Cadmium Excretion in Urine and Feces of Rats at Different Levels of Cadmium Toxicity

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Abstract: In rats given a subcutaneous injection of 0.5 mg of Cd/kg, 6 days/week for 15 weeks, daily excretion of cadmium in the urine and feces was determined. The relationship between cadmium accumulation and the excretion was studied in terms of cadmium toxicity. Urinary excretion of cadmium was markedly affected by cadmium toxicity, but fecal cadmium was scarcely affected. A linear relationship was obtained between the accumulation of cadmium and its urinary excretion only before the onset of renal damage. A linear relationship between the cadmium accumulation and fecal excretion was seen throughout the whole experimental period. The present experiment reveals that the main route of cadmium excretion is the feces before both renal and hepatic damage occur, but it is the urine thereafter.

Key words: Cadmium accumulation—Toxicity—Excretion—Urine—Feces—Metallothionein

INTRODUCTION

Cadmium is highly accumulative and is deposited mainly in the liver and kidneys. A very small part of the accumulated cadmium is excreted in the urine before cadmium toxicity appears, but the daily excretion of urinary cadmium increases sharply after the occurrence of renal and hepatic damage. It has been reported that feces are one of the main routes of cadmium excretion. Nordberg reported that fecal cadmium exceeded urinary cadmium during the interval before tubular proteinuria appeared in mice. However, little is known about the details of cadmium excretion in feces after damage to the kidneys and liver occurs. In this paper we compare urinary and fecal excretion of cadmium in rats at different levels of cadmium toxicity classified as stages I, II and III. These stages are characterized by latent toxicity, cadmium-induced renal damage, and both renal and hepatic damage, respectively. We also describe the relation-
ships between the accumulation of cadmium and its urinary or fecal excretion before and after the appearance of cadmium toxicity.

METHODS

Cadmium analysis of urine and feces

Five male Sprague-Dawley rats weighing 200–250 g were housed individually in stainless steel metabolic cages. They were fed a commercial pelleted diet (CE-2, Japan CLEA Inc., Tokyo) and sterilized tap water ad libitum. The cadmium content of the diet was described previously. These animals were given daily subcutaneous injections of CdCl₂ (0.5 mg of Cd/kg, 6 days/week) as described previously.

Urine and feces of the animals were collected for a period of 24 hr at the end of each week. The urine was immediately centrifuged at 3000 rpm for 10 min and precipitates were removed and analyzed for cadmium by atomic absorption spectrophotometry after digestion in the manner described previously. The whole feces of each animal were also analyzed after digestion as described above.

Cadmium analysis of organs and metallothionein

Total cadmium of liver, kidneys, heart, lung, spleen and testes, and cadmium distribution among these organs were derived from the previously reported data on cadmium analysis in rats receiving the same dosage as that in the present experiment.

Metallothionein was separated from the liver and kidneys of the above-mentioned cadmium-injected animals in the manner reported previously, and the cadmium content of this protein was determined.

RESULTS

Cadmium excretion in urine and feces

Fig. 1 shows the daily excretion of cadmium in the urine and feces after cadmium injection. During stage I, urinary excretion of cadmium was very slight, but showed a slow increase. At the beginning of stage II it showed a considerable increase followed by a plateau near 10 μg/day. In stage III it increased rapidly and reached high mean levels ranging from 75 to 105 μg/day. These results clearly indicate that the excretion levels of urinary cadmium were different in the different stages of cadmium intoxication.

Cadmium excretion in the feces increased steadily during stages I and II. The increasing rates showed no significant differences between these two stages. At the beginning of stage III the fecal excretion of cadmium showed a clearer increase. However, it was not so sharp as seen in the urine and the fecal cadmium was less than half of the urinary cadmium in stage III. These results show that fecal
excretion of cadmium was scarcely affected by renal damage only, but slightly affected by the presence of both renal and hepatic damage.

Ratios of the fecal to urinary cadmium levels are shown in Fig. 2. They showed a decline from 30 to 10 during stage I and dropped to nearly constant values of 2–3 in stage II and of about 0.5 in stage III.

Cadmium in the organs

Total cadmium of the liver, kidneys, heart, lung, spleen and testes and its distribution among these organs is shown in Table 1. The total cadmium content increased steadily until the 10th week (throughout stages I and II), but declined thereafter (stage III). Cadmium in the liver and kidneys accounted for nearly 90 and 10% of the total content, respectively. Increase and decrease in total cadmium were parallel to the changes in the cadmium content of both the liver and the kidneys.

Nearly 80% of hepatic and renal cadmium was recovered in metallothionein. Fig. 3 shows the changes in the concentration of metallothionein cadmium in the liver and kidneys after cadmium injection. The hepatic concentration of metallothionein cadmium increased with cadmium exposure during stages I and II, but showed a sharp decline in stage III. The concentration of metallothionein cadmium
Fig. 2. Ratios of fecal cadmium to urinary cadmium in rats given a subcutaneous injection of 0.5 mg of Cd/kg, 6 days/week.
Each point represents the mean value of 4 or 5 animals.

Table 1. Total cadmium of organs and its distribution

<table>
<thead>
<tr>
<th>Cadmium injection (weeks)</th>
<th>Total cadmium of organs (mg)</th>
<th>Cadmium distribution (%)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Liver</td>
</tr>
<tr>
<td>1</td>
<td>0.453</td>
<td>91.8</td>
</tr>
<tr>
<td>2</td>
<td>0.949</td>
<td>92.0</td>
</tr>
<tr>
<td>3</td>
<td>1.63</td>
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<td>8</td>
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</tr>
<tr>
<td>10</td>
<td>6.70</td>
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</tr>
<tr>
<td>12</td>
<td>6.65</td>
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</tr>
<tr>
<td>15</td>
<td>5.65</td>
<td>87.6</td>
</tr>
</tbody>
</table>

1) Subcutaneous injection of 0.5 mg of Cd/kg, 6 days/week.
2) Liver, kidneys, heart, lung, spleen and testes.
NT: not tested.
in the kidneys also increased during stage I. It leveled off in stage II and remained almost unchanged thereafter.

**Relationships between accumulation and excretion of cadmium**

Fig. 4 shows the relationships between the total cadmium of the organs and the daily excretion of cadmium in the urine or feces after cadmium injection. Different relationships were seen between the cadmium content and the urinary excretion in the different stages. However, a linear relationship was obtained between the cadmium content and fecal excretion of cadmium throughout all the stages.
This paper describes cadmium excretion in the urine and feces of rats at different levels of cadmium toxicity, stages I, II and III\(^7\). The toxicological significance of these stages is given in the introduction.

Cadmium excretion in the urine and feces showed different changing patterns at the different levels of cadmium toxicity (Fig. 1). These results indicate that the significant increase in urinary cadmium in stage II was involved in the onset of renal dysfunction and the more marked increase in stage III arose from the combination of the renal and hepatic damage. Fecal cadmium increased without any significant signs of renal damage, but was slightly more affected by hepatic damage. These results reveal that cadmium excretion in urine, but not in the feces, is markedly affected by cadmium toxicity.

The results of this study demonstrate that the relationship between the accumulation and urinary excretion of cadmium is affected by cadmium toxicity (Fig. 4). Urinary cadmium was proportional to the body burden only before renal damage occurred, and exceeded fecal cadmium after the occurrence of both renal and hepatic damage. From the observation by Nomiyama and Nomiyama\(^8\) on rapidly decreased excretion of urinary cadmium after cessation of cadmium administration, it is probable that most of the increased urinary cadmium seen...
in stage III was due to the daily exposure to the element.

The feces were the main route of cadmium excretion for the first several weeks of cadmium administration (Fig. 2). The same observation has been reported by Shaikh and Hirayama. In our results, the increase in fecal cadmium was only a slight reflection of hepatic damage, but a linear relationship can be seen between the accumulation and fecal excretion of cadmium throughout all the stages (Fig. 4). Nordberg demonstrated that fecal excretion of cadmium is related partly to the body burden and partly to the daily cadmium exposure. Our results strongly suggest that the relationship between the fecal excretion and the body burden or the daily exposure is scarcely affected by cadmium toxicity.

The decline in hepatic cadmium seen after the 12th week (Table 1) was accompanied by a rapid decrease in hepatic cadmium-thionein (Fig. 3). At the same time increased plasma concentrations of cadmium-thionein were observed. Urinary excretion of metallothionein increases after cadmium exposure. This protein contains most of the urinary cadmium after cadmium toxicity appears. It can be considered that the sharp increase in urinary cadmium seen in stage III may be a direct reflection of increased plasma levels of cadmium-thionein released from the injured hepatic cells.

One of the most striking findings in this study is the difference between the changing patterns of cadmium excretion in the urine and the feces in stage III as shown in Fig. 1. The reason for this difference may be that hepatic metallothionein is released from the injured cells mainly into the blood, but hardly at all into the bile, or that if is released into the bile, the released cadmium-thionein may be easily reabsorbed in the intestines.

References


