CARNOSINE PROTECTION AGAINST CADMIUM-INDUCED NEPHROTOXICITY IN MALE ALBINO RATS: A BIOCHEMICAL AND HISTOLOGICAL STUDY

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This study pertains to the role of carnosine against the toxic manifestations of chronic cadmium exposure. The kidney is a recognized target organ for chronic cadmium exposure, owing to the very long half-life of cadmium. Cadmium (as Cadmium chloride®) in a dose of 3 mg/kg body weight was administered subcutaneously for a total period of 14 weeks in male albino rats. This resulted in a significant decrease in the rats' terminal body weights, but the renal function tests including serum levels of urea, creatinine and uric acid showed a marked significant increase. This was further reflected on the morphological appearance of the kidneys which was found to be markedly affected following cadmium exposure. Carnosine (as Carnosine®) when supplemented orally in a dose of 0.15 mg/kg body weight, concurrently with cadmium administration, showed improvement in both body weight gain and renal biochemical function as well as morphological architecture, but it was still below the initial control values. In contrast to this, body weights as well as renal function and morphology were more corrected and became near the control values on increasing the dose of carnosine to 0.3 mg/kg. Furthermore, the level of cadmium in either the blood or kidney tissue of animals which received cadmium simultaneously with carnosine was also significantly lower than in those animals which received cadmium alone. Moreover, the present study showed that the nephrotoxic effects of cadmium could be correlated with a decreased body weight and an increased kidney weight together with increased blood cadmium concentrations as well as renal function tests. Therefore, it is concluded that protection from cadmium-induced nephrotoxicity is possible by continued co-administration of carnosine.

cadmium; nephrotoxicity; carnosine; albino rats

INTRODUCTION

Cadmium is a prevalent environmental pollutant in industrial countries (Hinkle, Osborne, 1994), which is known only for its toxic effects (Endo, Shaikh, 1993). Persistence in the environment makes it a problem for hazardous waste cleanup (Wester et al., 1992). Furthermore, because body excretion of cadmium is so slow, half-lives of cadmium in the body are correspondingly long (17 to 38 years). Therefore, cadmium accumulation over time becomes critical (Agency for Toxic Substances and Disease Registry, 1989).

Evidence of kidney damage after cadmium exposure was observed as early as in 1948 by Friberg (Friberg, 1950), and was confirmed by other investigators in the following years (Kazantzis et al., 1963; Scott et al., 1976, 1978; Greenberg et al., 1986; Cardenas et al., 1991). Acute exposure to inorganic cadmium produces hepatotoxicity (Shaikh et al., 1995), but with chronic administration, the target organ of toxicity changes from liver to kidney (Hochi et al., 1995; Nakashima et al., 1997).

The exact mechanism/s by which chronic exposure to cadmium produces nephrotoxicity is not known (Dorian et al., 1992a, b). However, there are presently two mechanisms explaining the pathogenesis of cadmium nephropathy. One mechanism of cadmium nephrotoxicity is attributed to the presence of non-metallothionein-bound fractions of cadmium in the kidney as cadmium increases in the kidney from reabsorption after glomerular filtration (Nomiyama, Nomiyama, 1986). The second mechanism may involve the extracellular cadmium metallothionein complex (Cd-MT) itself which is shown to be toxic (Liu et al., 1994). Two hypotheses are currently held to explain the nephrotoxic effects of Cd-MT. One hypothesis attributes the nephrotoxicity to the Cd-MT complex (Cherian et al., 1976). The complex might damage the membranes of the proximal tubular cells as it is being reabsorbed (Dorian et al., 1992a, b). Another hypothesis attributes the nephrotoxicity of Cd-MT to the metal released intracellularly during lysosomal degradation of the reabsorbed complex (Nordberg et al., 1994). If more cadmium is released in the kidney than can bind to renal metallothionein, this excess cadmium may produce nephrotoxicity (Nomiyama, Nomiyama, 1986). In the cell, this excess cadmium may interact with cell membranes, resulting in lipid peroxidation (Stacey et al., 1980), and/or may displace essential metals from metallothionein, depriving metalloenzymes of essential cofactors (Petering et al., 1984). Furthermore, the toxic effects of cadmium may result from its ability to bind tightly to sulfhydryl groups, its ability to replace calcium in calmodulin and other calcium-binding proteins, and its ability to substitute for zinc in zinc-containing

enzymes and transcription factors (Sutoo et al., 1990). Moreover, Bagchi et al. (1997), have stated that chronic administration of cadmium chloride induced an oxidative stress that resulted in tissue damaging effects which might contribute to the toxicity of cadmium. More recently, Markovich and James (1999), have reported the first characterization of heavy metal-induced inhibition of both the hepatic and renal sulfate/bicarbonate transporter sat-1, through various mechanisms, which might lead to sulfaturia following heavy metal intoxication including cadmium.

On the other hand, carnosine (beta-alanyl-L-histidine) is a naturally occurring dipeptide which is normally present in long-lived tissues at concentrations up to 20 mM in humans (Hipkiss, Chano, 1998). It seems more likely that in the human, carnosine is continuously secreted or released from skeletal muscle into the blood stream, where it is hydrolyzed to B-alanine and histidine by the action of serum carnosinase (Jackson et al., 1991). In most mammals, which have no serum carnosinase, the carnosine released from muscle is hydrolyzed by tissue carnosinase, which is abundant in kidney (Lenney, 1990). In either case, the resulting free histidine in the blood stream mixes with histidine from other sources, such as dietary protein digestion or intracellular protein turnover. The histidine is taken up by various tissues, where it is used in protein synthesis or decarboxylated to form histamine. In addition, some is taken up by skeletal muscle, where it is recycled into carnosine by the action of carnosine synthetase (Jackson, Lenney, 1996).

Carnosine has been recognized for a long time as a potent intracellular pH-buffer (Okuma, Abe, 1992). Recently, the anti-oxidant effect of carnosine in preventing membrane lipid peroxidation and stabilizing cell membranes and membrane-bound enzymes have been described (Candlish, Das, 1996; Preston et al., 1998). Subsequent studies have demonstrated that the anti-oxidant properties of carnosine might be associated with their ability to quench singlet oxygen (Dahl et al., 1998), to scavenge hydroxyl radicals (Kohen et al., 1998) and peroxyl radicals (Aruoma et al., 1999) and to interact with hypochlorous anions (Formazyuk et al., 1992).

Carnosine has protective functions additional to anti-oxidant and free-radical scavenging roles (Hipkiss, 1998). It extends cultured human fibroblast life-span (McFarland, Holliday, 1994), kills transformed cells (Holliday, McFarland, 1996), protects cells against aldehydes and an amyloid peptide fragment (Hipkiss et al., 1998), and inhibits *in vitro* protein glycation (formation of cross links, carbonyl groups and advanced glycation end-products "AGEs") and DNA/protein cross linking (Hipkiss et al., 1995, 1997). Other roles ascribed to this dipeptide include actions as neurotransmitter, modulation of enzymic activities and chelation of heavy metals (Quinn et al., 1992; Trombley et al., 1998).

There are little studies – only one paper – dealing with the effects of carnosine on copper toxicity, but – to the knowledge of the authors –, there appears to be no data on the quantitative description of the protective effects of carnosine against the toxicity of cadmium. Therefore, the purpose of the present study was to investigate the toxicity of cadmium administered subcutaneously to male albino rats at prolonged time-intervals to produce nephrotoxicity. Furthermore, the possible protective effect of carnosine on cadmium-induced nephrotoxicity was also studied.

MATERIAL AND METHODS

Experimental animals

Random-bred, male albino rats weighing approximately 107–145 g were obtained form Animal House Laboratory, National Research Centre, Giza, Egypt. Animals were evaluated prior to initiation of the study to ensure a healthy condition and acclimation to the study environment. Clinically acceptable animals were randomly assigned into 6 groups (10 animals/group), so that there were no statistically significant differences among group body weight means.

Environmental conditions

A total of 60 rats were housed in stainless steel wire mesh cages on a bedding of wood chips (maximum of five animals per cage). They were kept in an ambient temperature of 25 ± 3 °C, on a light/dark cycle of 12/12 hours, and supplied rat chow (The Egyptian Company for Oils and Soaps, El-Badrashin Industry, Giza, Egypt) in stainless steel food containers, fresh water was supplied *ad libitum*.

Test articles and treatments

Cadmium chloride® was purchased from Sigma Chemicals Company, U.S.A. Solutions of $CdCl_2$ in 0.9% saline – as a vehicle – were prepared on the day of administration. The chemical was administered subcutaneously at 3 mg/kg (Chan et al., 1993), using a constant dosage volume of 1 ml/kg (Group IV). The negative control animals (Group I) received an equivalent volume of 0.9% saline by subcutaneous injection. This route of exposure provides a suitable supply of Cd-MT to the systemic circulation, thus allowing renal accumulation of cadmium and the development of renal tubular dysfunction in a controlled way (Nordberg et al., 1975). The animals were dosed once daily for five consecutive days per week for a total of 14 weeks.

Carnosiner was purchased form Sigma Chemicals Company, U.S.A. It was also dissolved in 0.9% saline solution, and was given once daily through the oral route using a gastric tube. The positive control groups of animals (Groups II and III) received an equivalent volume of 0.15 and 0.3 mg/kg body weight respectively. This dosing regimen is equivalent to half the normal and the normal concentrations of carnosine present in human beings respectively (Decker, 1995). Groups V and VI received the same doses of carnosine respectively, simultaneously with the same previously-mentioned dose of cadmium chloride.

Necropsies

The total duration of the study was 98 days. On the day 99, the whole rats were euthanatized for clinical chemistry and histology studies.

Clinical pathology

Blood was obtained by cardiac puncture from all rats for subsequent clinical chemistry determinations.

Clinical chemistries

1) Determination of cadmium in both blood and kidneys

Blood samples were digested with an equal volume of concentration nitric acid (65%). Renal cortex tissue (50–100 mg) was dried at 150 °C for 16 hours and ashed at 450 °C for 24 hours. Ashed samples were dissolved in 1 M nitric acid. Cadmium concentrations in blood (Lauwerys et al., 1979), and in renal cortex (Roels et al., 1983) were measured by atomic absorption in the flame mode (Perkin-Elmer Model 5000 Zeeman atomic absorption spectrophotometer equipped with a Model 500 graphite furnace "GFAAS" or an inductively coupled plasma atomic emission spectrometer "ICP-AES" "Thermo Jarrell-Ash Model 61-975" for low or high concentrations of cadmium, respectively). The concentrations were expressed as µg/dl and µg/g for blood and kidneys, respectively.

2) Estimation of renal function tests

Clotted blood samples were centrifuged and the serum was removed by aspiration for subsequent determination of urea (mg/dl) (Sampson et al.,

1980), creatinine (mg/dl) (Heinegard, Tiderstrom, 1973), and uric acid (mg/dl) (Trivedi et al., 1978).

Histology and kidney weights

Complete necropsies were performed on all rats. The kidneys were weighed separately. Organ-to-body weight ratios were calculated. Samples of the kidney were fixed in 10% neutral buffered formaldehyde for 48 hours and then processed for standard light microscopy. Sections (5 μm) of paraffin-embedded tissue were mounted on glass slides, stained with haematoxylin and eosin as well as Mallory Trichrome stains, and then examined with a light microscope (Pearse, 1985).

Statistical analysis

The data were analyzed using IBM computer and SPSS-PC 4.1 Statistical package. Both statistical analysis and tabulation were done according to Knap and Miller (1992). We have used both the paired *t*-test and the analysis of variance ANOVA to detect differences in the means between the control groups and the other groups of animals. The Newman-Keuls was applied in post-hoc analysis when needed. The correlation coefficient *r* between the different quantitative variables was calculated. The level of significance was set at $p < 0.05$.

RESULTS

Body weight and kidney weights

There was a significant decrease in the body weights of cadmium-treated rats when compared with the control groups (Tables I–III and Fig. 13). Meanwhile, kidney weights showed a significant increase in cadmium-treated rats more than those of the control groups, or those which were pretreated with carnosine (Tables II and III). On the other hand, the addition of carnosine significantly increased the body weights (Tables I–III and Fig. 13), but significantly decreased the kidney weights (Tables II and III) of cadmium-treated rats.

Clinical chemistry

Both blood cadmium and kidney cadmium concentrations showed a significant increase in cadmium-treated animals (Tables IV, V and Fig. 14). On

I. Comparison between the initial and terminal body weights in all studied groups

Groups	Initial body weight (g)		Terminal body weight (g)		Mean difference	S.D. difference	Paired *t*	*p*
Group I	129.60	7.95	292.30	15.36	165.40	7.62	68.652	< 0.001*
Group II	127.70	9.52	294.50	19.50	166.80	10.71	49.268	< 0.001*
Group III	127.90	14.12	295.80	22.83	167.90	9.21	57.668	< 0.001*
Group IV	126.60	8.46	227.40	14.79	100.80	6.43	46.607	< 0.001*
Group V	127.00	11.62	250.10	17.03	123.10	5.61	69.433	< 0.001*
Group VI	127.60	9.22	291.20	17.23	163.60	9.49	54.520	< 0.001*

* = significant

II. Mean values ± S.D. of body as well as kidney weights in all studied groups

Groups	Initial weight (g)		Terminal weight (g)	
	mean	S.D.	mean	S.D.
Group I	126.90	7.95	292.30	15.36
Group II	127.70	9.52	294.50	19.50
Group III	127.90	14.12	295.80	22.83
Group IV	126.60	8.46	227.40	14.79
Group V	127.00	11.62	250.10	17.03
Group VI	127.60	9.22	291.20	17.23
F	0.0251		26.3134	
p	0.9997		< 0.001*	
Group	right kidney weight (g)		left kidney weight (g)	
	mean	S.D.	mean	S.D.
Group I	0.88	0.03	0.87	0.03
Group II	0.88	0.04	0.87	0.03
Group III	0.88	0.04	0.87	0.02
Group IV	1.29	0.28	1.27	0.25
Group V	1.09	0.16	1.08	0.14
Group VI	0.89	0.05	0.88	0.02
F	16.0406		19.7363	
p	< 0.001*		< 0.001*	

* = significant

III. Mean values ± S.D. of terminal body as well as kidney weights in all studied groups (Newman-Keuls post-hoc test)

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI
Terminal body weight (g)						
Mean	292.300	294.500	295.800	227.400	250.100	291.200
Group I		0.7857	0.9012	0.0002*	0.0001*	0.8919
Group II	0.7857		0.8724	0.0001*	0.0002*	0.9117
Group III	0.9012	0.8724		0.0001*	0.0001*	0.9402
Group IV	0.0002*	0.0001*	0.0001*		0.0068*	0.0001*
Group V	0.0001*	0.0002*	0.0001*	0.0068*		0.0001*
Group VI	0.8919	0.9117	0.9402	0.0001*	0.0001*	
Right kidney weight (g)						
Mean	0.876	0.878	0.877	1.288	1.091	0.890
Group I		0.9995	0.9870	0.0001*	0.0070*	0.9957
Group II	0.9995		0.9870	0.0002*	0.0026*	0.8438
Group III	0.9870	0.9870		0.0001*	0.0047*	0.9750
Group IV	0.0001*	0.0002*	0.0001*		0.0021*	0.0001*
Group V	0.0070*	0.0026*	0.0047*	0.0021*		0.0017*
Group VI	0.9957	0.8438	0.9750	0.0001*	0.0017*	
Left kidney weight (g)						
Mean	0.876	0.878	0.877	1.288	1.091	0.890
Group I		0.9705	0.9999	0.0001*	0.0015*	0.9932
Group II	0.9705		0.9993	0.0001*	0.0020*	0.9989
Group III	0.9999	0.9993		0.0002*	0.0008*	0.9115
Group IV	0.0001*	0.0001*	0.0002*		0.0010*	0.0001*
Group V	0.0015*	0.0020*	0.0008*	0.0010*		0.0005*
Group VI	0.9932	0.9989	0.9115	0.0001*	0.0005*	

* = significant

the other hand, the addition of carnosine significantly decreased both the blood cadmium and kidney cadmium concentrations (Tables IV, V and Fig. 14).

Furthermore, there was also a significant increase in the serum levels of urea, creatinine and uric acid of cadmium-treated animals (Tables VI and VII). On the other hand, carnosine significantly reversed these levels nearly to the initial values of the control groups (Tables VI and VII).

IV. Mean values ± S.D. of blood as well as renal cadmium levels in all studied groups

Groups	Blood cadmium (µg/ml)		Renal cadmium (µg/g)	
	mean	S.D.	mean	S.D.
Group I	31.75	18.06	24.20	13.24
Group II	26.87	15.41	17.88	9.72
Group III	18.20	10.07	9.24	4.67
Group IV	305.60	94.63	231.80	101.13
Group V	196.10	78.23	135.70	65.46
Group VI	27.69	12.07	16.15	6.87
F	55.470		33.827	
p	< 0.001*		< 0.001*	

* = significant

V. Mean values ± S.D. of blood as well as renal cadmium levels in all studied groups (Newman-Keuls post-hoc test)

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI
Blood cadmium (µg/dl)						
Mean	31.750	26.870	18.200	305.600	196.100	27.690
Group I		0.9756	0.9351	0.0001*	0.0001*	0.8607
Group II	0.9756		0.7079	0.0001*	0.0002*	0.9718
Group III	0.9351	0.7079		0.0001*	0.0001*	0.9107
Group IV	0.0001*	0.0001*	0.0001*		0.0001*	0.0002*
Group V	0.0001*	0.0002*	0.0001*	0.0001*		0.0001*
Group VI	0.8607	0.9718	0.9107	0.0002*	0.0001*	
Renal cadmium (µg/g)						
Mean	24.200	17.880	9.240	231.800	135.700	16.150
Group I		0.7776	0.9072	0.0001*	0.0001*	0.9306
Group II	0.7776		0.9204	0.0002*	0.0001*	0.9384
Group III	0.9072	0.9204		0.0001*	0.0001*	0.7575
Group IV	0.0001*	0.0002*	0.0001*		0.0002*	0.0001*
Group V	0.0001*	0.0001*	0.0001*	0.0002*		0.0002*
Group VI	0.9306	0.9384	0.7575	0.0001*	0.0002*	

* = significant

VI. Mean values ± S.D. of kidney function tests in all studied groups

Groups	Serum urea (mg/dl)		Serum creatinine (mg/dl)		Serum uric acid (mg/dl)	
	mean	S.D.	mean	S.D.	mean	S.D.
Group I	33.29	4.16	0.49	0.12	1.47	0.67
Group II	34.12	3.35	0.50	0.12	1.50	0.82
Group III	34.17	4.71	0.50	0.11	1.49	0.47
Group IV	64.55	5.10	1.13	0.25	3.05	1.49
Group V	51.35	5.07	0.91	0.26	2.39	1.33
Group VI	35.46	5.14	0.51	0.13	1.55	0.86
F	78.059		24.427		4.342	
p	< 0.001*		< 0.001*		0.022*	

* = significant

There was an inverse correlation between blood cadmium concentrations and body weights of animals (Table VIII), while this correlation was found to be positive "direct" between blood cadmium concentrations and kidney weights (Table VIII), kidney cadmium concentrations (Table VIII and Fig. 15), serum urea (Table VIII and Fig. 16), serum creatinine (Table VIII and Fig. 17), and serum uric acid (Table VIII and Fig. 18).

Histology

Sections of the kidney of either the negative control animals, i.e. Group I (Figs. 1–2) or the positive control animals, i.e. Groups II and III (Figs. 3–4) showed its normal histological structure.

However, cadmium-treated rats, i.e. Group IV, showed congestion of both the cortical and medullary blood vessels (Fig. 5). Furthermore, interstatial haemorrhages in both the cortex and medulla were also seen (Figs. 5–6). Moreover, marked tubular degeneration affecting mainly the proximal convoluted tubules was also demonstrated (Figs. 6–8). In addition, interstatial fibrosis and atrophic glomeruli were also observed (Figs. 7–8).

On the other hand, on addition of carnosine in the smaller dose, i.e. Group V, few degenerated tubules together with interstatial fibrosis were still demonstrated (Fig. 9). Furthermore, few atrophic glomeruli were also observed (Fig. 10). On increasing the dose of carnosine, i.e. Group VI, marked improvement in the kidney morphology occurred. Some sections showed congestion of cortical blood vessels (Fig. 11), while other sections revealed nearly that normal histological appearance of the kidney (Fig. 12).

VII. Mean values ± S.D. of kidney function tests in all studied groups (Newman-Keuls post-hoc test)

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI
Serum urea (mg/dl)						
Mean	33.290	34.120	34.170	64.550	51.350	35.460
Group I		0.6904	0.9056	0.0001*	0.0001*	0.7226
Group II	0.6904		0.9809	0.0001*	0.0002*	0.7951
Group III	0.9056	0.9809		0.0002*	0.0001*	0.5363
Group IV	0.0001*	0.0001*	0.0002*		0.0001*	0.0001*
Group V	0.0001*	0.0002*	0.0001*	0.0001*		0.0001*
Group VI	0.7226	0.7951	0.5363	0.0001*	0.0001*	
Serum creatinine (mg/dl)						
Mean	0.491	0.503	0.504	1.125	0.908	0.513
Group I		0.8791	0.9851	0.0001*	0.0002*	0.9923
Group II	0.8791		0.9900	0.0001*	0.0002*	0.9912
Group III	0.9851	0.9900		0.0002*	0.0001*	0.9092
Group IV	0.0001*	0.0001*	0.0002*		0.0079*	0.0001*
Group V	0.0002*	0.0002*	0.0001*	0.0079*		0.0001*
Group VI	0.9923	0.9912	0.9092	0.0001*	0.0001*	
Serum uric acid (mg/dl)						
Mean	1.470	1.500	1.490	3.050	2.390	1.550
Group I		0.9976	0.9648	0.0113*	0.2594	0.9980
Group II	0.9976		0.9824	0.0061*	0.1276	0.9120
Group III	0.9648	0.9824		0.0090*	0.2008	0.9903
Group IV	0.0113*	0.0061*	0.0090*		0.1483*	0.0045*
Group V	0.2594	0.1276	0.2008	0.1483		0.0675
Group VI	0.9980	0.9120	0.9903	0.0045*	0.0675	

* = significant

DISCUSSION

Environmental pollution with the nephrotoxic metal cadmium is considered a potential health risk for the general population (Friis et al., 1998). Cadmium-induced nephrotoxicity usually occurs only after long-term chronic exposure to low levels of cadmium salts in experimental animal models

VIII. Correlation study between the different parameters in all investigated animals ($n = 60$)

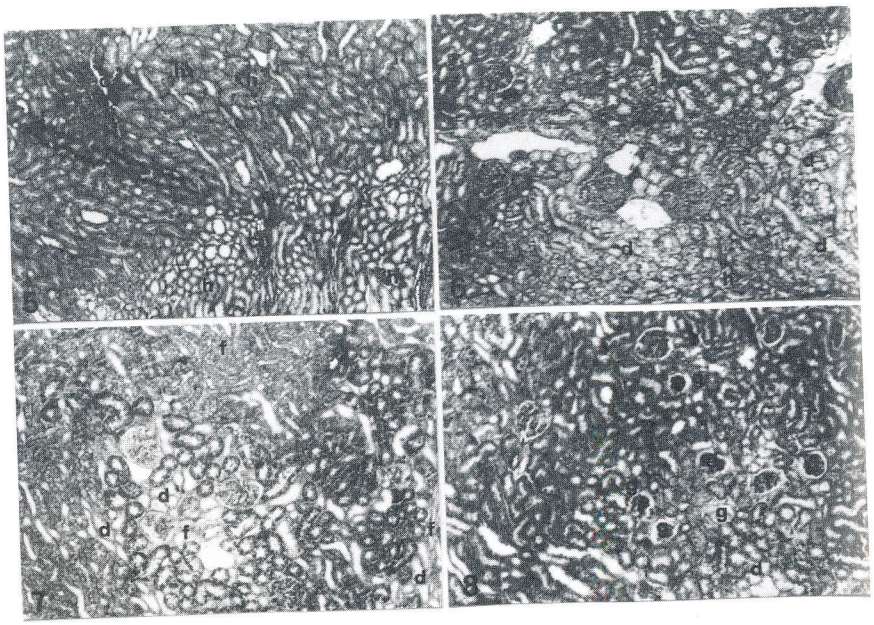
Variable	Initial weight	Terminal weight	Right kidney weight	Left kidney weight	Blood cadmium	Renal cadmium	Serum urea	Serum creatinine	Serum uric acid
Initial weight (g)		0.5532 * $p < 0.001$	0.4014 * $p = 0.001$	0.3491 * $p = 0.006$	0.0514 $p = 0.696$	–0.0911 $p = 0.489$	–0.0343 $p = 0.794$	–0.1348 $p = 0.305$	0.0267 $p = 0.839$
Terminal weight (g)	0.5532 * $p < 0.001$		–0.4182 * $p = 0.001$	–0.4727 * $p < 0.001$	–0.7279 * $p < 0.001$	–0.7596 * $p < 0.001$	–0.784 * $p < 0.001$	–0.7613 * $p < 0.001$	–0.4202 * $p = 0.001$
Right kidney weight (g)	0.4014 * $p = 0.001$	–0.4182 * $p = 0.001$		0.9943 * $p < 0.001$	0.7854 * $p < 0.001$	0.6108 * $p < 0.001$	0.7179 * $p < 0.001$	0.5498 * $p < 0.001$	0.5245 * $p < 0.001$
Left kidney weight (g)	0.3491 * $p = 0.006$	–0.4727 * $p < 0.001$	0.9943 * $p < 0.001$		0.8012 * $p < 0.001$	0.6361 * $p < 0.001$	0.7497 * $p < 0.001$	0.5786 * $p < 0.001$	0.5445 * $p < 0.001$
Blood cadmium (µg/ml)	0.0514 $p = 0.696$	–0.7279 * $p < 0.001$	0.7854 * $p < 0.001$	0.8012 * $p < 0.001$		0.7275 * $p < 0.001$	0.8206 * $p < 0.001$	0.7394 * $p < 0.001$	0.4851 * $p < 0.001$
Renal cadmium (µg/g)	–0.0911 $p = 0.489$	–0.7596 * $p < 0.001$	0.6108 * $p < 0.001$	0.6361 * $p < 0.001$	0.7275 * $p < 0.001$		0.8397 * $p < 0.001$	0.7346 * $p < 0.001$	0.4837 * $p < 0.001$
Serum urea (mg/dl)	–0.0343 $p = 0.794$	–0.784 * $p < 0.001$	0.7179 * $p < 0.001$	0.7497 * $p < 0.001$	0.8206 * $p < 0.001$	0.8397 * $p < 0.001$		0.7539 * $p < 0.001$	0.4664 * $p < 0.001$
Serum creatinine (mg/dl)	–0.1348 $p = 0.305$	–0.7613 * $p < 0.001$	0.5498 * $p < 0.001$	0.5786 * $p < 0.001$	0.7394 * $p < 0.001$	0.7346 * $p < 0.001$	0.7539 * $p < 0.001$		0.3839 * $p < 0.002$
Serum uric acid (mg/dl)	0.0267 $p = 0.839$	–0.4202 * $p = 0.001$	0.5246 * $p < 0.001$	0.5445 * $p < 0.001$	0.4851 * $p < 0.001$	0.4837 * $p < 0.001$	0.4664 * $p < 0.001$	0.3839 * $p = 0.002$	

* = significant

1–4. Photomicrographs of sections in the kidneys of the control groups, i.e. Groups I, II and III showing:

1. Normal histological structure of the kidney of a rat in the negative control group "Group-I" (Hx. & E. x 100)
2. Normal histological structure of the kidney of a rat in the negative control group "Group-I " (Mallory Trichrome x 100)
3. Normal histological structure of the kidney of a rat in the positive control group "Group-II" (Hx. & E. x 100)
4. Normal histological structure of the kidney of a rat in the positive control group "Group-III" (Mallory Trichrome x 100)

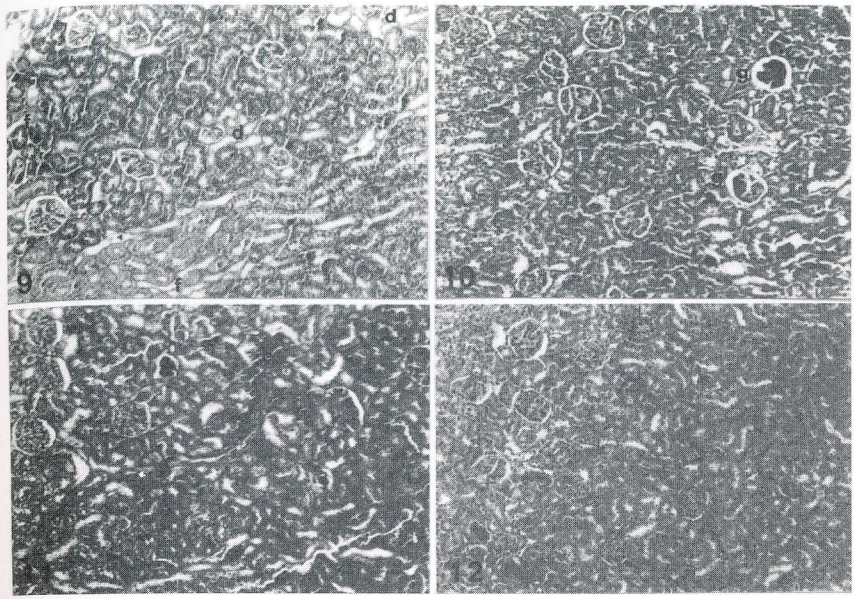
except in hamsters where nephropathy can occur acutely (Rehm, Waalkes, 1990). After repeated injections of cadmium chloride, the movement of cadmium from liver to kidney is observed only after weeks (Dudley et al., 1985). Since the kidney is the main target organ for cadmium, the generation of the products of lipid peroxidation due to accumulation of this toxic metal in the kidney may have importance in the mechanism of its nephrotoxicity (Oner et al., 1996). Furthermore, Herak-Kramberger et al. (1998), have concluded that cadmium may impair acidification in cell organelles by (a) causing a loss of vacuolar ATPase protein in their limiting membranes, (b) inhibiting the intrinsic vacuolar ATPase activ-



5–8. Photomicrographs of sections in the kidneys of cadmium-treated rats, i.e. Group IV showing:
5. Congestion of both cortical and medullary blood vessels (c), together with interstitial haemorrhage (h) in both cortex and medulla (Mallory Trichrome x 100)
6. Marked degeneration (d) affecting mainly the proximal convoluted tubules, together with interstitial haemorrhages (h) (Mallory Trichrome x 100)
7. Marked interstitial fibrosis (f) with degenerated tubules (d) (Mallory Trichrome x 100)
8. Markedly atrophic glomeruli (g) together with proximal tubular degeneration (d) (Mallory Trichrome x 100)

ity, and (c) dissipating the trans-membrane pH gradient. This may inhibit endocytosis of filtered proteins and impair vesicle-mediated recycling of some membrane transporters, thus contributing to the loss of reabsorptive capacity of the proximal tubules.

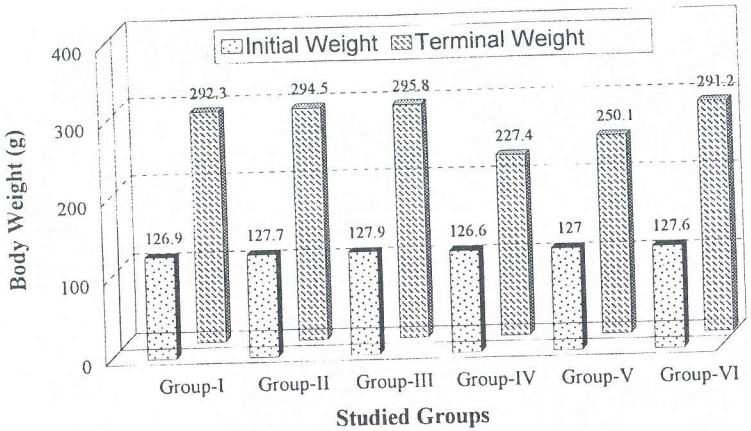
In the present study, cadmium-treated animals showed more significant weight loss or weight gain suppression than the control animals. Similar results were obtained by Karmaker et al. (1999). However, kidney weights of cadmium-treated rats showed a significant increase than those of the control animals. Similar results were reported by Cardenas et al. (1992). Furthermore, significant elevations in relative liver weight and particularly in kidney weight (93 % of control) were documented by Karmaker et al. (1999) in mice that received 2.0 mg/kg body weight of



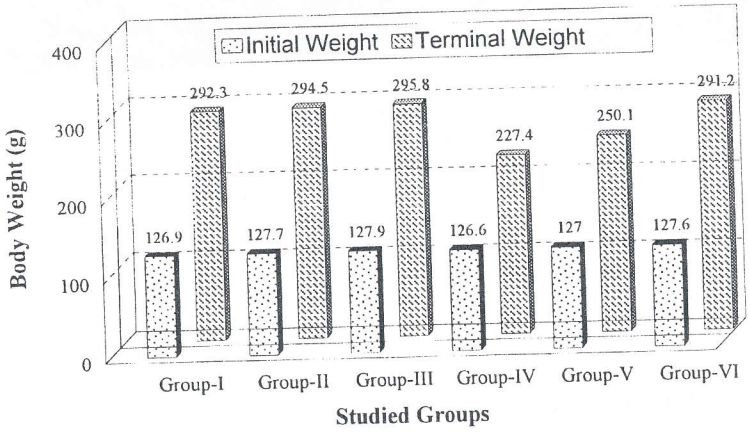
9–12. Photomicrographs of sections in the kidneys of cadmium/carnosine-treated groups, Group V (Figs. 9–10) and Group VI (Figs. 11–12) showing:
9. Few degenerated tubules (d) with mild interstitial fibrosis (f) (Mallory Trichrome x 100)
10. Only two atrophic glomeruli (g) in the whole field (Hx. & E. x 100)
11. Congestion (c) of cortical blood vessels (Mallory Trichrome x 100)
12. Nearly normal histological architecture of the kidney (Hx. & E x 10)

cadmium chloride. On the other hand, the simultaneous addition of carnosine to cadmium-treated rats resulted in a significant increase in their body weights in a dose-dependent manner. Furthermore, the weight of the kidneys of cadmium-treated rats was significantly reduced after the simultaneous administration of carnosine in also a dose-dependent manner. Moreover, the higher dose of carnosine brought both the total body weight and the kidney weight of cadmium-treated animals approximately to the initial control values.

The results of our study showed a significant increase in both blood cadmium and renal cadmium concentrations in cadmium-treated animals. Furthermore, small concentrations of cadmium were found in either the blood or the kidneys of the negative control animals. On the other hand, the addition of carnosine significantly decreased both the blood cadmium and renal cadmium concentrations in an apparent dose-related fashion. Moreover, the

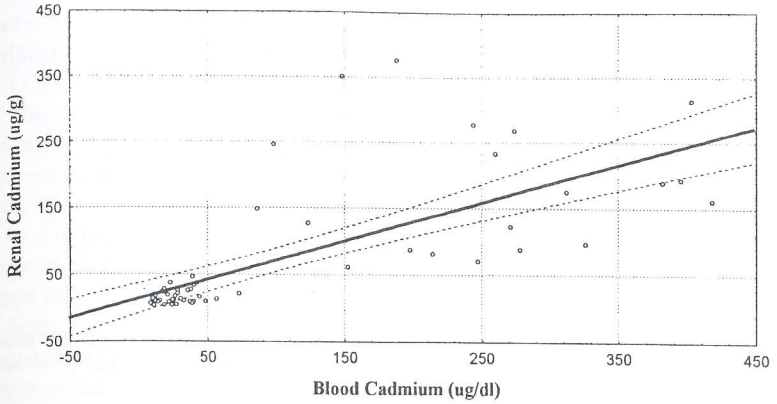


13. Mean initial as well as terminal body weights in all studied groups

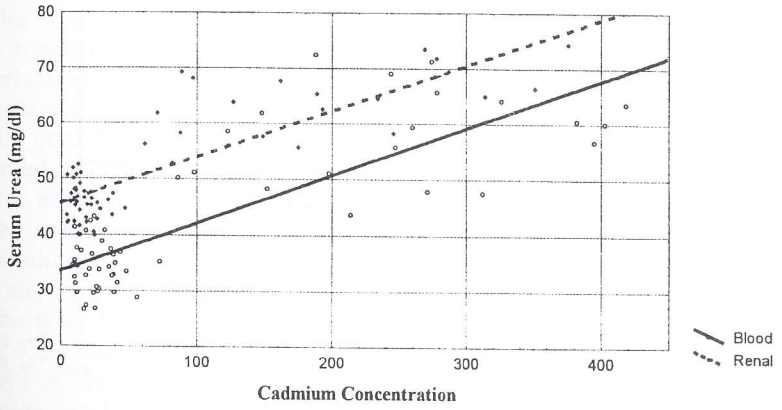


14. Mean blood as well as renal cadmium concentrations in all studied groups

higher dose of carnosine brought both the blood cadmium and the renal cadmium concentrations of cadmium-treated rats approximately to the initial values of the control groups. In accordance with our results, Janik and Gawlik (1993), have discovered the presence of small quantities of cadmium in the kidneys and livers of normal rats. Furthermore, Goyer et al. (1989), have concluded that renal toxicity has been observed when renal

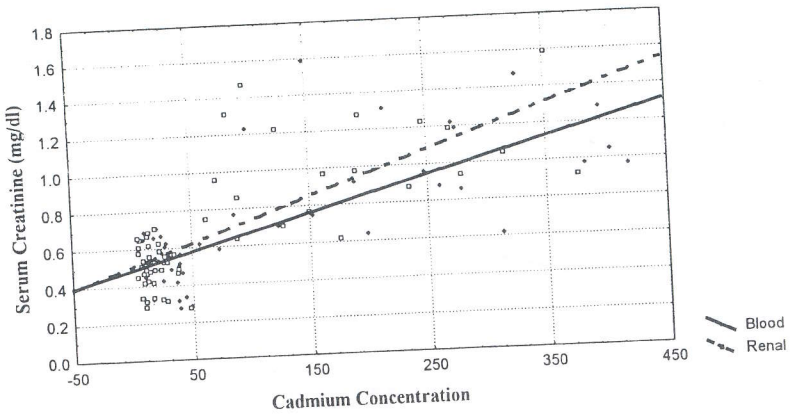


15. Correlation study between blood (µg/ml) and renal cadmium (µg/g) concentrations in all animals

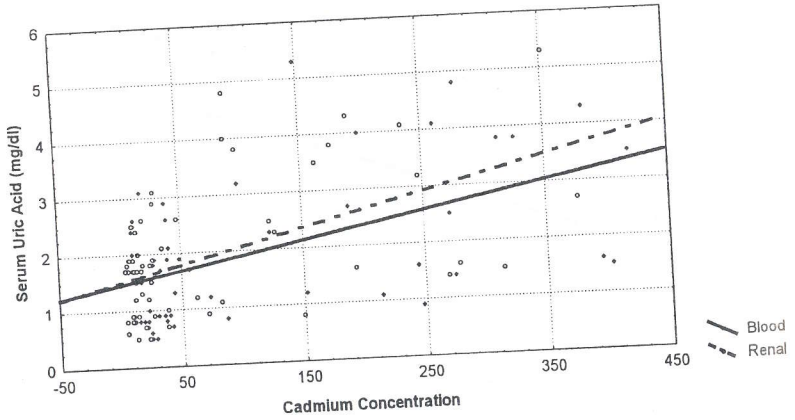


16. Correlation study between blood (µg/ml) as well as renal cadmium (µg/g) concentrations and serum urea (mg/dl) in all animals

cadmium concentrations were 200 µg/g following repeated injections of cadmium chloride, as compared to 10–20 µg/g wet weight after cadmium-metallothionein injection (Nordberg, Nordberg, 1987). Moreover, Chan et al. (1993), have stated that the renal cadmium concentrations reached about 200 µg/g within 2 to 3 weeks after the transplantation of livers from cadmium injected rats, and remained almost constant until 47 days.



17. Correlation study between blood (µg/ml) as well as renal cadmium (µg/g) concentrations and serum creatinine (mg/dl) in all animals



18. Correlation study between blood (µg/ml) as well as renal cadmium (µg/g) concentrations and serum uric acid (mg/dl) in all animals

In the present study, the kidney of animals treated with carnosine alone showed neither biochemical, nor histological differences from those of the negative control animals. On the other hand, there was a significant increase in the serum levels of urea, creatinine and uric acid among the cadmium-treated rats. Similar results were obtained by a large number of investigators (Yasuda et al., 1995; Jiang et al., 1996; Nortier et al., 1997). Furthermore, an increased overall mortality among residents with cadmium-induced renal damage in cadmium-polluted areas at Japan has been reported (Friberg et al., 1986). However, the simultaneous addition of carnosine – in the present study – resulted in a significant improvement of the renal function tests – in an apparent dose-related fashion – in cadmium-treated rats. Moreover, the higher dose of carnosine has brought the mean values of these tests approximately to the initial control ones.

In the present study, cadmium induced both numerous and marked alterations in the morphology of the kidney. Congestion of both the cortical and medullary blood vessels was shown. Furthermore, interstatial haemorrhages in both the cortex and medulla were also seen. Moreover, marked tubular degeneration affecting mainly the proximal convoluted tubules were also demonstrated. In addition, interstatial fibrosis and atrophic glomeruli were also observed. In accordance with our results, Webb, Etienne (1977) and Fowler, Nordberg (1978), have reported that cadmium-induced renal injury affected predominantly the proximal tubules of the kidney. Dorian et al. (1992a), have further added that the first segments of these tubules were more specifically affected. Furthermore, Liu et al. (1992), have stated that renal dysfunction (glycosuria, low-molecular weight proteinuria) and morphological changes (swelling, vacuolization, necrosis) were consistently observed after long-term exposure to cadmium. Moreover, Chan et al. (1993), have documented that the main morphological changes observed in the kidney – with chronic exposure to cadmium – were proximal tubular atrophy and degeneration, and in severe cases, interstetial fibrosis (nephrosclerosis). In addition, further evidence that prolonged administration of cadmium induced a glomerular injury in rats was provided by studies that have shown a glomerular swelling in these animals (Aughey et al., 1984). On the other hand, the simultaneous addition of carnosine – in the present study – resulted in marked improvement of the morphological changes of the kidneys of cadmium-treated animals in an apparent dose-related fashion. Furthermore, the higher dose of carnosine reversed the morphological changes of the kidneys of cadmium-treated rats approximately to the morphological architecture of the initial control animals.

In accordance with the results of our study, Goyer et al. (1984), have concluded that in experimental studies with repeated injections of cadmium chloride, chronic interstatial nephropathy occurred only when the cadmium concentrations in renal cortex reached about 200 µg/g, which coincided with an increase of cadmium-metallothionein in the plasma (Chan et al., 1993). However, Mitsumori et al. (1998), did not observe any renal lesions in a group of rats receiving 40 ppm of cadmium chloride for 8 months, despite the presence of 91–183 µg/g of cadmium in their kidneys. These results thus

suggested that renal toxicity would not be induced by treatment with minimum amounts of cadmium chloride for periods longer than 8 months, although accumulation of cadmium might gradually progress.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, we found an evidence of an inverse correlation between the consumption of carnosine and the risk of cadmium-induced nephrotoxicity. Treatment with carnosine produced a significantly greater reduction in both blood cadmium and renal cadmium concentrations in albino rats. Furthermore, both the biochemical renal functions and the morphological architecture of the kidney were approximately returned back to the normal control figures on increasing the dose of carnosine. These results suggest that the possibility that carnosine may be useful for the prevention of health hazards resulting from cadmium-exposure in humans.

Carnosine preparations in composition of products of nutrition can be effective for different system of prophylactice nutrition and dietotherapy. Supplemental histidine (to enhance carnosine levels) or carnitine can be added to the diet of workers who are occupationally exposed to cadmium for the aim of reducing the hazards of cadmium exposure and subsequently improving their survival time.

Future research work

Further studies on different time-intervals using different concentrations of cadmium with/without carnosine, and different routes of administration might be needed. Furthermore, more than one dose of carnosine could also be used in such studies to achieve the best results.

If research data from clinical trial/s were to show promise for carnosine and favourable detoxification metabolism, additional studies would be needed to further characterize the role of carnosine in the area of diet and prophylaxis against heavy metal intoxication.

References

Agency for Toxic Substances and Disease Registry: Toxicological Profile for Cadmium. ATSDR /TP-88/08. U.S. Public Health Service 1989.

ARUOMA, O. I. – LAUCHTON, M. J. – HALLIWELL, B.: Carnosine, homocarnosine and anserine: Could they act as antioxidants in vivo? Biochem. J., *264*, 1999: 863–869.

AUGHEY, E. – FELL, G. S. – SOCTT, R. – BLACK, M.: Histopathology of early effects of oral cadmium in the rat kidney. Environ. Health Perspect., *54*, 1984: 153–161.

BAGCHI, D. – VUCHETICH, P. J. – BAGCHI, M. – HASSOUN, E. A. – TRAN, M. X. – TANG, L. – STOHS, S. J.: Induction of oxidative stress by chronic administration of sodium dichromate (Chromium VI) and cadmium chloride (Cadmium II) to rats. Free Radic. Biol. Med., *22*, 1997: 471–478.

CANDLISH, J. K. – DAS, N. P.: Antioxidants in food and chronic degenerative diseases. Biomed. Environ. Sci., *9*, 1996: 117–123.

CARDENAS, A. – BERNARD, A. – LAUWERYS, R.: Disturbance of sialic acid metabolism by chronic cadmium exposure and its relation to proteinuria. Toxicol. Appl. Pharmacol., *108*, 1991: 547–558.

CARDENAS, A. – RAMIS, I. – HOTTER, G. – ROSELLO, J. – GELPI, E. – ROELS, H. – BERNARD, A. – LAUWERYS, R.: Human and experimental studies on renal eicosanoid response to long-term cadmium exposure. Toxicol. Appl. Pharmacol., *116*, 1992: 155–160.

CHAN, H.M. – ZHU, L.F. – ZHONG, R. – GRANT, D. – GOYER, R. A. – CHERIAN, M. G.: Nephrotoxicity in rats following liver transplantation from cadmium-exposed rats. Toxicol. Appl. Pharmacol., *123*, 1993: 89–96.

CHERIAN, M. G. – GOYER, R. A. – DELAQUERRIERS-RICHARDSON, L.: Cadmium metallthionein induced nephropathy. Toxicol. Appl. Pharmacol., *38*, 1976: 399–408.

DAHL, T. – MIDDEN, R. – HARTMAN, P.: Some prevalent biomolecules as defenses against singlet oxygen damage. Photochem. Photo-biol., *47*, 1998: 357–362.

DECKER, E. A.: The role of phenolics, conjugated linoleic acid, carnosine, and pyrroloquinoline quinone as non-essential dietary antioxidants. Nutr. Rev., *53*, 1995: 49–58.

DORIAN, C. – GATTONE II, V. H. – KLAASSEN, C. D.: Accumulation and degradation of the protein moiety of cadmium-metallothionein (Cd-MT) in the mouse kidney. Toxicol. Appl. Pharmacol., *117*, 1992a: 242–248.

DORIAN, C. – GATTONE II, V. H. – KLAASSEN, C. D.: Renal cadmium deposition and injury as a result of accumulation of cadmium-metallothionein (Cd-MT) by the proximal convoluted tubules. A light microscopic autoradiography study with 109Cd-MT. Toxicol. Appl. Pharmacol., *114*, 1992b: 173–181.

DUDLEY, R. E. – GAMMAL, L. M. – KLAASSEN, C. D.: Cadmium-induced hepatic and renal injury in chronically exposed rats: Likely role of cadmium-metallothionein in nephrotoxicity. Toxicol. Appl. Pharmacol., *77*, 1985: 414–426.

ENDO, T. – SHAIKH, Z. A.: Cadmium uptake by primary cultures of rat renal cortical epithelial cells: Influence of cell density and other metal ions. Toxicol. Appl. Pharmacol., *121*, 1993: 203–209.

FORMAZYUK, V. E. – GORSHKOVA, N. – BOLDYREV, A. A. – SERGIENKO, V. I.: Characterization of chloramine complexes of carnosine with hypochlorite anions. Biokhimya, *57*, 1992: 1324–1329.

FOWLER, B. A. – NORDBERG, G. F.: The renal toxicity of cadmium-metallothionein: Morphometric and X-ray microanalytical studies. Toxicol. Appl. Pharmacol., *46*, 1978: 609–623.

FRIBERG, L.: Health hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. Acta Med. Scand., *138*, 1950 (Suppl. 240): 1–124.

FRIBERG, L. – ELINDER, C. G. – KJELLSTROM, T.: Cadmium and health. In BOCA-RATON, F. L. (ed.): A Toxicological and Epidemiological Appraisal. Cleveland, OH, New York,, CRC Press, Inc., 1986, Vol. 2. 485 pp.

FRIIS, L. – PETERSSON, L. – EDLING, C.: Reduced cadmium levels in human kidney cortex in Sweden. Environ. Health Perspect., *106*, 1998: 175–178.

GOYER, R. A. – CHERIAN, M. G. – DELAQUERRIERE-RICHARDSON, L.: Correlation of parameters of cadmium exposure with onset of cadmium-induced nephropathy in rats. J. Environ. Pathol. Toxicol. Oncol., *5*, 1984: 89–100.

GOYER, R. A. – MILLER, C. R. – ZHU, S. Y. – VICTERY, W.: Non-metallothionein-bound cadmium in the pathogenesis of cadmium nephrotoxicity in the rat. Toxicol. Appl. Pharmacol., *101*, 1989: 232–244.

GREENBERG, A. – PARKINSON, D. K. – PUSCHETT, J. B. – ELLIS, K. J. – WIELOPOLSKI, L. – VASWANI, A. N. – COHN, S. H. – LANDRIGAN, P. J.: Effects of elevated lead and cadmium burdens on renal function and calcium metabolism. Arch. Environ. Health, *41*, 1986: 69–76.

HEINEGARD, D. – TIDERSTROM, K.: Determination of serum creatinine by a direct colorimetric method. Clin. Chem. Acta, *43*, 1973: 305–310.

HERAK-KRAMBERGER, C. M. – BROWN, D. – SABOLI, I.: Cadmium inhibits vacuolar H(+) – ATPase and endocytosis in rat kidney cortex. Kidney Int., *53*, 1998: 1713–1726.

HINKLE, P. M. – OSBORNE, M. E.: Cadmium toxicity in rat pheochromocytoma cells: Studies on the mechanism of uptake. Toxicol. Appl. Pharmacol., *124*, 1994: 91–98.

HIPKISS, A. R.: Carnosine, a protective, anti-ageing peptide? Int. J. Biochem. Cell Biol., *30*, 1998: 863–868.

HIPKISS, A. R. – CHANO, H.: Carnosine protects proteins against methylglyoxal-mediated modification. Biochem. Biophys. Res. Commun., *248*, 1998: 28–32.

HIPKISS, A. R. – MICHAELIS, J. – SYRRIS, P.: Non-enzymatic glycosylation of the dipeptide L-carnosine, a potential anti-protein-cross-linking agent. FEBS Lett., *371*, 1995: 81–85.

HIPKISS, A. R. – PRESTON, J. E. – HIMSWOTH, D. T. – WORTHINGTON, V. C. – ABBOT, N. J.: Protective effects of carnosine against malondialdehyde-induced toxicity towards cultured rat brain endothelial cells. Neurosci. Lett., *238*, 1997: 135–138.

HIPKISS, A. R. – PRESTON, J. E. – HIMSWORTH, D. T. – WORTHINGTON, V. C. – KEOWN, M. – MICHAELIS, J. – LAWRENCE, J. – MATEEN, A. – ALLENDE, L. – EAGLES, P. A. – ABBOT, N. J.: Pluripotent protective effects of carnosine, a naturally occurring dipeptide. Ann. N. Y. Acad. Sci., *854*, 1998: 37–53.

HOCHI, Y. – KIDO, T. – NOGAWA, K. (1995): Dose-response relationship between total cadmium intake and prevalence of renal dysfunction using general linear models. J. Appl. Toxicol., *15*, 1995: 109–116.

HOLLIDAY, R. – McFARLAND, G. A.: Inhibition of the growth of transformed and neoplastic cells by the dipeptide carnosine. Br. J. Cancer, *73*, 1996: 966–971.

JACKSON, M. C. – LENNEY, J. F. (1996): The distribution of carnosine and related dipeptides in rat and human tissues. Inflamm. Res., *45*, 1996: 132–135.

JACKSON, M. C. – KUCERA, C. M. – LENNEY, J.: Purification and properties of human serum carnosine. Clin. Chim. Acta, *196*, 1991: 193–206.

JANIK, A. – GAWLIK, M.: Behavior of selected indicators of lipid metabolism in kidney and liver of rats continuously exposed to effects of cadmium. Folia Med. Cracov., *34*, 1993: 211–217.

JIANG, T. – FAN, J. – TAN, B.: Toxicity of cadmium and its mechanism on renal tubular epithelial cells in vitro. Chung. Hua. Yu. Fang. I. Hsueh. Tsa. Chih., *30*, 1996: 84–87.

KARMAKER, R. – ROY, S. – CHATTERJEE, M. (1999): The effects of cadmium on the hepatic and renal levels of reduced glutathione, the activity of glutathione S-transferase and gamma glutamyl transpeptidase. J. Environ. Pathol. Toxicol. Oncol., *18*, 1999: 29–35.

KAZANTZIS, G. – FLYNN, F. V. – SPOWAGE, J. S. – TROTT, D. G.: Renal tubular malfunction and pulmonary emphysema in cadmium pigments workers. Q. J. Med., *32*, 1963: 165–192.

KNAP, R. G. – MILLER, M. C.: Clinical Epidemiology and Biostatistics. Pennsylvania, Harwal Publication Co. 1992: 43–51.

KOHEN, R. – YAMAMOTO, Y. – CUNDY, K. – AMES, B.: Antioxidant activity of carnosine, homocarnosine and anserine present in muscle and brain. Proc. Natl. Acad. Sci., *85*, 1988: 3175–3179.

LAUWERYS, R. B. – ROELS, H. A. – REGNIERS, M.: Significance of cadmium concentrations in blood and in urine in workers exposed to cadmium. Environ. Res., *20*, 1979: 375–391.

LENNEY, J. F.: Separation and characterization of two carnosine-splitting cytosolic dipeptidases from hog kidney (carnosinase and non-specific dipeptidase). Biol. Chem. Hoppe-Seyler, *371*, 1990: 433–440.

LIU, J. – LIU, Y. – KLAASSEN, C.: Nephrotoxicity of $CdCl_2$ and cadmium-metallothionein in cultured rat kidney proximal tubules. Toxicol. Appl. Pharmacol., *128*, 1994: 264–270.

LIU, X. Y. – JIN, T. Y. – NORDBERG, G. F. – RANNAR, S. – SJOSTROM, M. – ZHOU, Y.: A multivariate study of protective effects of Zn and Cu against nephrotoxicity induced by cadmium metallothionein in rats. Toxicol. Appl. Pharmacol., *114*, 1992: 239–245.

MARKOVICH, D. – JAMES, K. M.: Heavy metals mercury, cadmium, and chromium inhibit the activity of the mammalian liver and kidney sulfate transporter sat-1. Toxicol. Appl. Pharmacol., *154*, 1999: 181–187.

McFARLAND, G. A. – HOLLIDAY, R.: Retardation of the senescence of cultured human diploid fibroblasts by carnosine. Exp. Cell. Res., *212*, 1994: 167–175.

MITSUMORI, K. – SHIBUTANI, M. – AATO, S. – ONODERA, H. – NAKAGAWA, J. – HAYASHI, Y. – ANDO, M.: Relationship between the development of hepato-renal toxicity and cadmium accumulation in rats given minimum to large amounts of cadmium chloride in the long-term preliminary study. Arch. Toxicol., *72*, 1998: 545–552.

NAKASHIMA, K. – KOBAYASHI, E. – NOGAWA, K.: Concentration of cadmium in mice and urinary indicators of renal dysfunction. Occup. Environ. Med., *54*, 1997: 750–755.

NOMIYAMA, K. – NOMIYAMA, H.: Tissue metallothionein in rabbits exposed to cadmium with special reference to the critical concentration of cadmium in the renal cortex. In: FOULKES, E. C. (ed.): Biological Roles of Metallothionein. New York, Elsevier Publishing Co. 1986: 47–67.

NORDBERG, M. – NORDBERG, G. F.: On the role of metallothionein in cadmium induced renal toxicity. Experientia Suppl., *52*, 1987: 669–675.

NORDBERG, G. F. – GOYER, R. – NORDBERG, M.: Comparative toxicity of cadmium-metallothionein and cadmium chloride on mouse kidney. Arch. Pathol., *99*, 1975: 192–197.

NORDBERG, G. F. – JIN, T. – NORDBERG, M.: Subcellular targets of cadmium nephrotoxicity: Cadmium binding to renal membrane proteins in animals with or without prospective metallothionein synthesis. Environ. Health Perspect., *102*, 1994 (Suppl.3): 191–194.

NORTIER, J. – BERNARD, A. – ROELS, H.: Urinary endopeptidase in workers exposed to cadmium: Interaction with cigarette smoking. Occup. Environ. Med., *54*, 1997: 432–436.

OKUMA,E. – ABE, H.: Major buffering constituents in animal muscles. Comp. Biochem. Physiol., *102 A*, 1992: 37–41.
ONER, G. – SENTURK, U. K. – IZGUT-UYSAL, V. M.: Role of cadmium-induced lipid peroxidation in the kidney response to atrial natriuretic hormone. Nephron, *72*, 1996: 257–262.
PEARSE, A. G. E.: Histochemistry. Theoretical and Applied Analytical Technology. 4th ed. London, Churchill Livingstone 1985.
PETERING, D. H. – LOFTSGAARDEN, J. – SCHNEIDER, J. – FOWLER, B. (1984): Metabolism of cadmium, zinc and copper in rat kidney: The role of metallothionein and other binding sites. Environ. Health Perspect., *54*, 1984: 73–81.
PRESTON, J. E. – HIPKISS, A. R. – HIMSWORTH, D. T. – ROMERO, I. A. – ABBOT, J. N. (1998): Toxic effects of beta-amyloid (25–35) on immortalised rat brain endothelial cell: protection by carnosine, homocarnosine and beta-alanine. Neurocsi. Lett., *242*, 1998: 105–108.
QUINN, P. J. – BOLDYREV, A. A. – FORMAZUYK, V.: Carnosine, its properties, functions and potential therapeutic applications. Mol. Aspects Med., *13*, 1992: 379–444.
REHM, S. – WAALKES, M. P.: Acute cadmium chloride-induced renal toxicity in the Syrian hamster. Toxicol. Appl. Pharmacol., *104*, 1990: 94–105.
ROELS, N. J. – LAUWERYS, R. B. – DARDENNE, A. N.: The critical concentration of cadmium in human renal cortex: a reevaluation. Toxicol. Lett., *15*, 1983: 357–360.
SAMPSON, E. J. – BAIRD, M. A. – BURTIS, C. A.: A coupled enzyme equilibrium method for measuring urea in serum. Optimization and evaluation of the AACC study group on urea candidate reference method. Clin. Chem., *26*, 1980: 816–826.
SCOTT, R. – PATERSON, P. J. – BURNS, R. – OTTOWAY, J. M. – HUSSAIN, F. E. R. – FELL, G. S. – DUMBUYAS, S. – IQBAL, M.: Hypercalciuria related to cadmium exposure. Urology, *11*, 1978: 462–465.
SCOTT, R. – MILLS, E. A. – FELL, G. S. – HUSSAIN, F. E. R. – YATES, A. J. – PATERSON, P. J. – MCKIRDY, A. – OTTOWAY, J. M. – FITZGERALD-FINCH, O. P. – LAMONT, A. – ROXBURGH, S.: Clinical and biochemical abnormalities in coppersmiths exposed to cadmium. Lancet, 2, 1976: 396–398.
SHAIKH, Z. – BLAZKA, M. – ENDO, T.: Metal transport in cells: Cadmium uptake by rat hepatocytes and renal cortical epithelial cells. Environ. Health Perspect., *103*, 1995: 73–75.
STACEY, N. H. – CANTILENA, L. R. – KLAASSEN, C. D.: Cadmium toxicity and lipid peroxidation in isolated rat hepatocytes. Toxicol. Appl. Pharmacol., *53*, 1980: 470–480.
SUTOO, D. – AKIYAMA, K. – IMAMIYA, S.: A mechanism of cadmium poisoning: The cross effect of calcium and cadmium in the calmodulin-dependent system. Arch. Toxicol., *64*, 1990: 161–164.
TRIVEDI, R. D. – REBARL, B. E. – STRANG, L.: Enzymatic colourimetric method of uric acid. Clin. Chem., *124*, 1978: 1908–1911.
TROMBLEY, P. Q. – HORNING, M. S. – BLACKEMORE, L. J.: Carnosine modulates zinc and copper effects on amino acid receptors and synaptic transmission. Neuroreport, *9*, 1998: 3503–3507.
WEBB, M. – ETIENNE, A. T.: Studies on the toxicity and metabolism of cadmium-thionein. Biochem. Pharmacol., *26*, 1977: 25–30.
WESTER, R. C. – MAIBACH, H. I. – SEDIK, L. – MELENDRES, J. – DIZIO, S. – WADE, M.: In vitro percutaneous absorption of cadmium from water and soil into human skin. Fundam. Appl. Toxicol., *19*, 1992: 1–5.

YASUDA, M. – MIWA, A. – KITAGAWA, M.: Morphometric studies of renal lesions in itai-itai disease: Chronic cadmium nephropathy. Nephron, *69*, 1995: 14–19.

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Ochrana karnosinem před nefrotoxicitou vyvolanou kadmiem u potkaních samců-albínů: biochemická a histologická studie.

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Práce se zabývá rolí karnosinu při toxických projevech chronického vystavení kadmiu. Ledviny jsou považovány za cílový orgán chronického vystavení kadmiu, a to z důvodu velmi dlouhému poločasu rozpadu kadmia. Kadmium (jako Cadmium chlorid®) v dávce 3 mg/kg tělesné hmotnosti bylo po dobu 14 týdnů subkutánně podáváno potkaním samečkům-albínům. Mělo to za následek značný pokles konečné tělesné hmotnosti potkanů, zatímco testy na funkci ledvin, včetně hladin séra močoviny, kreatininu a kyseliny močové prokázaly značný nárůst. Projevilo se to také na morfologickém vzhledu ledvin, který byl významně ovlivněn expozicí kadmiu. Karnosin (jako Carnosine®) podávaný orálně v dávce 0,15 mg/kg tělesné hmotnosti současně s kadmiem vykázal jak přírůstek tělesné hmotnosti, tak i renální biochemickou funkci spolu s morfologickou strukturou, ale tato struktura byla stále ještě pod počátečními kontrolními hodnotami. Na rozdíl od toho tělesná hmotnost i funkce ledvin a jejich morfologie se zlepšily, čímž se přiblížily kontrolním hodnotám při zvyšování dávek karnosinu na 0,3 mg/kg. Hladina kadmia jak v krvi, tak ve tkáni ledvin u zvířat, která dostala kadmium společně s karnosinem, byla značně nižší než u zvířat, kterým bylo podáváno pouze kadmium. Tato práce také prokázala, že nefrotoxický vliv kadmia by mohl souviset se sníženou tělesnou hmotností a zvýšenou hmotností ledvin společně se zvýšenými koncentracemi kadmia v krvi, jakož i s testy na renální funkci. Proto jsme dospěli k závěru, že ochrana před nefrotoxicitou způsobenou kadmiem je možná současným podáváním karnosinu.

kadmium; nefrotoxicita; karnosin; samečci-albíni

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