***N*-Benzyl-D-glucamine Dithiocarbamate and *N*-*p*-Isopropylbenzyl-D-glucamine Dithiocarbamate Improve the Protective Effect of Diethyldithiocarbamate against Cadmium-Induced Testicular Toxicity in Rats**

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The protective effects of combined treatment with diethyldithiocarbamate (DED) plus *N*-benzyl-D-glucamine dithiocarbamate (BGD) or DED plus *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate (PBGD) against the testicular toxicity caused by acute exposure to cadmium (Cd) in rats were studied. Rats were injected subcutaneously with $^{109}\text{CdCl}_2$ (3 mg Cd and 74 kBq of $^{109}\text{Cd/kg}$) and 30 min later, they were injected intraperitoneally with the chelating agents (1 mmol/kg each). Cd injection increased lipid peroxidation and concentrations of hemoglobin, Ca and Fe in the testes, decreased the testicular weight and nonprotein SH (NP-SH), and caused sterility. The coadministration of DED with BGD or PBGD significantly prevented the increase in the lipid peroxidation, hemoglobin, Ca and Fe in the testes, the decrease in the testicular weight and NP-SH, and the sterility caused by Cd injection. DED plus BGD or DED plus PBGD significantly decreased the Cd concentration in the testes without the redistribution of Cd to the brain and kidney, which is observed following treatment with DED alone. The coadministration of DED plus BGD or DED plus PBGD significantly increased the blood Cd concentration and the Cd distribution in the red blood cells compared to Cd alone. These results indicate that the coadministration of BGD or PBGD with DED prevents the accumulation of Cd in the testes on the basis of greater blood distribution of Cd, which results from the uptake of Cd by the red blood cells, without the redistribution of Cd to the brain, resulting in an improvement of the protective effect of DED against the Cd-induced testicular toxicity.

Keywords cadmium; testicular toxicity; chelate effect; diethyldithiocarbamate; *N*-benzyl-D-glucamine dithiocarbamate; *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate

Introduction

Cadmium (Cd) has a long biological half-life in humans and has been recognized as one of the most toxic industrial and environmental elements. A single injection of Cd into animals results in a number of lesions in various organs, such as the liver, kidney, and testes.^{1–4)} However, Cd induces severe acute toxicity to rat testes at injection doses appreciably lower than those required for toxicity to other organs.^{5,6)} The testicular toxicity induced by Cd injection involves hemorrhage, necrosis, and atrophy.^{5,7–10)} Chelation therapy for Cd has been effective in preventing Cd-induced diseases. Walker *et al.*^{11,12)} studied the effects of five dithiocarbamates, dimercaptosuccinate, and diethylenetriaminepentaacetate (DTPA) on the testicular toxicity of Cd using morphological techniques, and indicated that diethyldithiocarbamate (DED) and DTPA were the most effective antidotes. It has been reported that DED rapidly promotes the excretion of Cd from the liver and kidney, but that it markedly increases the brain levels of Cd.^{13,14)} We reported that at 3 h after intraperitoneal injection of CdCl_2 (1 mg Cd/kg) to rats, *N*-benzyl-D-glucamine dithiocarbamate (BGD)^{15–17)} and *N*-*p*-isopropylbenzyl-D-glucamine dithiocarbamate (PBGD) were more effective than other dithiocarbamates in decreasing the Cd concentrations in liver and kidney without redistribution of Cd to the brain. Our recent study indicated that PBGD and DED (dose level of 3 mmol/kg) protected against the sterility caused by Cd in rats, that the effect of DED on increasing the brain level of Cd is more undesirable than the lack of effect of PBGD in preventing an increase in the testicular calcium (Ca) level, and that BGD provides

no satisfactory protection against Cd-induced testicular toxicity.¹⁸⁾

In order to develop better chelation therapy to prevent Cd-induced testicular toxicity without redistribution of Cd to tissues such as the brain and kidney, we studied the protective effects of combined treatment with DED plus BGD or DED plus PBGD against the testicular toxicity caused by acute exposure to Cd in rats.

Materials and Methods

Materials CdCl_2 and DED were obtained from Wako Pure Chemical Ind. (Osaka). ^{109}Cd (specific activity, 58.2 GBq/mg) was obtained from New England Nuclear Corp. (Boston, Mass.). BGD and PBGD were synthesized according to the procedures reported previously from our laboratory.^{15,19)} Other chemicals were of reagent grade.

Animals and Treatments Male Wistar rats, weighing 180–220 g, were purchased from Kyudo Co., Ltd. (Kumamoto) and housed in individual metabolic cages with diet (Nosan Lab Chow) and drinking water *ad libitum* in temperature- and humidity-controlled rooms and on a 12-h light/dark cycle.

The rats were injected subcutaneously with saline (0.5 ml/animal) or CdCl_2 (3 mg Cd/kg) in 0.5 ml saline. Thirty minutes later they were injected intraperitoneally with DED, BGD or PBGD alone (1.0 mmol/kg), DED (1.0 mmol/kg) plus BGD (1.0 mmol/kg), or DED (1.0 mmol/kg) plus PBGD (1.0 mmol/kg) in 0.5 ml saline. Seven days after Cd injection the rats were killed by cervical fracture and their testes were removed. Liver and kidney were perfused by injecting an ice-cold 0.01 M phosphate buffer (pH 7.4) containing 1.15% KCl with 0.025% ethylenediaminetetraacetic acid (EDTA) into the inferior vena cava, and the liver and kidney were removed. Testes, liver, and kidney were analyzed for lipid peroxidation and hemoglobin. In the experiment for the determination of Cd, Ca, and iron (Fe), the rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after the subcutaneous injection of $^{109}\text{CdCl}_2$ (3 mg Cd and 74 kBq of $^{109}\text{Cd/kg}$), and the testes, liver, kidney, heart, and brain were removed

7 d after Cd injection.

Lipid Peroxidation Testes, liver, and kidney were homogenized with 9 vol. of ice-cold 0.01 M phosphate buffer (pH 7.4) containing 1.15% KCl and 0.025% EDTA. Lipid peroxidation was assayed according to the thiobarbituric acid (TBA) method of Uchiyama and Mihara²⁰ using 1,1,3,3-tetraethoxypropane as the standard and expressed as nmol TBA reactive substances (TBARS).

Hemoglobin Testes were homogenized with 9 vol. of ice-cold 0.01 M phosphate buffer (pH 7.4) as described earlier and the homogenate was centrifuged at $2000 \times g$ for 10 min at 4°C. Hemoglobin concentration in the supernatant was determined according to the method of Sajiki *et al.*²¹ and expressed as mg/g wet tissue.

Protein Protein was determined according to the method of Lowry *et al.*²² using bovine serum albumin as the standard.

Nonprotein Sulfhydryl (NP-SH) Testes were homogenized with 9 vol. of ice-cold 0.01 M phosphate buffer (pH 7.4) containing 1.15% KCl and 0.025% EDTA. The mixture of 5 ml of the homogenate, 1 ml of 50% trichloroacetic acid, and 4 ml of water was shaken for 15 min and centrifuged at $3000 \times g$ for 15 min. The supernatant was analyzed for NP-SH. NP-SH was determined according to the method of Sedlak and Lindsay²³ and expressed as μmol L-cysteine per g wet tissue.

Metals Cd concentration in various organs was determined by measuring the amount of ^{109}Cd radioactivity with an Aloka auto well gamma scintillation counter (model ARC 300). Testes, liver, and kidney were wet-ashed by the $\text{HClO}_4\text{-HNO}_3$ method, and essential metals (Ca and Fe) were determined using a Hitachi-8000 atomic absorption instrument.

Distribution of Cadmium in Blood Rats were anesthetized with urethane (1 g/kg, intraperitoneally) and the bile duct was cannulated with polyethylene tubing as described previously.²⁴ Thereafter, the rats were injected subcutaneously with $^{109}\text{CdCl}_2$ (3 mg Cd and 74 kBq of ^{109}Cd /kg) and 30 min later they were intraperitoneally given saline or chelating agents (1.0 mmol/kg each). After 12 h, the chest was opened, and blood samples were removed from the heart with syringes containing 0.1 ml of heparin (1 mg/ml). The blood was centrifuged at $1600 \times g$ for 15 min to separate the red blood cells and plasma. The levels of ^{109}Cd radioactivity in the red blood cells and plasma were determined.

Fertility Test Fertility of male rats treated with Cd or Cd plus chelating agents was determined according to the method of Jackson *et al.*²⁵ The rat was mated with a virgin female rat for 8 d, starting 52 d after the administration of Cd with or without chelating agents. The fertility rate was expressed as the number of females impregnated *versus* the number of males tested.

Statistical Analysis Data were analyzed by a one-way analysis of variance. When the analysis indicated that a significant difference existed, the treated groups were compared to the controls by Duncan's new multiple range test.

Results

Lipid Peroxidation, NP-SH, and Hemoglobin Because the preventive effect of the dithiocarbamates on the increase in lipid peroxidation by Cd was observed only when they were injected within a short time (30 min) after Cd administration (data not shown), the chelating agents

were injected 30 min after Cd administration. Table I shows the lipid peroxidation in testes, liver, and kidney of rats after administration of Cd or Cd and the chelating agents. Cd administration significantly increased the lipid peroxidation in the testes, but did not increase the lipid peroxidation in the liver and kidney. The increase in the lipid peroxidation in the testes was completely prevented by combined treatment with DED plus BGD or DED plus PBGD as well as by DED alone, but was not prevented by treatment with BGD or PBGD alone. A significant decrease in the NP-SH level in the testes after Cd

TABLE I. Effects of Chelating Agents on Lipid Peroxidation in Testes, Liver, and Kidney of Rats after Cd Administration

Treatment	Dose of chelating agent (mmol/kg)	Lipid peroxidation ^{a)} (nmol TBARS/mg protein)		
		Testes	Liver	Kidney
Control	—	1.39 ± 0.21	0.52 ± 0.09	0.79 ± 0.14
Cd	—	3.63 ± 0.29 ^{b)}	0.70 ± 0.07	0.82 ± 0.16
Cd + BGD	1.0	3.72 ± 0.58 ^{b)}	0.41 ± 0.06	0.79 ± 0.12
Cd + PBGD	1.0	3.82 ± 0.47 ^{b)}	0.50 ± 0.01	0.64 ± 0.02
Cd + DED	1.0	1.02 ± 0.27 ^{c)}	0.45 ± 0.03	0.65 ± 0.06
Cd + DED + BGD	1.0 + 1.0	0.91 ± 0.09 ^{c)}	0.45 ± 0.01	0.68 ± 0.11
Cd + DED + PBGD	1.0 + 1.0	0.92 ± 0.16 ^{c)}	0.49 ± 0.07	0.69 ± 0.02

Rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of CdCl_2 (3 mg Cd/kg). The rats were killed 7 d after Cd injection and lipid peroxidation in the organs was determined. ^{a)} The values represent the mean ± S.D. for four animals. ^{b)} Significantly different from control ($p < 0.05$). ^{c)} Significantly different from Cd ($p < 0.05$).

TABLE II. Effects of Chelating Agents on Testicular Weight and NP-SH and Hemoglobin Concentrations in Testes of Rats after Cd Administration

Treatment	Testicular weight ^{a)} (% of body weight)	NP-SH ^{a)} (μmol cysteine/g wet tissue)	Hemoglobin ^{a)} concentration (mg/g wet tissue)
Control	1.05 ± 0.11	4.16 ± 0.49	3.50 ± 0.50
Cd	0.72 ± 0.06 ^{b)}	0.21 ± 0.01 ^{b)}	9.84 ± 2.39 ^{b)}
Cd + BGD	0.65 ± 0.05 ^{b)}	0.35 ± 0.10 ^{b)}	8.25 ± 1.10 ^{b)}
Cd + PBGD	0.67 ± 0.17 ^{b)}	0.44 ± 0.14 ^{b)}	5.74 ± 1.66 ^{c)}
Cd + DED	1.03 ± 0.26 ^{c)}	3.62 ± 0.61 ^{c)}	5.24 ± 1.35 ^{c)}
Cd + DED + BGD	1.10 ± 0.02 ^{c)}	3.86 ± 0.25 ^{c)}	5.17 ± 0.23 ^{c)}
Cd + DED + PBGD	1.13 ± 0.22 ^{c)}	3.99 ± 0.25 ^{c)}	4.18 ± 0.53 ^{c)}

Rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of CdCl_2 (3 mg Cd/kg). The rats were killed 7 d after Cd injection and testicular weight and NP-SH and hemoglobin concentrations in testes were determined. ^{a)} The values represent the mean ± S.D. for four animals. ^{b)} Significantly different from control ($p < 0.05$). ^{c)} Significantly different from Cd ($p < 0.05$).

TABLE III. Effects of Chelating Agents on Tissue Concentration of Ca and Fe

Treatment	Concentration of metal ($\mu\text{g/g}$ wet tissue) ^{a)}					
	Ca			Fe		
	Testes	Liver	Kidney	Testes	Liver	Kidney
Control	21.4 ± 1.8	5.58 ± 0.72	12.4 ± 0.8	11.6 ± 2.5	39.4 ± 10.4	19.7 ± 2.4
Cd	1421.7 ± 209.9 ^{b)}	6.15 ± 1.24	14.7 ± 7.2	33.1 ± 3.8 ^{b)}	44.1 ± 16.9	26.0 ± 4.7
Cd + BGD	2715.3 ± 179.3 ^{b)}	7.98 ± 1.51	15.8 ± 4.2	25.6 ± 3.1 ^{b)}	40.6 ± 8.7	24.6 ± 6.0
Cd + PBGD	1859.1 ± 20.1 ^{b)}	4.86 ± 1.26	9.7 ± 0.3	29.1 ± 4.1 ^{b)}	44.5 ± 10.6	23.4 ± 2.6
Cd + DED	27.3 ± 4.2 ^{c)}	9.56 ± 1.14	17.4 ± 4.6	13.1 ± 2.1 ^{c)}	34.6 ± 9.3	23.6 ± 14.4
Cd + DED + BGD	21.1 ± 5.3 ^{c)}	9.23 ± 2.73	14.4 ± 1.7	12.6 ± 0.6 ^{c)}	45.1 ± 12.0	34.8 ± 22.3
Cd + DED + PBGD	19.6 ± 2.0 ^{c)}	7.85 ± 1.76	12.7 ± 1.0	13.4 ± 2.3 ^{c)}	46.0 ± 10.2	21.0 ± 1.2

Rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of CdCl_2 (3 mg Cd/kg). The rats were killed 7 d after Cd injection and Ca and Fe concentrations were determined. ^{a)} The values represent the mean ± S.D. for four animals. ^{b)} Significantly different from control ($p < 0.05$). ^{c)} Significantly different from Cd ($p < 0.05$).

administration was observed (Table II). This reduction returned to the control values after treatment with DED, DED plus BGD, or DED plus PBGD. A significant increase in hemoglobin concentration in the testes after Cd injection was observed, and this increase was prevented by combined treatment with DED plus BGD or DED plus PBGD.

Testicular Weight The testicular weight expressed as a percentage of body weight provides an indication of the testicular damage. As shown in Table II, Cd caused a significant decline in the testicular weight, which decreased about 30% by 7 d. The decrease in testicular weight induced by Cd injection was completely prevented by combined treatment with DED plus BGD or DED plus PBGD as well as by DED alone, but was not prevented by treatment with BGD or PBGD alone.

Metals As shown in Table III, Cd caused a significant increase in the testicular Fe concentration, suggesting hemorrhage. The Ca concentration in the testes was remarkably increased by Cd injection. The increases in the Fe and Ca concentrations were completely prevented by DED alone, DED plus BGD, or DED plus PBGD.

Testicular Function Table IV shows the fertility of male rats injected with Cd with and without the chelating agents. Control male rats were all shown to be fertile. None of the male rats administered Cd were fertile. The sterility caused by Cd injection was completely protected by treatment with DED plus BGD or DED plus PBGD, but not by treatment with BGD or PBGD alone.

Table V shows the concentrations of Cd in tissues after the administration of Cd and the chelating agents. The concentrations of Cd in the testes, liver, and heart were significantly decreased by treatment with DED, DED plus

BGD, or DED plus PBGD. BGD and PBGD tended to further decrease the Cd concentrations in the testes, liver, and heart following treatment with DED after Cd injection. However, DED treatment caused the redistribution of Cd to the brain and kidney, but BGD and PBGD significantly prevented the redistribution of Cd to these organs.

Distribution of Cd in Blood The blood Cd concentration and the Cd distribution in the blood after the administration of Cd and the chelating agents are shown in Table VI. The blood Cd concentration after treatment with DED alone, DED plus BGD, or DED plus PBGD was significantly increased compared to that with Cd alone. However, BGD or PBGD alone had no effect on the Cd concentration. The treatment with BGD or PBGD alone after Cd injection significantly decreased the Cd distribution in the red blood cells and increased the Cd distribution in the plasma. By contrast, when DED was coadministered with BGD or PBGD, there was a significant increase in Cd distribution in the red blood cells, similarly to treatment with DED alone.

Discussion

Our previous study indicated that PBGD and DED at a dose level of 3 mmol/kg protected against the sterility caused by acute exposure to Cd in rats, but this resulted in the undesirable effect of DED to increase the brain level of Cd and the lack of effect of PBGD to prevent an increase in the testicular Ca level.¹⁸⁾ The present study was carried out to evaluate the effects of combined treatment with DED plus BGD or DED plus PBGD at a dose level of 1 mmol/kg each against testicular toxicity caused by Cd exposure. The Cd-induced sterility was not protected by treatment with BGD or PBGD alone, but was completely protected by coadministration of DED with BGD or with PBGD. The protective effectiveness of combined treatment with these two chelating agents on the Cd-induced testicular damage is also evident from the protection of the chelating agents on the atrophy which is indicated by a decrease in testicular weight. It has been shown that Cd can result in the enhancement of lipid peroxidation in the testes²⁶⁻²⁹⁾ and severe hemorrhagic necrosis of the testes.^{9,10)} Manca *et al.*³⁰⁾ also have demonstrated that lipid peroxidation is an early and sensitive consequence of Cd exposure as determined in various organs, such as the testes, lung, brain, liver, kidney, and heart. Our results indicated a significant increase in lipid peroxidation and hemoglobin concentration and a remarkable decrease in

TABLE IV. Effects of Chelating Agents on Fertility of Rats after Cd Administration

Treatment	Fertility rate
Control	7/7
Cd	0/7
Cd + BGD	0/7
Cd + PBGD	0/7
Cd + DED	6/7
Cd + DED + BGD	7/7
Cd + DED + PBGD	7/7

Male rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of CdCl₂ (3 mg Cd/kg). The rat was mated with a virgin female rat for 8 d, starting 52 d after Cd. The fertility rate was expressed as the number of females impregnated versus the number of males tested.

TABLE V. Effects of Chelating Agents on Tissue Concentration of Cd

Treatment	Concentration of Cd ($\mu\text{g/g}$ wet tissue) ^{a)}				
	Testes	Liver	Kidney	Heart	Brain
Cd	0.94 $\pm$ 0.14	24.7 $\pm$ 6.8	17.8 $\pm$ 3.9	2.35 $\pm$ 0.35	0.20 $\pm$ 0.09
Cd + BGD	0.93 $\pm$ 0.31	25.1 $\pm$ 7.0	22.2 $\pm$ 5.2	1.50 $\pm$ 0.41	0.16 $\pm$ 0.02
Cd + PBGD	0.69 $\pm$ 0.23	22.5 $\pm$ 5.9	18.7 $\pm$ 1.7	2.03 $\pm$ 0.35	0.25 $\pm$ 0.12
Cd + DED	0.48 $\pm$ 0.12 ^{b)}	11.9 $\pm$ 4.2 ^{b)}	30.0 $\pm$ 5.0 ^{b)}	1.28 $\pm$ 0.31 ^{b)}	0.33 $\pm$ 0.02 ^{b)}
Cd + DED + BGD	0.44 $\pm$ 0.05 ^{b)}	8.5 $\pm$ 0.6 ^{b)}	20.5 $\pm$ 3.0 ^{c)}	1.26 $\pm$ 0.17 ^{b)}	0.23 $\pm$ 0.03 ^{c)}
Cd + DED + PBGD	0.33 $\pm$ 0.04 ^{b)}	8.3 $\pm$ 0.5 ^{b)}	19.9 $\pm$ 1.0 ^{c)}	0.77 $\pm$ 0.06 ^{b,c)}	0.22 $\pm$ 0.02 ^{c)}

Rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of ¹⁰⁹CdCl₂ (3 mg Cd and 74 kBq of ¹⁰⁹Cd/kg). The rats were killed 7 d after Cd injection and Cd concentration was determined from radioactivity. a) The values represent the mean $\pm$ S.D. for four animals. b) Significantly different from Cd ($p < 0.05$). c) Significantly different from Cd + DED ($p < 0.05$).

TABLE VI. Effects of Chelating Agents on Distribution of Cd in Blood of Rats after Cd Administration

Treatment	Blood concn. of Cd ($\mu\text{g Cd/ml}$) ^{a)}	Distribution of Cd in blood (%) ^{a)}	
		Red blood cell	Plasma
Cd	0.10 $\pm$ 0.02	60.6 $\pm$ 7.7	39.4 $\pm$ 7.7
Cd + BGD	0.15 $\pm$ 0.08	12.1 $\pm$ 3.2 ^{b)}	87.8 $\pm$ 3.4 ^{b)}
Cd + PBGD	0.17 $\pm$ 0.09	20.0 $\pm$ 4.3 ^{b)}	80.0 $\pm$ 4.3 ^{b)}
Cd + DED	0.69 $\pm$ 0.15 ^{b)}	98.0 $\pm$ 0.4 ^{b)}	2.1 $\pm$ 0.4 ^{b)}
Cd + DED + BGD	0.87 $\pm$ 0.58 ^{b)}	90.3 $\pm$ 11.0 ^{b)}	6.0 $\pm$ 0.2 ^{b,c)}
Cd + DED + PBGD	0.67 $\pm$ 0.08 ^{b)}	83.1 $\pm$ 3.0 ^{b,c)}	17.0 $\pm$ 3.0 ^{b,c)}

Rats were injected intraperitoneally with chelating agents (1.0 mmol/kg each) 30 min after subcutaneous injection of $^{109}\text{CdCl}_2$ (3 mg Cd and 74 kBq of ^{109}Cd /kg). The rats were killed 12 h after Cd injection and the concentration was determined from radioactivity. a) The values represent the mean $\pm$ S.D. for four animals. b) Significantly different from Cd ($p < 0.05$). c) Significantly different from Cd + DED ($p < 0.05$).

NP-SH concentration, which is considered to be due to an increase in the lipid peroxidation, in the testes after Cd administration. The present results suggest a relationship between lipid peroxidation and hemorrhage in the testes, as reported by Sajiki *et al.*²⁷⁾ Our results also support one hypothesis of Wong and Klaassen³¹⁾ that Cd-induced testicular toxicity is due to vascular changes in the testes leading to hemorrhage, necrosis, and atrophy.^{9,31-35)} The coadministration of DED plus BGD or DED plus PBGD significantly prevented the increase in lipid peroxidation and hemoglobin concentration and the decrease in the NP-SH concentration, which were all observed in Cd-induced testicular damage.

A significant increase in the Fe concentration in the testes after Cd injection is considered to be due to hemorrhagic inflammation. A remarkable increase in the testicular Ca concentration induced by Cd injection is similar to what has been reported in earlier papers.^{36,37)} This rise in the Ca concentration is considered to result from the cellular damage due to the Cd-induced lipid peroxidation in the testes. However, the detailed mechanisms by which Cd increases the testicular Ca concentration remain unknown. The combined treatment with DED plus BGD or DED plus PBGD completely prevented the increase in the Fe and Ca concentrations in the testes after Cd injection, indicating protection against the Cd-induced testicular damage.

DED significantly decreased the Cd concentration in the testes but reversely increased the Cd concentration in the brain and kidney. However, the coadministration of DED plus BGD or DED plus PBGD lead to protection against Cd-induced testicular damage without the redistribution of Cd to the brain. In contrast to treatment with BGD or PBGD alone, the combined treatment with DED plus BGD or DED plus PBGD showed a markedly greater distribution of Cd in the red blood cells than in the plasma. Such a phenomenon is considered to result from greater uptake of the complex of Cd with DED, which is sufficiently lipid-soluble,¹⁹⁾ by the red blood cells. It is also suggested that BGD or PBGD containing a polar glucamine group may not transport Cd across the blood-brain barrier.

The present study indicates that the coadministration of BGD or PBGD with DED prevents the accumulation of Cd in the testes on the basis of greater blood distribution

of Cd, which results from the uptake of Cd by the red blood cells, without the redistribution of Cd to the brain, resulting in an improvement of the protection of DED against Cd-induced testicular toxicity.

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