consisting of nine animals, received distilled water and laboratory chow. Group 2 (eight animals) received cadmium from Cd $(NO_3)_2$ solution in the amount of 0.5 mg%. Group 3 (eight animals) received Cd from a Cd $(NO_3)_2$ solution in the amount of 1.0 mg% solution. The groups as divided are presented in Table 1. All animals were individually housed in a constant temperature animal room and laboratory chow and distilled water were available ad libitum.

During this regimen, records of weight, liquid consumption, and urinary output were maintained. Five animals from groups 1 and 2 were randomly selected and placed in metabolism cages. Urinary Δ-aminolevulenic acid levels (Δ-ALA) were measured with the use of a urinary Δ-ALA assay kit (Bio-Rad). Levels of glucose, protein, and urinary pH were approximated at weekly intervals with the use of Bili-Labstix (Ames).

Additionally, blood pressures were recorded at regular intervals utilizing a physiograph small animal study unit (E&M). The method employed was the indirect blood pressure recording technique which involves the occlusion of circulation in the tail with an annular cuff and detection of pulse as the cuff pressure is lowered. In this procedure, the pressure at which the first pulse appears is a measure of the systolic blood pressure of the animal.

Requests for reprints should be addressed to Dr. Henry A. Moses, Department of Biochemistry, Meharry Medical College, Nashville, TN 37208.

Table 1. Distribution and Treatment of Experimental Animals		
Group	Number	Treatment
I	9	H_2O
II	8	0.5 mg% Cd as $Cd(NO_3)_2$
III	8	1.0 mg% Cd as $Cd(NO_3)_2$

Table 2. Effect of Cadmium on Weight, Liquid Consumption, Urinary Output, and Delta-Aminolevulinic Acid (Δ-ALA) Excretion

			Average Daily Values†					
Time (weeks)	Weight (gm) Control*	Weight (gm) $Cd(NO_3)_2$**	Liquid Consumption (ml) Control	Liquid Consumption (ml) $CD(NO_3)_2$	Urine Volume (ml) Control	Urine Volume (ml) $Cd(NO_3)_2$	Δ-ALA (Mg %) Control	Δ-ALA (Mg %) $Cd(NO_3)_2$
0	135 ± 8	145 ± 14	—	—	—	—	—	—
5	183 ± 5	189 ± 9	25 ± 4	25 ± 6	7 ± 2	7 ± 2	0.42 ± .05	0.33 ± .06
10	212 ± 10	215 ± 13	18 ± 9	16 ± 7	6 ± 4	6 ± 3	0.41 ± .07	0.34 ± .10
15	213 ± 7	228 ± 10	29 ± 10	27 ± 10	12 ± 5	11 ± 5	0.45 ± .01	0.50 ± .05
20	—	—	19 ± 6	25 ± 10	7 ± 2	10 ± 3	—	—
25	234 ± 14	236 ± 7	22 ± 7	26 ± 10	8 ± 2	12 ± 5	0.49 ± .07	0.46 ± 13
30	241 ± 9	254 ± 14	20 ± 4	21 ± 9	6 ± 2	7 ± 2	0.54 ± .06	0.60 ± 12

*Nine animals receiving distilled H_2O ad libitum
**Eight animals receiving $Cd(NO_3)_2$ as the only liquid source (supplying 1 mg % Cd)
†Based on values of five animals from each group

At the end of the experiment (36 weeks), the animals were sacrificed. The liver and kidney were removed and weighed. The tissues were wet-ashed and digested using perchloric and nitric acid and analyses were run for Cd and Pb using a trace metal analyzer (ESA Model 3010) and by atomic absorption spectrophotometer (Perkin-Elmer Model 403).

Results

The administration of oral cadmium resulting from the intake of Cd $(NO_3)_2$ salt at 0.5 and 1.0 mg % levels had no effect on the weight, liquid consumption, or urine excretion of the test animals as compared to the controls. Data presented in Table 2 show that there were no significant differences in the average weekly values of weight, liquid consumption, and urinary output. However, there was almost a twofold increase in the (Δ-ALA) delta-aminolevulinic acid excretion in the 1.0 percent Cd-treated animals. This increase is evidence that the metabolic pathway to the synthesis of heme had been altered.

When the basal diet was supplemented with 0.5 percent Cd available ad libitum in the water supply, increased levels of Cd were found to occur in liver and kidney tissue somewhat proportional to the supplement consumed. The higher Cd concentrations found in the kidney support findings by others[7,12] that is, that Cd accumulates in the kidney three times as much per unit tissue weight as in the liver.

Since the Cd dosages had caused an increase in the excretion of Δ-ALA, the effect of Cd on liver and kidney lead levels was determined. The data presented in Table 3 suggest that the supplemented Cd induces mobilization of Pb from the kidney and the released Pb may be metabolically active; this is manifested by the increased urinary Δ-ALA. It is well known that urinary Δ-ALA increase is prevalent in lead toxicity, such increase resulting from the effect of lead on the enzyme Δ-ALA dehydrase.

Table 4 summarizes the weight and blood pressures of the animals from week 28 through week 36. Blood levels were observed weekly over a period of 36 weeks. By the 36th week, the systolic blood pressure of the animals supplemented with the 1.0 mg% Cd solution was 155±10 as compared to a systolic pressure of 96±5 for the controls.

In physical appearance, there was no noticeable difference in the controls vs the Cd-supplemented animals. All animals were quite active.

As kidney involvement is demonstrated by the Cd levels that accumulated in the kidney, it is possible that the orally supplemented Cd causes cadmium concentration in the kidney sufficient to trigger renin secretion.

There are studies that suggest a critical threshold level of toxicity exists for cadmium.[13] Below this level, the Cd is complexed to metallothioneine,[14] a small molecular weight protein (11,000 to 12,000) that appears to prevent toxicity. Above this level, the additional Cd appears to be a critical factor in physiological changes and renal damage, causing elevated blood pressures.

Nishizumi, in an electron microscopic study of Cd nephrotoxicity in the rat, noted that Cd damaged the mitochrondria and caused an increase of microbodies, focal proliferation of the smooth endoplasmic reticulum, and the appearance of intranuclear inclusions.[15]

These changes may be associated with the release of renin by the post

Table 3. Effect of Oral Cadmium on Liver and Kidney Cadmium and Lead*				
Group**	Cadmium		Lead	
	Liver	Kidney	Liver	Kidney
0.0 Cd	2.38 ± 0.51	5.38 ± 2.00	28.52 ± 8.88	75.24 ± 3.50
0.5 Cd	9.12 ± 2.45	36.07 ± 3.73	33.67 ± 6.07	61.75 ± 9.65
1.0 Cd	13.55 ± 5.67	40.22 ± 1.99	32.08 ± 6.75	45.16 ± 7.24

*Values in parts per million
**Basal chow contained less than 30 ppb Cd and 48 ppb lead
Supplements are in mg % Cd in the drinking water

Table 4. Effect of Long-Term Cadmium Consumption on Systolic Blood Pressure*				
Time (weeks)	Weight (gm)		Systolic Pressure (mmHg)	
	Controls	$Cd(NO_3)_2$	Controls	$Cd(NO_3)_2$
28	237 ± 14	243 ± 11	119 ± 15	120 ± 7
29	241 ± 10	248 ± 15	108 ± 16	106 ± 8
30	239 ± 9	245 ± 12	100 ± 12	114 ± 12
31	229 ± 12	233 ± 12	103 ± 6	123 ± 11
36	208 ± 24	207 ± 17	96 ± 5	155 ± 10

*Five animals in each experimental group

bodies at the end of the afferent vessels; thus, the stage would be set for renin-induced hypertension. Renin acts upon angiotensinogen (α_2-globulin) from the liver to produce angiotensin I, which in turn is acted upon by the converting enzyme (in the lungs) to produce angiotensin II.

Also of interest was a study done by Lewis, Jusko, Coughlin, and Hartz in which smoking habits were related to organ Cd content and a correlation was found between cigarette smoking and Cd accumulation in the kidney, liver, and lungs of 172 adults.[2]

Trace metal interrelationships have been described for many years. Among these studies was one done by Schroeder and Buckman[14] in which an observation was made on the effects of zinc (Zn) on Cd in renal tissue. It was found that the ratio of renal Cd to Zn was significantly elevated in hypertensive animals and was reduced after injection of a zinc chelate. As tissue Cd concentration decreased, tissue Zn concentration increased.

In another study by Schroeder, it was also observed that Cd and Zn are intimately related, and are bound by the same protein(s) which are synthesized only in response to Cd.[1]

In a study done by Piscator and Lind involving Cd, Zn, and copper (Cu) in human renal cortex, it was found that the accumulation of Zn was parallel to that of Cd.[16] Also it was found that when there is no excessive exposure to Cd, Cu metabolism in the kidney will not be disturbed. The Pb level, while showing increases with age, was quite small in comparison with the Cd levels.

Results presented in Table 3 show that Cd has the capability of removing Pb. It is tempting to speculate in light of the increased urinary output of Δ-ALA of the Cd-treated animals, since they had a lower Pb value than the non-Cd-treated rats, that the Cd may be a factor in determining the toxicity of endogenous Pb.

Currently, the authors' studies are still in progress and even though the strongest evidence linking Cd with hypertension comes from animal studies, there are data suggesting that renal Cd concentrations are abnormally high in hypertensive human beings.

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