The Effects of Cadmium on Microsomal Drug Metabolizing Enzyme System in Rat Livers

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SUMMARY

Cadmium chloride administered intraperitoneally to rats caused a mainly dose-dependent decrease of microsomal protein and the cytochrome P-450 contents in the hepatic microsomal drug-metabolizing enzyme system. This dose-dependent decrease of cytochrome b_5 was slight. The concentrations of cadmium that decreased the activity of this system show no effect on sGOT and sGPT activity in this experiment.

Cadmium added *in vitro* caused the denaturation of cytochrome P-450 to cytochrome P-420, and the denaturation was dependent on the concentration of cadmium.

Experiments on the effect of cadmium on the activity of aminopyrine demethylase and aniline hydroxylase dependent cytochrome P-450 were conducted *in vivo* and *in vitro*. The specific activity of the former was decreased more remarkably than that of the latter by cadmium administered *in vivo*. On the other hand, in *in vitro* experiment, aniline hydroxylase was inhibited much more than aminopyrine demethylase.

Enzyme kinetics to determine the inhibitory mechanism of aminopyrine demethylase and aniline hydroxylase were also conducted.

These results may indicate that the decrease of drug-metabolizing enzyme activity is mainly due to the denaturation of cytochrome P-450 rather than the inhibition of the terminal oxidase by cadmium.

INTRODUCTION

Cadmium compounds are well known to be toxic for men and animals. Cadmium absorption, accumulation, excretion, biological halftime and binding to metallothionein has been studied widely by many workers and reviewed by Friberg et al.¹⁾

It is known that the metabolic abnormalities induced by cadmium are observed in liver, kidney, testes and lung^{2,3)}. However, there are but few studies regarding the effect of cadmium on the drug-metabolizing enzyme system. The microsomal drug-metabolizing enzyme system are responsible for metabolizing foreign compounds such as drug or environmental pollutants^{4,5)}. Unger and Clausen⁶⁾ reported the inhibitory effect of cadmium on the cytochrome P-450 dependent p-nitroanisole demethylating activity. Pence et al.,⁷⁾ reported that the hepatic microsomal metabolism of hexobarbital was significantly decreased in male rats after cadmium administration.

The present work was designed to discover the mechanism of harmful effect of cadmium on the cytochrome P-450 and cytochrome b_5 linked drug-metabolizing enzyme system in rat liver.

MATERIALS AND METHODS

Chemicals. Aminopyrine (Sanko Kogyo Co. Ltd.,) and aniline hydrochloride (Wako Pure

Chem. Co. Ltd.,) were recrystallized from water. NADP and Glucose-6-phosphate dehydrogenase (G-6-PD) were purchased from Oriental Yeast Co. Ltd., Glucose-6-phosphate disodium salt (G-6-P) from Sigma Chemical Co. Ltd.. Other chemicals were obtained from Wako Pure Chemical Co. Ltd., in the purest grade.

Animals. Wistar-JCL male rats weighing 240 g to 290 g were used. Thirty eight rats were divided into four injected groups that received, respectively, 0.0, 0.23, 0.32, and 0.45 mg Cd^{2+} per kg of body weight at every injection, and the group contained 11, 7, 7, and 13 rats, respectively. Cadmium was injected intraperitoneally as CdCl_2 in 0.9% sterile saline. Injections were repeated eight times during the period of eleven days; the injection was avoided at the fourth, fifth and ninth day. Twenty-eight days after the initial cadmium injection, the animals were killed by removing blood from the carotid arteries under light anesthesia with ethyl ether.

Preparation of microsomes. Liver microsomes were prepared by the method of Omura and Sato⁸⁾. The microsomes were washed twice with 1.15% KCl, and the final precipitate by ultracentrifugation at $105,000\times g$ was placed in an ice bath overnight.

Then, the precipitate was suspended in 1.15% KCl to give a protein concentration of 8 mg per ml.

Determination of cytochrome P-450 and b_5 . The amounts of cytochromes in microsomes were determined by the modified method of Omura and Sato⁸⁾. The difference in spectra of the cytochromes were measured in HITACHI 356 spectrophotometer. The difference in spectra of cytochrome P-450 was induced by the addition of carbon monoxide (CO) after reduction of cytochrome P-450 in microsomes with sodium dithionite, and that of cytochrome b_5 was induced by the reduction with the same chemical.

Sodium dithionite was used as 0.28 M solution on 0.1 M phosphate buffer which was dissolved with equal weight of potassium bicarbonate, and CO added as 0.1 M phosphate buffer saturated with CO gas.

0.2 ml of sodium dithionite solution and CO solution were added to 2.5 ml of the diluted microsomes for the determination of cytochrome contents. These solutions were prepared freshly shortly before using. This modified method was efficient for measurement of cytochrome contents because it was compared with the original method of Omura and Sato⁸⁾. The coefficient (extinction difference) used for the calculation of cytochrome P-450 contents was 0.091 at 450 nm and 490 nm, and for cytochrome b_5 was 0.171 at 424 nm and 500 nm.

Assay of drug metabolizing enzyme activities. Aminopyrine demethylase activities were determined at 37°C in a medium containing 0.25 M phosphate buffer, pH 7.4; 6.6 mM semicarbazide (for preventing from further oxidation of formed products), 4 mM MgCl_2 , 0.16 mM NADP, 1.66 mM G-6-P, 5 units of G-6-PD, 1.6 mg protein of microsomes, and 0.8 mM aminopyrine in a final volume of 6 ml. In the *in vitro* assay, Tris-HCl buffer and 0.8 mM NADPH were used in compensation for phosphate buffer and NADPH regenerating system, respectively.

After preincubation for 5 min, at 37°C, the reaction was started by the addition of G-6-PD. The reaction was stopped by the addition of 2 ml each of 15% ZnSO_4 and saturated $\text{Ba}(\text{OH})_2$ solution after 30 min, incubation period at 37°C.

Formaldehyde formed by the demethylation reaction was determined according to the method of Nash⁹⁾. Aniline hydroxylase activities were determined at 37°C in a medium containing 60 mM phosphate buffer, pH 7.4, 5 mM MgCl_2 , 0.2 mM NADP, 2 mM G-6-P, 5 units of G-6-PD, 1.6 mg protein of microsomes, and 1 mM aniline in a final volume of 5 ml. In the *in vitro* assay, Tris-HCl buffer and 1 mM NADPH were used in compensation for phosphate buffer and NADPH regenerating system, respectively.

After preincubation for 5 min, at 37°C, the reaction was started by the addition of G-6-PD. The reaction was stopped by the addition 2 ml of 23.5% trichloroacetic acid solution after 30 min, incubation period at 37°C. p-Aminophenol formed was determined by the method of Imai et al.¹⁰⁾.

Assay of protein. Protein was measured by the Lowry method¹¹⁾ using bovine serum albumin as a standard.

Determination of Metal contents. Metals were measured by using HITACHI 508-atomic absorbance spectrophotometer. Decomposition of organic materials in liver was accomplished by heating in nitric acid and perchloric acid mixture (4:1), and extraction of metals accomplished by DDTC extract method¹²⁾.

Statistical analysis. The data was analyzed throughout using the Student's t teste, with p 0.05 as the level of significance.

RESULTS

Table 1 shows the conditions of the animals used in this experiment. Body weight, liver wet weight and microsomal protein per g of liver wet weight of rats administered cadmium were decreased. Liver wet weight per g of body weight however did not differ from the control. The decrement of microsomal protein may indicate the destruction of endoplasmic reticulum. The four rats in the group administered 0.45 mg Cd²⁺/kg died after the final cadmium administration.

Table 2 shows cadmium contents in liver and its subcellular fractions. Cadmium contents in the microsomal fraction was 1.46 ppm to 3.29 ppm and they corresponded to about 6% of

Table 1 The Effect of Cadmium on the Condition of Rats

Administered Cd. conc. mg/kg, B.W.	number of animals	Body weight (g) ^a	Liver wet weight (g) ^a	Liver wet weight / Body weight (g/g) ^b	Microsome protein/ Liver wet weight (g/g) ^c %
0.00	11	379.6 ± 8.2	15.94 ± 0.36	0.042	0.023 (100)
0.23	7	356.7 ± 8.1	14.84 ± 0.68	0.042	0.022 (96)
0.32	7	353.9 ± 14.5	14.88 ± 0.56	0.042	0.019 (83)
0.45	9	320.1 ± 8.5	14.36 ± 0.56	0.045	0.015 (65)

^a: Values expressed as means ± SE

^b: The values were expressed by the ratio between the means of liver wet weight and the means of body weight

^c: The values expressed by the ratio between the dry weight of the pooled microsome protein and the means of liver wet weight

Table 2 Cadmium Contents in Liver and Its Subcellular Fractions

Administered Cd. dose mg/kg B.W.	Cadmium Contents (μg/g wet weight of liver) ^a		
	Whole Liver	105,000 × g Supernatant Fraction	Microsome Fraction
0.00	0.07	0.03	0.03
0.23	23.1	20.1	1.46
0.32	32.6	29.2	1.84
0.45	50.4	44.0	3.29

^a: The specimens of equal wet weight, which was obtained from all samples, and pooled, was used or fractionized

^b: Supernatant fraction was prepared by the ultracentrifugation of 105,000 × g for 60 min

Fig. 1 The relationship between cadmium injection doses and metal concentrations in rat livers. Ferric ion (A), Zinc ion (B), Cadmium ion (C) and Copper ion (D)

that of whole liver, respectively.

Fig. 1 indicates the some metal contents in liver as a function of the dosed cadmium. Cadmium administration caused the increment of zinc and ferric ion in liver, while copper content was not changed.

Table 3 shows the effect of cadmium administration on the amounts of hepatic microsomal cytochrome P-450 and b_5 . The amounts of cytochrome P-450 were remarkably decreased by cadmium administration. The mean value of cytochrome P-450 content in hepatic microsomes of the rats administered 0.45 mg Cd^{2+} /kg was 0.973 nmole/mg protein, corresponding to 67%

Fig. 2 Lineweaver-Burk plots showing inhibition of aminopyrine demethylase by cadmium administered under *in vivo* conditions at doses of 0.45 (A), 0.32 (B), 0.23 (C) mg Cd/kg and the corresponding control (D)

Table 3 Effect of Cadmium on the Contents of Cytochrome P-450 and b_5 in Liver Microsomes

Cd Administered mg/kg, B.W.	Cytochrome P-450 ^a contents		Cytochrome b_5 ^a contents	
	mg	%	mg	%
0.00	1.461 ± 0.070	100	0.930 ± 0.021	100
0.23	1.197 ± 0.160 ^b	82	0.825 ± 0.052 ^b	89
0.32	1.010 ± 0.098 ^c	69	0.780 ± 0.017 ^c	84
0.45	0.973 ± 0.065 ^c	67	0.795 ± 0.038 ^c	85

^a: Cytochrome P-450 and b_5 contents are expressed as nanomole per mg protein. Values expressed as means ± SE.

^b: Not significantly different from control group as judged by Student's *t* test

^c: $p < 0.01$

of the control value. On the other hand, the decrement of cytochrome b_5 content in hepatic microsomes from cadmium-treated rats was slight as shown in Table 3. These results indicate the possibility that cadmium inhibited the synthesis of two cytochromes or destroyed two cytochromes. Furthermore, it was found that cytochrome P-450 is more sensitive to cadmium than cytochrome b_5 .

The specific activity of aminopyrine demethylation and aniline hydroxylation dependent cytochrome P-450 was determined by cadmium administration (Table 4).

The specific activity of aminopyrine demethylation in the rats administered 0.45 mg Cd^{2+} /kg

Table 4 The Effects of Aminopyrine Demethylase and Aniline Hydroxylase in Rat Liver Microsomes

Cd Administered mg/kg, B.W.	Aminopyrine Demethylase	
	nmole HCHO/min/mg protein	nmole HCHO/min/mg protein /nmole P-450
0.00	7.18 ± 0.25 (100)	4.91
0.23	6.66 ± 0.08 (93)	5.56
0.32	4.87 ± 0.25 (68) ^a	4.82
0.45	4.10 ± 0.53 (57) ^a	4.21
Cd Administered mg/kg, B.W.	Aniline Hydroxylase	
	nmole HCHO/min/mg protein	nmole HCHO/min/mg protein /nmole P-450
0.00	0.361 ± 0.008 (100)	0.247
0.23	0.350 ± 0.041 (97)	0.293
0.32	0.286 ± 0.031 (79) ^b	0.283
0.45	0.253 ± 0.015 (70) ^a	0.260

^a: $p < 0.001$

^b: $p < 0.05$

Fig. 3 Lineweaver-Burk plots showing inhibition of aniline hydroxylase by cadmium administered under *in vivo* conditions at doses of 0.45 (A), 0.32 (B) mg Cd/kg and the corresponding control (C)

was 4.10 nmole/mg protein, corresponding to 57% of the control value.

On the other hand, the decrement of aniline hydroxylation activity by cadmium administration was slight as compared with aminopyrine demethylation activity as shown in Table 4.

Fig. 2 shows a Lineweaver-Burk plot of aminopyrine demethylase activity dependent cytochrome P-450 in the microsomes. Cadmium administered to rats caused the decrease in the V_{max} values of aminopyrine demethylase however, the K_m value (0.53 mM) was not changed. A Lineweaver-Burk plot for aniline hydroxylase dependent cytochrome P-450 is given in Fig. 3. V_{max} values of aniline hydroxylase from hepatic microsomes of rats administered cadmium were decreased, and K_m values were increased corresponding to the cadmium doses. The experiment to determine if cadmium, added directly *in vitro* to the reaction mixture containing the hepatic microsomes isolated from untreated rats, could inhibit the metabolism of aminopyrine and aniline, was conducted. Microsomes derived from control rats were incubated with aminopyrine or aniline in the presence of cadmium in concentration of 10^{-6} M to 10^{-3} M.

Fig. 4 shows the remaining activity of aminopyrine demethylase and aniline hydroxylase by cadmium added directly *in vitro*. The activity of aminopyrine demethylase was decreased lineally with the concentration of added cadmium. Whereas the activity of aniline hydroxylase was decreased sigmoidally with the concentration of added cadmium. The

Fig. 4 The change of aminopyrine demethylase and aniline hydroxylase activity by cadmium addition *in vitro* system. The curve showing aminopyrine demethylase (A) and aniline hydroxylase (B). Cadmium concentrations were expressed with log scale.

Fig. 5 The difference spectrum change of cytochrome P-450 by cadmium addition *in vitro*. The specimens were incubated for 30 min at 37°C after cadmium addition and the difference spectrum measured. The curve shows control (A), 0.112 ppm (B), 1.12 ppm (C), 11.2 ppm (D), 112 ppm (E) and base line (F). Protein used was 1.75 mg/ml concentrations.

activity of aniline hydroxylase observed in the presence of 10^{-3}M and $3 \times 10^{-3}\text{M}$ of cadmium was higher than that in 10^{-4}M cadmium. This discrepancy may be due to the decrease of cadmium ion concentration caused by the formation of a complex between cadmium and phosphate. These results indicate that both enzymes were inhibited by cadmium added directly *in vitro*. In the measurement of cytochrome P-450 *in vivo*, the shoulder or peak at 420 nm was observed. So, the change of cytochrome P-450 by cadmium added directly *in vitro* was determined to characterize this shoulder or peak at 420 nm (Fig. 5). The addition of cadmium *in vitro* caused the denaturation of cytochrome P-450 to cytochrome P-420, and the denaturation was dependent on the cadmium concentration. It was found that cadmium also caused the denaturation of cytochrome P-450 *in vivo*. These results may indicate that the inhibition of aminopyrine demethylase and aniline hydroxylase by cadmium *in vitro* is mainly due to the denaturation of cytochrome P-450.

DISCUSSION

Results in the present study indicate that the drug-metabolizing enzyme system is very sensitive to cadmium. The concentrations of cadmium that decreased the activity of the system shows no effect on serum glutamate oxaloacetate transferase (sGOT) and serum glutamate pyruvate transferase (sGPT) in this experiment. This indicates that this system was more sensitive to cadmium than clinical assay with serum, and that this system was excellent target to determine the toxicity of cadmium.

Stowe et al.¹³⁾ reported the morphological abnormalities of endoplasmic reticulum of hepatocytes by electron microscopy without the change of the above two serum enzymes in rabbit by cadmium administration. The decrease of microsomal protein observed in this experiment (Table 1) may correspond to the decrease of endoplasmic reticulum as well as the observation by Stowe et al. It is well known that most of the cadmium accumulated in livers is bound to metallothionein¹⁴⁾ in soluble supernatant fraction, and that a few cadmium also binds to some particulates fraction, i.e., microsomes, mitochondria and nuclei¹⁵⁾. The supernatant fraction contained about 90% of the cadmium in whole liver, and microsome fraction contained about 6%. This result corresponded to the result reported by Colucci et al.¹⁵⁾. It was presumed from the results of Fig. 4 and Fig. 5 that the contents of cadmium accumulated in hepatic microsomes were sufficient to destroy cytochrome P-450 and to inhibit the activity of aminopyrine demethylase and aniline hydroxylase. The contents of other metals were determined as shown in Fig. 1. Cadmium administration caused the increment of zinc and iron in livers.

It is ascertained that the source of zinc results from metallothionein mainly, and the increment of zinc in liver is dependent on the increment of metallothionein by cadmium administration, and that metallothionein play the role of detoxification of cadmium¹⁾. The source of iron in liver is ferritin mainly, but the significance of increasing ferritin can not be explained from this data. It was found that at least the decrease of cytochrome P-450 is not due to the deficiency of iron in liver.

On the other hand, copper content was not changed in the liver by cadmium administration.

Cadmium decreased cytochrome P-450 remarkably in the drug-metabolizing enzyme system of hepatic microsomes; cadmium decreased the cytochrome P-450 contents *in vivo* (Table 3). It was found that cytochrome P-450 was changed to cytochrome P-420 by cadmium *in vitro*, and that the denaturation was dependent on the concentration of cadmium as shown in Fig. 5.

It is ascertained that the denaturation of cytochrome P-450 to cytochrome P-420 is due to the destruction of ferric-thiol ligand in case of some mercury compounds.

So, the decrease of cytochrome P-450 contents by cadmium administration may be also due to the evidence that cadmium destroyed ferric-thiol ligand of cytochrome P-450 in hepatic microsomes. Cadmium also caused the decrease of cytochrome b_5 contents, but the decrease ratio was less than that of cytochrome P-450.

Recently, Levin and Kuntzman¹⁶⁾ reported that the turnover rate of cytochrome P-450 was 48 hr. in its slow phase, and that it was faster than that of cytochrome b_5 .

The difference between cytochrome P-450 and cytochrome b_5 content by cadmium administration may be reflecting to the difference in the turnover rate of the two cytochromes because cadmium causes not only the destruction of cytochrome, but the inhibition in hem synthesis of cytochromes. Cadmium caused *in vivo* the decrease in specific activity of aminopyrine demethylase and aniline hydroxylase dependent cytochrome P-450. The former was decreased more than the latter as shown in Table 4.

These results indicate that the sensitivity of aminopyrine demethylase and aniline hydroxylase to cadmium is different. On the other hand, it was found that aniline hydroxylase was more sensitive to cadmium than aminopyrine demethylase *in vitro* as shown in Fig. 4. The sensitivity of the two enzymes to cadmium is reversed *in vivo* and *in vitro*. The effect of cadmium on the active site of aminopyrine demethylase and aniline hydroxylase dependent cytochrome P-450 was evaluated from Lineweaver-Burk plot *in vivo*. In the aminopyrine demethylase assay, V_{max} values were changed in correlation to cadmium doses, and no difference in K_m value was observed.

This observation may indicate the possibility that cadmium had no effect on the active site of cytochrome P-450 regarding aminopyrine demethylation reaction, and caused only the decrease of cytochrome P-450.

Lineweaver-Burk plot of aniline hydroxylase demonstrated the increase in K_m values and the decrease in V_{max} values in correlation to cadmium doses, respectively.

This may indicate the possibility that cadmium had some effect on the active site of aniline hydroxylase dependent cytochrome P-450, and caused also the destruction of cytochrome P-450 in rat liver. These results may indicate that the decrease of the drug-metabolizing enzyme activity is mainly due to the decrease of cytochrome P-450 rather than the inhibition of the terminal oxidase by cadmium.

This explanation was also supported by the decrease of microsomal protein and the denaturation of cytochrome P-450 by cadmium because the decrement ratio of cytochrome P-450 corresponded to the decrease ratio of microsomal protein.

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ラット肝臓における薬物代謝酵素系に対するカドミウムの影響

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ラットに低濃度の塩化カドミウムを頻回、腹腔内投与しその肝臓の薬物代謝酵素系に対する影響を調べた。この時血清学的肝機能検査での異常はなかった。このような条件下でもカドミウムはミクロソーム画分を減少させ、更に薬物代謝酵素系の中心をなしているチトクローム P-450 含量の減少をひき起した。

一方、チトクローム b_5 も減少したがチトクローム P-450 の減少に比べると極めて少なかった。このチトクローム P-450 の減少は *in vitro* の実験でチトクローム P-420 への変化が観察されたことから、その変性・破壊によるものかもしれない。又チトクローム P-450 のターミナルオキシダーゼ活性に対するカドミウムの影響をアミノピリンとアニリンを基質として *in vivo* と *in vitro* で調べた。*in vivo* でアミノピリン脱メチル化活性はアニリン水酸化活性よりも低下しており *in vitro* とは逆の結果を示した。

その他の結果をも含めると、カドミウムは肝臓の薬物代謝機能の低下をひき起すが、これはカドミウムがミクロソーム画分を破壊し、特にそのチトクローム P-450 の破壊を主としていることがわかった。

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