The Metabolism of $^{109}$Cd Administered to Mice Previously Given an Oral Dose of Cadmium

Tetsuya Taguchi* and Shosuke Suzuki

Department of Health Sciences, Faculty of Medicine, Tokyo University, Tokyo

INTRODUCTION

There are several reports that cadmium added to the diet of experimental animals is concentrated in the liver and kidneys1-3. Once cadmium enters the body, its excretion is extremely slow, and the biological half times of cadmium in the kidney and liver are longer than in other organs4.

Other reports indicate that the accumulation rate of orally administered cadmium becomes lower in proportion to the period of ingestion. Tsuchiya and Seki5 (1971) reported that the cadmium accumulated in mouse kidney and liver only increased slightly from 2 to 3 month intake. Therefore, the gastrointestinal tract may play an important role in protecting the body against the noxious effects of dietary cadmium.

Numerous factors influence cadmium absorption from the intestine6-8. When cadmium is orally to experimental animals with other metals, they influence the absorption of cadmium. For example, it has been reported that Hg reduces cadmium absorption and that Zn increases it9. Valberg et al.10 (1976) found that mice raised on an iron deficient diet showed an augmented absorption of cadmium.

The present study investigated the absorption rate of $^{109}$Cd administered to mice previously treated with an oral dose of cadmium for set periods.

METHOD

Male ICR mice were used. The animals were given drinking water that contained 50 ppm cadmium, in the form of cadmium chloride, in distilled water for 3, 8, 16 and 32 days. Each group contained three mice. The control group (5 mice) was given drinking water that contained no cadmium. Each mouse was injected with a single dose of 1.0 $\mu$Ci of $^{109}$CdCl$_2$ (carrier free) to the stomach on the last day of the water with cadmium period.

Twenty-four hours after the administration of $^{109}$Cd, the mice were killed by fracturing the cervix. The liver, kidneys, heart, lung, salivary glands and alimentary canal (from the lower part of esophagus to the anus) were immediately resected.

The radioactivity of each resected organ, the carcass (whole body except for the resected portions) and the collected feces was determined in a well-type scintillation counter after weighing. The radioactivity of the $^{109}$Cd taken up in the mucosal epithelium was determined in the same counter after the small intestine had been everted and the contents of the lumen had been washed out with ice-cold 0.9% NaCl solution.

RESULTS

1). Absorption rate: The ratio of the amount absorbed by the carcasses to the dose administered to the stomach.

* Present address: Department of Environmental Health, Jichi Medical School, Tochigi
The average absorption rates of all groups were control (0.94%), 3 day (0.81%), 8 day (0.90%), 16 day (0.64%) and 32 day (0.56%).

The 32-day group was the only one showing a significant decrease in the absorption rate ($p<0.01$). No differences in absorption rates were observed when the rates of the other groups were compared with the rate of the control group (Fig. 1).

2). The mucosal epithelium of the small intestine: The average uptake of $^{109}$Cd in the mucosal epithelium per gram of small intestine was 620 cpm for the 32-day group, but the $^{109}$Cd of the control group was 3,000 counts per minute. The amount of cadmium in the epithelium of the 32-day group was significantly lower ($p<0.05$) than that of the control group. There was statistical difference among the other groups and the control group (Fig. 2).

3). Liver: The results show that there were statistically no differences in the average counts of $^{109}$Cd per gram of liver among the cadmium treated groups and the control group, but the 16- and 32-day groups tended to a reduction in proportion to the control group (Fig. 3): 16-day (703 cpm/g), 32-day (901 cpm/g), as compared to the control group (1,517 cpm/g).

4). Kidneys: The counts of $^{109}$Cd per gram of kidney in the different groups are given in Fig. 4. Animals exposed for 16 and 32 days had significant decreases ($p<0.05$) in the average count of $^{109}$Cd per gram of kidney, but the other animals showed no differences their counts when compared to the control animals.

5). Heart, lung and salivary glands: No differences were observed in the heart, lung

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**Fig. 1** Absorption rates of $^{109}$Cd administered to mice, previously given a continuous oral dose of CdCl₂ (50 μg/ml)

**Fig. 2** Amounts of $^{109}$Cd per gram of the small intestine in mice, previously given a continuous oral dose of CdCl₂ (50 μg/ml)
and salivary glands of all groups.

6). Excretion rate: This rate is the ratio of $^{109}\text{Cd}$ in the feces and urine collected for 24 hrs after the injection of cadmium to the stomach (Fig. 5).

The average excretion rates of all groups were control (73.5%), 3 day (75.1%), 8 day (74.1%), 16 day (80.3%) and 32 day (96.1%).

The 32-day group was the only one showing a significant increase in its excretion rate ($p<0.05$).

**DISCUSSION**

When $^{109}\text{Cd}$ was orally administered in a single dose to mice, previously treated orally
with cadmium for set periods, only the 32-day group showed an absorption rate of newly administered $^{109}$Cd that significantly decreased in comparison to that of the control group. No differences were observed in the heart, lung, liver, and salivary glands of the animals of all the groups. The kidney was the only organ that showed a significant decrease in the 16- and 32-day groups when compared to the control group. This indicates that the liver regulates the accumulation of cadmium in the kidney.

The average amounts of cadmium ingested in advance by the animals of each group were 3 day (0.89 mg), 8 day (2.3 mg), 16 day (5.5 mg) and 32 day (15 mg). When the cumulative amounts of ingested cadmium began to exceed 5.5 mg, a reduction trend in the absorption rate was observed. At about 15 mg, the absorption rate of newly administered $^{109}$Cd decreased, the amount of cadmium taken up by the mucosal epithelium was reduced, and the excretion rate of cadmium was increased. This shows that the increase of ejected cadmium in the feces and decrease in cadmium uptake in the mucosal epithelium resulted in a reduction in the absorption rate of cadmium.

Sugawara and Sugawara (1974) reported that when pasto-form food containing cadmium was administered to rats, the accumulation rate in the liver and kidney for 41 weeks was 0.53%. Kobayashi et al. (1971) reported that when rice containing cadmium was administered to mice, the accumulation rate in the liver and kidney for 70 weeks was about 0.3%. Brancato et al. (1976) reported that after several weeks of cadmium ingestion, the accumulation of this metal in the liver and kidney stops in spite of continuous exposure to cadmium in drinking water. These observations suggest that the accumulation rate of cadmium may be altered due to a change in the absorption rate of cadmium by the intestine.

Our results indicate that the small intestines of mice which treated preliminarily with cadmium for set periods acquire a defense mechanism against the toxic cadmium ion.

Preliminary treatment with a small dose of cadmium is known to influence acute cadmium toxicity. Yoshikawa (1970) reported that mice injected with small amounts of cadmium tolerated a lethal dose of the metal given 24 hr later. Nordberg (1971) reported that prior treatment with cadmium protected animals against testicular necrotic effects of cadmium. Leber and Miya (1976) observed that the tolerance of an animal to a cadmium challenge is related to prior cadmium exposure.

Metallothionein, a low molecular weight cadmium-binding protein, has been identified in the liver and kidney of animals after cadmium administration. These data suggest that metallothionein may act as a protective agent against cadmium toxicity.

In a previous report we observed that a cadmium-binding component is induced in the soluble cytoplasm of the intestinal mucosa of rats administered cadmium. The results of this study suggest that this cadmium-binding component may play the main role in the defense mechanism of the small intestine against toxic cadmium ion.

**SUMMARY**

The absorption rate of $^{109}$Cd administered to mice previously treated continuously with cadmium for 3, 8, 16, and 32 days.

The results were

1. The 32-day group was the only one that showed a significant decrease in the absorption rate as compared to the control group.
2. The uptake of $^{109}$Cd in the mucosal epithelium of the small intestine of the 32-day group was significantly lower than that of the control group.
3. Animals exposed for 16 and 32 days showed significant decrease in the average count of $^{109}$Cd per gram of kidney when compared to the control animals.
(4) The 32-day group was the only group with a significant increase in its excretion rate when compared to the control group.

REFERENCES

経口投与 Cd の吸収率に及ぼす Cd 前処置の影響

田 口 徹 也*, 鈴 木 庄 亮
東京大学医学部保健学科

マウスに飲水とともに Cd (50 ppm) を 3, 8, 16, 32日間経口投与し、実験期間の最終日に新たに 199CdCl₂ を経口投与し、24時間後臓器を切除し、Cd 吸収率に及ぼす Cd 前処置の影響を検討し、次の結果を得た。
1. 32日群でのみ対照群に比し Cd 吸収率の低下が認められた。
2. 小腸粘膜上皮細胞内にとり込まれた Cd 量に関しては、対照群に比し、32日群で有意の低下が認められた。
3. 腎臓グラム当り Cd とり込み量を比べてみると、16日、32日群で対照群に比し、低下が認められた。
4. 32日群でのみ対照群に比し Cd 排泄量の増加が認められた。

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* 現住所：自治医科大学衛生学教室