Bull. Environm. Contam. Toxicol. 30, 33–36 (1983)

Absorption and Tissue Distribution of Cadmium in Mice After Chronic Feeding with Cadmium Chloride and Cadmium-metallothionein

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The mechanisms of gastrointestinal absorption of cadmium from food are poorly understood and may be important to control the absorption of this non-essential metal. One of the factors which may influence the absorption of metals is their chemical form. Previous studies (CHERIAN et al. 1978; CHERIAN 1979) from our laboratory have shown that a single oral feeding of cadmium in the form of cadmium-metallothionein (Cd-Mt) or cadmium chloride ($CdCl_2$) to mice resulted in similar absorption, but different tissue distribution of cadmium. The increased deposition of Cd in the kidney following oral feeding of Mt was similar to that observed after injection of Cd-Mt in experimental animals (NORDBERG et al. 1975; CHERIAN & SHAIKH 1975; TANAKA et al. 1975).

Since most of the Cd in beef liver and kidney and also in some shell fish is present in the form of Mt-like proteins, the studies on feeding of Cd-Mt are closely related to the environmental exposure of Cd. Recent reports (WAGNER & TROTTER 1982) suggest that the form of Cd in plants and vegetables also may be similar to Mt. The environmental exposure to Cd has been continuously increasing since the end of the 19th century (ELINDER & KJELLSTROM 1977), and the use of sewage sludge and phosphate fertilizers (SHARMA 1981) may further increase this level.

In the present study, the absorption and tissue distribution of Cd in mice repeatedly fed with $CdCl_2$ or Cd-Mt are reported.

MATERIALS AND METHODS

Male mice (20-28 g) of the C57BL/6J strain and 6-10 wk of age were obtained from Jackson Laboratory (Bar Harbor, Maine). Animals were housed in plastic cages and had free access to water and a semisynthetic powdered diet containing 120 mg Fe and 40 mg Zn/kg.

Cd-Mt was isolated from livers of rats injected with 0.6 mg Cd/kg as $^{109}CdCl_2$ (New England Nuclear Corp., Lachine, Quebec) daily for two weeks. The method of isolation of $^{109}CdMt$ was similar to that described elsewhere (CHERIAN 1979). Final purification was achieved by DEAE - Cellulose columns and the major Mt fraction DEAE-II was used for the oral feeding study. A solution of

0007-4861/83/0030-0033 $01.00

$^{109}CdCl_2$ with identical specific activity as isolated CdMt was prepared.

The mice were starved overnight and were orally administered with 20 ug Cd as $^{109}CdCl_2$ or ^{109}CdMt (about 5 uCi) in 0.2 mls with a gastric tube under mild ether anesthesia. Mice were all counted in a whole body counter (CHERIAN et al. 1978) immediately and also two days after Cd administration. The Cd feeding was continued once in a week for five weeks, and mice were counted after each feeding. The mice were sacrificed two weeks after the last dosing, and the tissues were removed for Cd estimation by radioactivity measurement in a well-type solid scintillation counter (Amersham-Searle, Oakville, Ontario). The tissue distribution of Cd in $CdCl_2$ and Cd-Mt fed groups were compared as a percent of the final retained dose. The concentration of Cd in liver and kidney was also calculated.

RESULTS AND DISCUSSION

The results of the body burden of cadmium in the mice fed with $^{109}CdCl_2$ and ^{109}CdMt are shown in Figure 1. The whole body counting of mice fed with ^{109}Cd as $CdCl_2$ or CdMt showed a similar body retention of cadmium from these compounds for the first

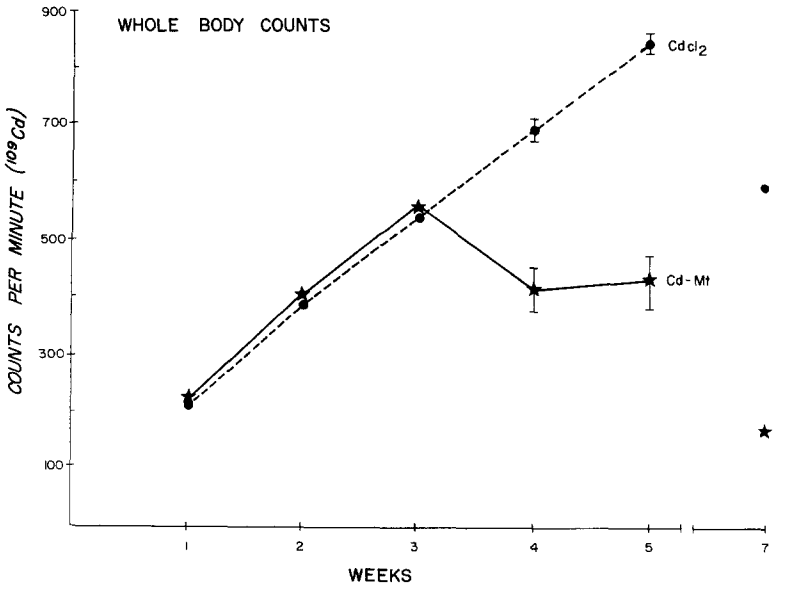

Figure 1. Total body retention of cadmium in mice fed with $CdCl_2$ (------) or CdMt (———). Mice were given ^{109}Cd as $CdCl_2$ or CdMt (20 ug Cd; 5 uCi ^{109}Cd) once in a week for 5 weeks through a gastric tube and were counted for ^{109}Cd in a whole body counter, 2 days later. The final count was taken two weeks after the 5th feeding.

three weeks. Although the $^{109}CdCl_2$-fed mice continued to retain more Cd, the ^{109}CdMt-fed mice did not retain any more cadmium during the 4th and 5th week of feeding. These differences cannot be explained by increased toxicity of Cd-Mt and its effect on absorption because such effects were not observed during the first three weeks of feeding. These results suggest that the retention of Cd during continuous intake of CdMt may be less than that during cadmium salt intake.

A comparison of the tissue distribution of Cd in mice after repeated oral administration of CdCl and Cd-Mt also showed marked differences (Table 1). Because of the differences in the total retained dose of Cd in the two groups, the results are expressed as a percent of the retained Cd in each group. More than 73% of the retained Cd in $CdCl_2$ fed group was accumulated in the liver, whereas only 18% of the Cd from the Cd-Mt group was deposited in the liver. The major site of accumulation of Cd in the CdMt group was kidney, and 69.8% of retained Cd was recovered from kidney in this group. Thus there were distinct differences in the tissue distribution of Cd after repeated feeding with $CdCl_2$ or Cd-Mt.

Table 1. Tissue distribution of cadmium in mice after chronic oral administration of cadmium chloride or cadmium-metallothionein.

Tissues	Percent of retained Cd (Mean ± SEM) $CdCl_2$ Group (12)	Cd-Mt Group (9)
Blood (1 ml)	0.23 + 0.03	0.24 + 0.05
Bone (1 g)	0.10 + 0.01	0.11 + 0.03
Heart	0.39 + 0.03	0.24 + 0.04
Kidney	15.62 + 0.81	69.80 + 1.89[a]
Liver	73.63 + 0.94	18.01 + 0.26[a]
Lung	0.41 + 0.04	0.28 + 0.04[a]
Pancreas	2.52 + 0.10	0.81 + 0.11[a]
Spleen	0.28 + 0.02	0.35 + 0.06
Testes	0.14 + 0.01	0.22 + 0.03
Stomach	2.92 + 0.22	1.07 + 0.16
Small intestine	2.04 + 0.08	4.24 + 0.39[a]
Cecum	0.46 + 0.04	1.76 + 0.21[a]

Male mice (C56BL/6J) were administered with 20 ug Cd as $CdCl_2$ or CdMt orally with a gastric tube once in a week for five weeks. They were sacrificed 14 days after the last dosing. a - denotes significant differences (P 0.001) between groups.

These results were similar to our previous study on single oral administration of these two forms of Cd (CHERIAN et al. 1978). The total amount of Cd deposited in liver and kidney was also calculated. The hepatic content of Cd in $CdCl_2$-fed mice was about five times more than the CdMt-fed group (Table 2). On the other hand, the renal Cd content of CdMt-fed mice was four times more than $CdCl_2$-fed mice. These results confirm the

Table 2. Deposition of cadmium in liver and kidney after oral feeding with $CdCl_2$ or Cd-Mt

Tissue	Cadmium (ng/organ)	
	$CdCl_2$ Group (12)	Cd-Mt Group (9)
Liver	275 ± 8	57 ± 5
Kidney	62 ± 11	238 ± 8

Mice were fed with 20 µg Cd as $CdCl_2$ or Cd-Mt once in a week for five weeks and sacrificed after 14 days.

the increased accumulation of Cd in the kidney during Cd-Mt feeding, despite the low body retention of Cd as compared to that in $CdCl_2$ feeding.

A major portion of cadmium in food stuffs such as beef liver and kidney and shell fish is present as a heat-stable protein - metallothionein. Therefore, the preferential accumulation of Cd from oral Cd-Mt in the kidney, the critical organ in Cd toxicity, should be considered in the evaluation of the risks involved in the increased intake of Cd. It should also be noted that Cd has a long biological half-life in the renal cortex (KJELLSTROM 1971). Since only small amounts of Cd were used in the present feeding study, it was difficult to compare the toxic effects, especially the renal effects of $CdCl_2$ and CdMt feeding. However, these observations may have great importance with regard to the health effects of chronic exposure to different forms of Cd in food. These results also suggest that, if Cd can be transported directly to the kidney from oral Cd-Mt, it may be a potential inducer of renal disease in a shorter period of time than inorganic Cd salts.

Acknowledgements. The skillful technical assistance of K. Rodgers is gratefully acknowledged. Work was supported by grants from Health and Welfare, Canada and KHM Project 535, Sweden.

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Accepted November 23, 1982