Effects of Cadmium Exposure on Rat Kidneys

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There is presently a great deal of information suggesting that exposure to cadmium both in the industrial and general environment results in human toxicity (cf. Friberg et al., 1971). However, the mechanism of cadmium induced renal damage and the development of biochemical tests reflecting the onset and severity of that damage have not been worked out. Histochemical studies on the distribution of enzymes in the kidney have shown that specific structures of the renal nephrons are rich in acid phosphatase, alkaline phosphatase, glutamic oxoloacetic transaminase, carbonic anhydrase and lactic dehydrogenase (Wachisten, 1955; Bonting et al., 1960; Pollak and Mattenheimer, 1962: Mattenheimer, 1968). Cadmium-induced renal damage may cause the release of these enzymes into the urine (Nomiyama et al., 1973).

The enzyme γ-glutamyl transpeptidase (GT) is present in various tissues of the body, but the highest activity is found in the kidney (Albert et al., 1961). Large changes in serum activity of GT have, however, been noted in certain diseases of the liver (Szczeklik et al., 1961; Zein and Discombe, 1970).

Evidence has shown that acute and destructive diseases of the urorenal system results in increased activity of GT in urine. Chronic diseases produce significantly reduced activity (Levy and Dubach, 1972).

It has been postulated that when the kidney becomes saturated with cadmium, re-absorption decreases and tubular proteinuria appears.

The objectives of this investigation were to study the effects of cadmium toxicity on the kidney at chronic and acute dosing and to determine whether there is a release of the tubular enzyme GT into the urine.

Bulletin of Environmental Contamination & Toxicology, Vol. 16, No. 5 © November 1976 by Springer-Verlag New York Inc.

MATERIALS AND METHODS

Male Sprague Dawley rats (225-250 g) were divided into five groups, four rats per group. One control group was given 3 subcutaneous (sc) injections per week, for four weeks, of 200 ul sterile, isotonic saline. Two groups were acutely dosed: high acute dose was a single sc injection 9 mg Cd/kg body weight; low acute dose was 3 mg Cd/kg body weight. Two groups were chronically dosed, 3 times per week for four weeks: high chronic dose was 0.75 mg Cd/kg body weight, low chronic dose was 0.25 mg Cd/kg body weight. All animals were sacrificed at 4 weeks, and the kidneys removed for metal analysis.

The condition of the animals was evaluated during the course of treatment by the following measurements; total body weight, 8 hour urine collection every 3 days, GT activity in urine, and total urinary protein excretion. Every third day urine samples were collected in cold (2-4°) vials for eight hours from rats individually housed in metabolic cages. The volume of urine collected was recorded. Urine samples were centrifuged at 1100xg for ten minutes to remove cellular debris and dialyzed with 3 changes of cold deionized water for 16 hours. Total acid insoluble protein excreted was measured by a modified Lowry method (Layne, 1957). GT was assayed using the method of Szasz (1969). Cadmium analysis in urine, and cadmium and zinc analysis of kidney were done according to the method of Hinners et al. (1975).

RESULTS AND DISCUSSION

The dosing regimen was established in such a way that after four weeks, the low chronic group had received about the same total amount of cadmium as the low acute group, and the high chronic group received about the same total amount of cadmium as the high acute group. Table 1 summarizes the metal accumulation data. Kidney cadmium concentrations in the acutely dosed animals reached higher levels than in the corresponding chronically dosed groups. Zinc levels remained essentially the same for all dosed groups. Cadmium levels in urine, for all groups, throughout the experiment, were less than 0.05 ug/ml.

TABLE 1 Metal Accumulation in Kidneys[1]

Group	Total Cd Injected mg	Total Cd Accumulated mg	[Cd] ug/g	[Zn] ug/g
Control	--	--	<1.5±1	17.8±1.0
Low Chronic	.92	.07±.02	22.3±3.3	24.5±1.7
High Chronic	2.72	.21±.04	62.8±14.6	26.8±1.7
Low Acute	1.04	.11±.04	33.7±4.5	28.0±2.7
High Acute	3.20	.26±.05	91.3±8.2	29.3±4.4

[1] Means ± Standard deviation

Figure 1 shows the differences in body weight gain for all groups.

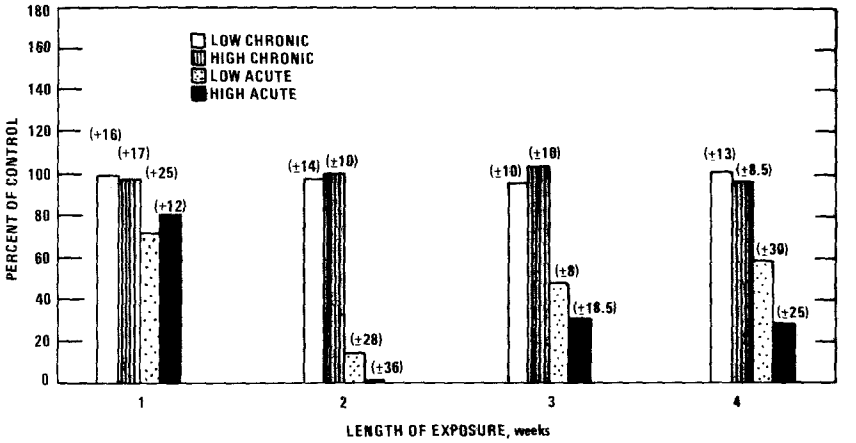

Fig. 1. Weight gain of animals as a function of weeks after onset of the experiment. Values are expressed as a per cent of the control for that week. Numbers in brackets represent standard deviations.

Both acutely dosed groups gained substantially less weight than the chronically dosed goups. The latter showed normal gains when compared to controls ($p<0.05$).

Figure 2 shows total urinary protein output for 24 hr periods. Acutely exposed animals showed greatly depressed protein excretion for all days measured. Chronically exposed animals showed essentially the same protein excretion as control animals. Urine volumes for all exposed groups ranged between 70 and 150 per cent of control volumes. Scatter and standard deviations in the data were such that we observed no significant ($p<0.05$) changes in urine volume, when compared to controls.

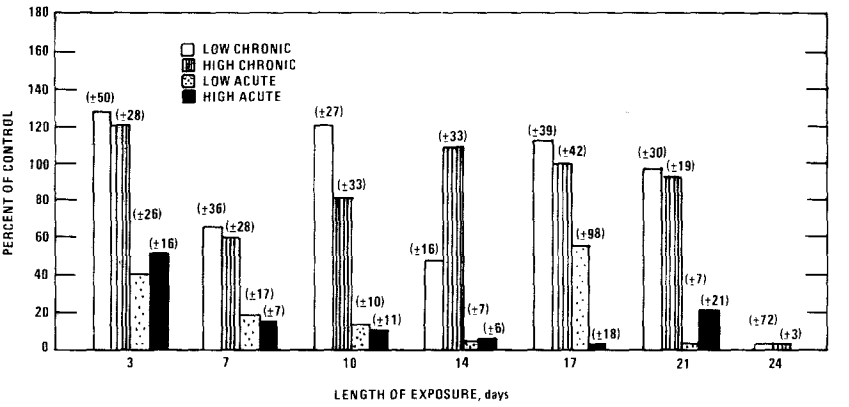

Fig. 2. Total urinary protein excreted as a function of days of exposure. Values are expressed as a per cent of the control for that day.

Normal proteinuria in male mice originates mainly from the production of testosterone-dependent low molecular weight proteins in the liver and the excretion of these proteins through the kidney (Finlayson et al., 1968; Thung, 1956; Reuter et al., 1968).

The significant decrease in excretion of urinary protein by acutely dosed animals may be caused (Nordberg, unpublished observation) by cadmium accumulation in and around the walls of the capillaries in the interstitial tissue of the testicles. An effect on testosterone production of the Leydig cells could thereby result in decreased urinary excretion. A decrease in urinary protein excretion could also be attributed to a decrease in protein consumption.

Urinary GT levels are presented in Fig. 3. Acutely dosed animals show significant decreases from day 3 to day 21. Chronically dosed animals also show diminished GT levels after day 7. The decrease in urinary amounts of GT may be due to processes causing changes similar to chronic kidney degenerative diseases (Levy and Dubach, 1972). Alternatively there may have been a decrease in protein consumption or absorption resulting in a change in amino acid transport requirement by the kidney (Meister, 1973). A decreased need for GT might ensue.

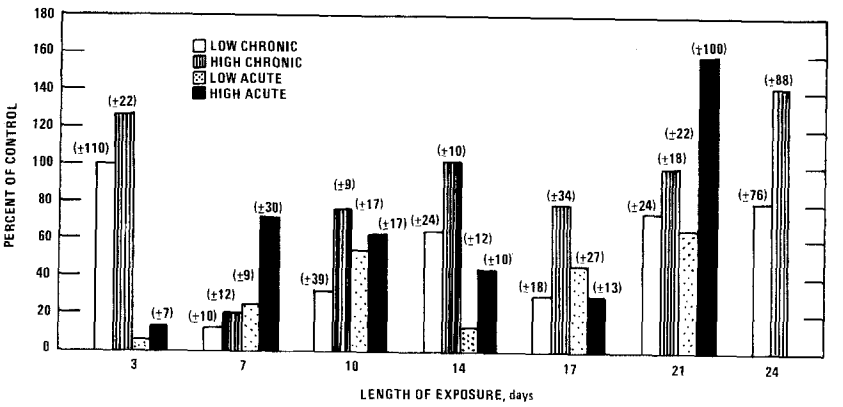

Fig. 3. GT Levels in urine as a function of days after onset of the experiment. Values are expressed as a per cent of the control value for that day.

GT, although highly concentrated in the kidney, showed only small changes during this 4 week investigation. If the duration of exposure were increased one might see greater changes in excretion of the protein. The hypothesis of dose-level and response of the kidney to cadmium could be more conclusively evaluated. The data presented here are consistent with minimal destruction of renal tubules during the 4 weeks of exposure at the chronic and acute level.

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