Studies on the Chronic Cadmium Intoxication: Effect on the Hepatic Function in Rats

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ABSTRACT

After long term administration of cadmium (100 ppm, orally, 30 days) and fed on a heavy metal deprived diet ad libitum, the rat serum enzyme activity of alkaline phosphatase significant decreased compared with those of the control group. The serum enzyme activities of aspartate aminotransferase, alanine aminotransferase and cholinesterase showed no significant difference, whereas significant increase of hepatic aspartate aminotransferase and alanine aminotransferase were observed as compared with those of the controls. The level of serum cholesterol significant increased. On the other hand, hepatic triglyceride and cholesterol concentrations markedly decreased. In addition, hepatic metallothioneins and hepatic levels of cadmium and zinc were increased by cadmium exposure; whereas, hepatic total sulfhydryls, oxidized glutathione reductase and glutathione peroxidase were significantly decreased. Hepatic thiobarbituric acid-reactive substances and lactate dehydrogenase activity were decreased significantly in rats administered with cadmium.

The above results suggested that cadmium could enhance or improve the liver amino acids metabolism and lipid transporting ability in this experimental condition. It also indicated that the liver glutathione peroxidase-associated enzymes and metallothionein are important in modulating cadmium-induced hepatotoxicity.

Key words: hepatic function, cadmium intoxication, amino acids metabolism, lipid transporting ability, glutathione peroxidase-associated enzymes, metallothionein

Cadmium is widely distributed in the lungs and other tissues, and accumulated in the liver and kidneys [1-3]. Liver, rather than the kidney, is a major target organ for the acute oral tox-

icity of cadmium [4-5]. The damage of liver was generally measured by the aspartate aminotransferase, alanine aminotransferase both in liver and serum, and alkaline phosphatase in serum. Cholinesterase activity in serum is a sensitive biological indicator for cadmium toxicity[6]. Recently, it has been found that metallothioneins and glutathione peroxidase-associated enzymes play a very important role in cadmium-induced hepatotoxicity [7-8]. Many researchers also pointed out that dietary metals are significant factors in lipid metabolism [8-12].

In our previous study [13], we reported that long-term administration of cadmium gave better results in hepatic function such as aminotransferase activity than the control group. The present study is, through the experiments of chronic cadmium intoxicated rats fed on a heavy metal-deprived diet and acute cadmium intoxicated rats fed on a standard diet, to investigate the hepatotoxicity of cadmium, including its influence on aminotransferase, lipid transporting ability, glutathione peroxidase-associated enzymes and metallothioneins.

MATERIALS AND METHODS

Animal and diets: Male Wistar rats were used. They were fed either on a standard diet (Taiwan Sugar Co. Ltd.) or on a heavy metal deprived (HMD) diet. The composition of HMD-diet and heavy metal contents of the diets were shown in our previous report [13]. The rats were fed on a standard diet until 50-60 g of body weight was achieved, and then divided randomly into two groups. The diet and deionized water were supplied ad libitum. One month after grouping the rats were administered with cadmium.

Cadmium administration: One hundred ppm of cadmium (cadmium acetate) in deionized water was supplied daily as drinking water for 30 consecutive days. And acute intoxication was performed by subcutaneous injection of cadmium, and the results were obtained 24 hrs after injection. All cadmium doses refer to the concentrations of cadmium and not to its salt.

Tissue preparation: The rats were anesthetized with sodium pentobarbital. Blood was collected from the femoral arteries, and allowed to clot at room temperature for 30-60 min and then centrifuged at $2,300 \times g$ for 10 min at 4°C for serum collection. The liver was perfused in situ with ice-cold 1.15% KCl until it is uniformly pale, then it was blotted and minced. The liver homogenate was prepared in suitable amount of ice-cold 1.15% KCl by motor-driven teflon pestle in a glass homogenizing vessel. These preparations were used for the determinations of enzyme activities, such as alkaline phosphatase (ALP; EC 3.1.3.1), aspartate aminotransferase (GOT; EC 2.6.1.1), alanine aminotransferase (GPT; EC 2.6.1.2), cholinesterase (ChE; EC 3.1.1.8), glutathione (GSH)peroxidase (EC 1.11.1.9), oxidized glutathione (GSSG) reductase (EC 1.6.4.2) and glucose-6-phosphate dehydrogenase (G-6-PD; EC 1.1.1.49), and thiobarbituric acid TBA)-reactive substances level. The liver homogenate prepared in ice-cold 0.02 M EDTA (Na_2) (16 ml/g) was used for the determinations of total sulfhydryl (TSH) and non-protein sulfhydryl (NPSH), according to the method described by Sedlak and Lindsay [14].

Extraction of hepatic lipid: The lipid was extracted by the procedure of Folch et al [15]. One gm of liver was homogenized with 19 ml of 2:1 chloroform-methanol mixture, the

homogenate was left at 37°C for 3 hrs and then filtrated. The organic phase was shaken with 1/5 volume of 0.01 M NaCl and centrifuged, then it was evaporated to dry with N_2 gas. For the determinations of total lipid (TL), cholesterol (Cs) and triglyceride (TG) levels, the lipid was dissolved immediately into isopropyl alcohol containing 10% Triton X-100.

Determination of protein: Protein was determined with the Folin phenol reagent according to the method of Lowry et al [16] using bovine serum albumin as standard.

Determinations of ALP, ChE, GOT and GPT in liver and serum: ALP was measured as dec-scribed by Frankel et al [17], GOT and GPT were determined according to the Reitman-Frankel method [17], and the assay of ChE was carried out as described by Bergmeyer et al [18].

Determinations of TL, Cs and TG in liver and serum: The TL was determined as described by Fringe et al [19], Cs was measured by the principle of Liebermann-Burchard reaction [20] and the TG was determined with reagent kit (TG-5, product of The International Reagent Co. Ltd. Kobe, Japan) as described by Henry et al [21].

TBA-reactive substances in liver was mea-sured by the method described by Uchiyama et al [22]. The activities of hepatic GSH peroxidase and GSSG reductase were determined by measuring the disappearance of NADPH at 340 nm with a Hitachi 139 spectrophotometer at 37°C. The GSH peroxidase assay was conducted by a modification of the method of Paglia et al [23]. The assay procedure used for the determi-nation of GSSG reductase activity was based on the method described by Pinto et al [24]. The values of GSH peroxidase and GSSG reductase activities were defined as amount of NADPH

oxidizied per milligram protein per minute. And the activity of G-6-PD was determined by a modification of the method described by Berg-meyer et al [25]. For the assay of liver lactate dehydrogenase (LDH; EC 1.1.1.27) the method described by Bergmeyer et al [25]. For the assay of liver lactate dehydrogenase (LDH; EC 1.1.1.27) the method described by Baur et al [26] was used. Metallothionein in liver was measured by the cadmium-hemolysate method as described by Onosaka et al [27].

Determination of heavy metals: The liver was dry-ashed and the ash digested with nitric acid. After proper dilution with water, metals in the solution were measured by a Hitachi atomic absorption spectrophotometer with an air-acety-lene flame (Zn) or a graphite-furnace (Cd).

Data analysis: All results were given as mean ± SD values. Differences between experi-mental and control results were evaluated for significance by Student's t-tests and analysis of variance. A p value of < 0.05 was considered as significant.

RESULTS

Effect of cadmium on hepatic function (Table 1): In the HMD-diet fed rats, the serum alkaline phosphatase activity of the long-term cadmium administered group was lower than that of the control group. The serum enzyme activities of alanine aminotransferase (GPT), aspartate aminotransferase (GOT) and cholinesterase (ChE) showed no significant dif-ference. The hepatic GOT and GPT activities were higher than those of the control group ($P < 0.05$ – $P < 0.001$), but ChE activity showed no significant difference. Therefore, cadmium chronic exposure seemed to have a

Table 1. Effect of Cadmium on Hepatic Function in Rats Fed with Heavy Metal Deprived Diet

Subject		Cadmium administered (100 ppm; 30 days; oral)	Deionized water (control)
Serum	GOT (u/ml)	23.5±10.5	25.5±5.7
	GPT (u/ml)	9.5±0.1	9.9±0.5
	ALP (u/ml)	1.4±0.1**	3.3±1.2
	ChE (u/ml)	581.6±105.7	555.0±35.5
Liver	GOT (u/mg)	1563.8±171.3*	1168.1±290.5
	GPT (u/mg)	607.2±141.4**	303.8±79.5
	ChE (u/mg)	303.7±49.8	306.0±62.4
Serum	TL (mg/dl)	190.7±34.2	194.7±12.4
	TG (mg/dl)	40.5±6.9	33.6±9.7
	Cs (mg/dl)	108.5±11.2**	82.8±2.9
Liver	TL (mg/mg)	52.0±17.9	145.2±110.1
	TG (mg/gm)	20.0±15.9**	85.3±30.2
	Cs (mg/gm)	5.3±2.0**	17.2±3.8

Abbreviation: Aspartate aminotransferase (GOT), alanine aminotransferase (GPT), alkaline phosphatase (ALP), cholinesterase (ChE), total lipid (TL), triglyceride (TG) and cholesterol (Cs). Each group consisted of 5 rats. Significant difference from control group (df= 8): *$P<0.05$, **$P<0.01$ and ***$P<0.001$.

promotive effect on the amino acid metabolism in liver.

As shown in Table I, the total lipid (TL), triglyceride (TG) and cholesterol (Cs) in serum of the tested group were higher than or similar to those of the control group. However, the TL, TG and Cs of the liver were distinctly lower than those of the control group. Therefore, long-term administration of Cd also had an improving effect on the lipid transporting ability of the liver.

The effect of acute toxicity of Cd on the liver function of the standard diet fed rats was shown in Table 2. Serum GOT activity increased as Cd dose increased, but ChE activity was distinctly decreased at higher dose. Hepatic GPT ($P<0.05$ – $P<0.01$) also had an inclination to decrease.

Effect of Cd on non-protein sulfhydryls (NPSH) and total sulfhydryls (TSH) levels in liver (Table 3): Cadmium caused increase of NPSH, but significant decrease of TSH ($P<0.01$).

Damage to the cell membrane of liver by cadmium (Table 4): Chronically Cd intoxicated rats showed less thiobarbituric acid (TBA)-reactive substances than that of the control group ($P<0.05$), their lactate dehydrogenase activity also decreased. However, acute Cd intoxication could cause damage to cell membrane of liver, since the TBA-reactive substances levels of tested groups were significantly higher than that of the control group.

Effect of cadmium on oxidized glutathione

reductase, glutatione peroxidase and glucose -6-phosphate dehydrogenase activities in liver (Table 5): In HMD diet fed rats, Cd chronic intoxication had distinct inhibitory effect on glutathione peroxidase-associated enzymes ($P < 0.05$). In the standard diet fed rats, 24 hrs after sc injection of Cd, these enzyme activities distinctly increased except G-6-PD activity as compared with those of the control group.

Effect of cadmium on metallothioneins production (Table 6): either chronic or acute intoxication of Cd could cause liver to produce more metallothioneins. A distinct increase of Cd and Zn in liver could be seen from Table 7.

DISCUSSION

From the results of long-term cadmium

Table 2. Acute Toxicity of Cadmium on Hepatic Function in Rats Fed with Standard Diet

Subject		Cadmium administration (mg/kg; SC; 24 hr later)		
		0.0 (n= 5)	1.5 (n= 5)	5.0 (n= 5)
Serum	GPT (u/ml)	19.9±7.3	13.0±1.8	20.0±11.3
	GOT (u/ml)	115.6±8.1	159.5±39.5*	222.6±21.6***
	ChE (u/ml)	471.7±85.7	484.0±133.2	341.9±71.0*
Liver	GPT (u/mg)	693.7±240.0	348.4±195.4*	227.4±190.4**
	GOT (u/mg)	1,897.3±282.3	1,540.7±90.1*	1,676.5±206.5
	ChE (u/mg)	516.6±67.7	570.0±136.4	534.5±24.0
Serum	TG (mg/dl)	67.3±16.1	112.6±28.9*	74.1±14.2
	Cs (mg/dl)	110.3±13.5	93.4±19.6	102.1±10.2
Liver	TG (mg/gm)	12.9±9.5	16.4±6.7	10.2±2.6
	Cs (mg/gm)	4.7±1.3	3.7±0.4	3.5±0.5

Significant difference from control group (0.0): *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$.

Table 3. Effect of Long-Term Exposure to Cadmium on the Hapatic Levels of NPSH and TSH in Rats

Subject	Cadmium administered (100 ppm; 30 days; oral)	Deionized water (control)
NPSH (Cysteine: μg/mg protein/min)	0.368±0.076	0.330±0.052
TSH (Cysteine: μg/mg protein/min)	7.714±0.574*	8.522±0.323

Each group consisted of 5 rats.
Significant difference from control group (df=8) : *$P < 0.01$.

Table 4. Effect of Cadmium on Liver TBA-reactive Substances Level and LDH Activity in Rats

Group	Cadmium administered	Route	TBA-reactive substances (μmole/mg protein/ml;x 10^{-3})	
			Tested	Control
HMD-diet	100 ppm (30 days)	oral	1.32±0.07*	1.62±0.27
Standard diet	1.5 mg/kg	SC	1.08±0.62*	0.39±0.09
	5.0 mg/kg		0.56±0.09*	
			LDH (NADPH μmole/mg protein/ml)	
HMD-diet	100 ppm (30 days)	Oral	0.999±0.372	1.524±0.849

Abbreviation: heavy metal-deprived diet (HMD-diet).
Significant difference from control group (df= 8): *P<0.05.
Each group consisted of 5 rats.

Table 5. Effect of Cadmium on the Hepatic GSSG Reductase, GSH Peroxidase and G-6-PD Activities in Rats

Group	Cadmium administered	Route	GSSG reductase (NADPH oxid. μmole/mg protein/ min; x 10^{-3})	GSH peroxidase (NADPH oxid. μmole/mg protein/ min; x 10^{-3})	G-6-PD (NADP red. μmole/mg protein/min; x 10^{-3})
HMD-diet	100 ppm (30 days)	Oral	2.159±0.839*	60.38±21.88*	4.49±1.02
	Control		3.525±0.569	91.65±18.83	6.50±2.05
Standard diet	1.5 mg/ kg	SC	19.01±2.58	153.02±5.25*	18.82±2.68***
	5.0 mg/ kg		24.88±3.12**	140.09±6.84	21.76±2.24***
	Control		17.01±2.38	135.90±14.30	12.44±0.26

Abbreviation: heavy metal-deprived diet (HMD-diet) and subcutaneous injection (SC).
Each group consisted of 5 rats.
Significant difference from control group (df= 8): *P<0.05 ,**P<0.01 and ***P<0.001.

administration rat experiments, we found that the serum enzyme activities of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase decrease slightly or significantly. Significant increase of hepatic aspartate aminotransferase and alanine aminotransferase activities were observed as compared with those of the controls. The sc injection of cadmium (5.0 mg/kg, 24 hr later) into a standard diet fed rats significantly enhanced serum aspartate aminotransferase activity but had no effect on alanine aminotransferase activity. On the other hand, the activity of serum cholinesterase was significantly inhib-

Table 6. Effect of Cadmium on Metallothionein Production in Rat Liver

Group	Cadmium administered	Route	Cd (ppm) Tested	Control
HMD-diet	100 ppm (30 days)	Oral	34.48±13.30*	2.98±1.72
Standard diet	1.5 mg/kg	SC	44.50±9.82*	2.40±1.66
	5.0 mg/kg		61.89±4.37*	

Abbreviation: Heavy metal-deprived diet (HMD-diet) and subcutaneous injection.
Significant difference from control group (df= 8): *P<0.001.
Each group consisted of 5 rats.

Table 7. Zinc and Cadmium Contents in Cadmium Administered Rat Liver

Group	Cadmium administered	Route	Heavy metal	Heavy metal content (ppm) Tested	Control
HMD-diet	100 ppm (30 days)	Oral	Zn	21.24±3.96*	12.33±1.52
			Cd	21.63±10.90*	0.00±0.00
Standard diet	1.5 mg/kg	SC	Zn	307.3±41.5**	148.2±9.3 (Zn)
			Cd	36.7±4.5**	
	5.0 mg/kg		Zn	277.5±19.3**	0.0±0.0 (Cd)
			Cd	57.7±6.2**	

Abbreviation: Heavy metal-deprived diet (HMD-diet) and subcutaneous injection (SC).
Significant difference from control group (df= 8): *P<0.01 and **P<0.001.
Each group consisted of 5 rats.

ited. In addition, it decreased the activities of hepatic alanine aminotransferase and aspartate aminotransferase. Ledda-Columbano et al [28] also reported that an elevation of total hepatic DNA content after a single intravenous injection of cadmium, and no increase of serum alanine aminotransferase activity was observed. According to Dudley et al [29] cadmium interferes with hepatic protein synthesis early after injection of a large dose and the further degenerative change occur later and possibly in response to protein synthesis inhibition. From these results, it suggested that acute cadmium intoxication possibly caused liver injury expressed as in the elevation of serum aminotransferase activity. Whereas, chronic cadmium exposure possibly enhanced and improved this enzyme activity.

The effect of chronic cadmium poisoning on blood and tissue metabolite level of fish was studied by Gill and Pant [30]. Enduring hypoglycemia and diminished levels of tissue choles-

terol manifested in the chronically intoxicated fish. Both acute and chronic cadmium poisoning caused hypocholesterolemia and glycogenolysis in liver. Sugawara [10] also reported that serum triglyceride was increased slightly by the cadmium exposure. In this experiment, we also found that a significant increase in serum cholesterol; and significant decrease in the hepatic triglyceride and cholesterol were observed in the chronically cadmium intoxicated rats as compared with those of the control group. Thus, improvement of lipid transporting ability may be induced by cadmium exposure in experimental animals.

Lipid peroxidation is the oxidative deterioration of polyunsaturated lipids. The major sites of lipid peroxidative damage are biomembranes and subcellular organelles [31]. The present study has demonstrated that in the chronically cadmium intoxicated rats the level of thiobarbituric acid-reactive substances and LDH activity in liver were reduced. The high level of TBA-reactive substances was obtained from acute cadmium intoxicated rats. These results has demonstrated that cadmium is toxic to hepatocytes of rats, as evidenced by the loss of cytoplasmic enzyme lactate dehydrogenase in chronically intoxicated rats and the increase of thiobarbituric acid-reactive substances in acutely intoxicated rats. Therefore it is a support of the general hypothesis relating lipid peroxidation and tissue injury [32].

The present investigation indicates the levels of glutathione peroxidase-associated enzymes and glucose-6-phosphate dehydrogenase activities in the liver of rats were markedly inhibited by long-term administration of cadmium. Stanley and Tappel [33] also reported that a single subacute dose of cadmium injection suppressed testicular glutathione peroxidase activity and increase testicular thiobarbituric acid-reactive substances in rats. Those authors suggested that testicular glutathione peroxidase may be the direct or indirect target of cadmium-induced testicular damage, and this damage results in lipid peroxidation.

Presynthesized levels of metallothioneins are important in producing tolerance to acute cadmium toxicity [34]. In this experiment, we found in chronically or acutely cadmium intoxicated rats that the hepatic levels of metallothioneins and heavy metals such as zinc and cadmium significantly increased. These results suggested that glutatione peroxidase-associated enzymes and metallothioneins are important in modulating cadmium-induced hepatotoxicity [6].

ACKNOWLEDGEMENT

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慢性鎘中毒之研究：對大白鼠肝功能之影響

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以重金屬缺乏飼料飼養之 Wistar 株大白鼠，經以飲水方式長期投與鎘後（100 ppm，30 天），鎘投與組大白鼠之血清酵素活性，如 aspartate aminotransferase, alanine aminotransferase 及 alkaline phosphatase 等較對照組稍微減少，但血清中之 cholinesterase 活性則增加，相反的，鎘投與組肝臟之 aspartate aminotransferase 及 alanine aminotransferase 活性則明顯的增加。血清中之 triglyceride 及 cholesterol 濃度，則實驗組較對照組增加，但其肝臟之 triglyceride 及 cholesterol 濃度則明顯地減少。同時鎘投與組大白鼠之肝臟 non-protein sulfhydryls metallothionein 及鎘鋅等之量則較對照組明顯的增加，相反的，肝中之 total sulfhydryls, oxidized glutathione reductase 及 glutathione peroxidase 之量或活性則明顯的減少。Glucose-6-phosphate dehydrogenase 活性亦有減少的趨勢。鎘投與組大白鼠肝檢體之 thiobarbituric acid-reactive substances 及 lactate dehydrogenase 活性則明顯的減少。

以鎘（1.5 及 5.0 mg/kg）皮下注射 24 小時之急性毒性來觀察其對大白鼠肝臟之影響，結果如下：兩組之血清 aspartate aminotransferase 及 5.0 mg/kg 組之 cholinesterase 活性較對照組有差異性增減之外其他如 alanine aminotransferase 則無變化，而兩組大白鼠之肝中 alanine aminotransferase 及 1.5 mg/kg 組之 aspartate aminotransferase 則有明顯的減少。僅 1.5 mg/kg 之血清 triglyceride 增加外則無任何變化。肝檢體之 TBA-reactive substance, metallothionein 及鎘鋅之含量試驗組都有明顯的增加。除 1.5 mg/kg 組之 oxidized glutathione reductase 及 5.0 mg/kg 組之 glutathione peroxidase 外，其他實驗組之 oxidized glutathione reductase, glutathione peroxidase 及 glucose-6-phosphate dehydrogenase 等活性較對照組都有明顯的增加。

由以上結果，加以分析鎘之急性中毒對肝之傷害包括氨基酸代謝，如鎘之慢性中毒則對氨基酸代謝及脂質輸送能力反而有改善的作用。故鎘慢性中毒時對肝之毒性主要由 glutathione peroxidase-associated enzymes 及 metallothionein 等來調節控制。