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Chronic Effects of Cadmium on Kidney, Liver, Testis, and Fertility of Male Rats

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ABSTRACT

Male Wistar rats (n:20), at 5 wk of age, were given cadmium in drinking water (10 mg/L water) for 52 wk; 8 males and 20 female rats, as controls, were given tap water. At the end of 28 and 40 wk, some of the cadmium-treated males and control group male rats were sacrificed for the histopathological examination of testis, kidney, and liver. At the end of 56 wk, histopathological examinations were performed in the same way. Liver, kidney, and testis cadmium levels were also determined by atomic absorption spectrophotometry.

All the cadmium-treated male rats showed pathological testicular alterations, and liver and kidney damage after chronic exposure. Cadmium levels were found to be highest in the kidney (1.009 ± 0.034 μg/g wet tissue in the infertile group). At the end of the 52-wk period, reproductive capacity of the cadmium-treated rats was investigated and was found to be lost in 39.89% of the animals.

Index Entries: Cadmium; chronic oral intake; liver; kidney; testis; reproductive functions.

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INTRODUCTION

The acute and chronic toxicity of cadmium is well known and has been reviewed by many investigators (*1–4*). Toxicity of cadmium may be related to binding to certain mammalian cells. Although most of the metals are stored in liver and kidney, testis also constitutes the target organ for cadmium (Cd^{2+}) toxicity (*5–7*). Damage to the testis of various species of mammals and alterations in enzymatic, histological, and morphological patterns after acute exposure to cadmium have been described by some authors (*8–10*). There are also a limited number of studies to indicate the subchronic and chronic effects of multiple administrations of cadmium by oral route on the testis of rats (*7*).

Nonoccupational (environmental) chronic exposure to cadmium can mainly result from dietary sources. When rats were fed with cadmium in drinking water within a 1-yr period, elevation of blood pressure was observed (*3*).

Our aim in this study was to indicate the effect of cadmium on the histological and morphological patterns of the testis, and on the fertility of rats given a low amount of cadmium in drinking water for at least 1 yr. Distribution of the metal in kidney, liver, and testis was also investigated.

MATERIALS AND METHODS

Animals and Cadmium Treatment

Experiments were performed on Wistar rats initially 5 wk old with an average body weight of 100 ± 5 g. The male (n:28) and female (n:20) rats were housed in an environment maintained at 20 ± 2°C, isolated from noise, and with a 12-h light/dark cycle. Diet and tap water were given *ad libitum*. Male and female rats were group-housed at a density of 4 rats/cage; 8 male rats were kept as controls, and 20 male rats were treated with 10 ppm cadmium containing tap water (10 mg cadmium/L water) (cadmium-treated group). Male control group and female rats were given normal tap water. The animals were observed daily, and body weights were determined at weekly intervals.

Histophathological Study

One animal each of the control group and cadmium-treated group after anesthesia was sacrificed for examination. Kidneys, testis, liver, lungs, stomach, intestine, and bladder were removed and examined macroscopically. Representative sections of each organ were fixed in 10% buffered formalin, and embedded in paraffin, sectioned at 5–6 μm, and stained with hematoxyline-eosin. The rest of the surviving animals were sacrificed at the end of 56 wk, and were treated in the manner described above for macroscopic and microscopic examinations.

Determination of Tissue Cadmium Levels

Cadmium levels in liver, kidneys, and testis were determined by atomic absorption spectrophotometry (Varian Techtron Model 1250 Automatic) using the method described by Berman (*11*). Cadmium standards in a series of 0.1, 0.2, 0.5, and 1.0 ppm were prepared with cadmium chloride ($CdCl_2 \cdot 2½ H_2O$) (Mallinckordt Chemical Works, St. Louis, MO, USA).

Samples from liver, kidney, and testis of the sacrificed animals for histopathological examination were used for the cadmium determination. Tissue sections (2–4 g) of representative samples were digested with a mixture of concentrated sulfuric acid (2 mL) and concentrated nitric acid (20 mL) in micro Kjeldahl flasks. Digested clear liquid was diluted to 25 mL in deionized distilled water, and a 5-mL aliquot was used for the complex formation with sodium diethyldithiocarbamate (NDDC) (Fluka). The cadmium complex was extracted with methylisobutylketone (MIBK) (Ega Chemie) at pH 6.5–7. Results were given as μg cadmium/g wet tissue. The tap water given to experimental animals was also controlled for the cadmium content.

Testing Reproductive Capacity Function of the Male Rats

Male rats in both control and cadmium-treated groups were divided one by one to each cage at the end of the 52 wk. Two female rats were also added to each cage. One male and two female rats in the same cage were kept for mating for 30 d. They were given normal tap water (containing no cadmium) during the 30-d period. After 23 d, birth was observed in some cages. The male rats in cages where births were observed were accepted as having positive fertility capacity (fertile males). The males in cages where no births were observed were accepted as having lost fertility capacity (infertile males).

Reproductive organs of the female rats in cages where no births were observed were tested. After fertility testing, all the male rats were sacrificed for the histopathologic examination and tissue cadmium measurements as described above.

RESULTS AND DISCUSSION

Pathologic Findings

Sacrificed animals after receiving a low amount of cadmium in drinking water (10 mg/L) did not indicate any testicular alterations within a 10-mo period on gross pathological examination. At the end of 13th mo, histologically, a slight atrophy of the testis and hyperemia was observed in the tunica vaginalis and serosal vessels of the interstitium as compared with the controls.

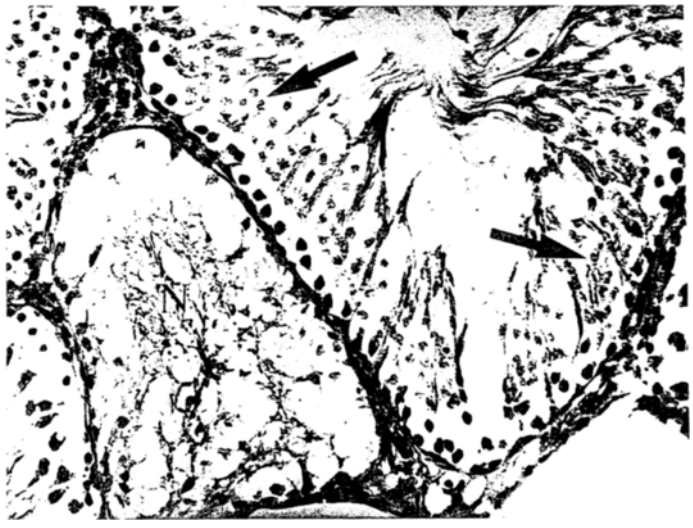

Fig. 1. Necrobiotic alterations in spermatocytes (arrows) and necrotic masses in tubuli (N) at the end of 13th mo. Hematoxylin-eosin stain × 150.

In the testis of the sacrificed animals, necrosis of spermatogonia, spermatocyte, and spermatid was observed in some tubuli seminiferi contorti and the end of 10th mo of cadmium intake. Some tubuli showed atrophy, edema, and vascular hyperemia in the interstitium.

At the end of the 13th mo, microscopic findings described above were more apparent. Some tubuli lumens (those filled with homogenous pink necrotic particles) had no spermatozoa (Fig. 1).

On the other hand, some tubuli were found to be atrophic. Interstitial tissue increase, edema, and vascular hyperemia were observed in the intertubular area.

Those histopathological findings we observed have been confirmed by the investigations carried out previously (*5,8*). In chronic cadmium exposure, the extent of testicular damage was the time sequence response. Similar observations were reported by some authors as a result of experimental chronic toxicity administration of cadmium by oral or ip route (*7,12,13*). Chronic cadmium exposure by oral intake (as a dietary source) in rats indicated similar testicular macroscopic and microscopic alterations in our investigation. The response was dependent on exposure period.

Although our experiment focused on the testicular alterations, kidneys were also examined macrocopically. Cystic dilatation in cortical tubuli, albumin degeneration, and vacuoler degeneration were observed. Some atrophy of glomerular also existed (Fig. 2). Other organs were found to be histologically normal.

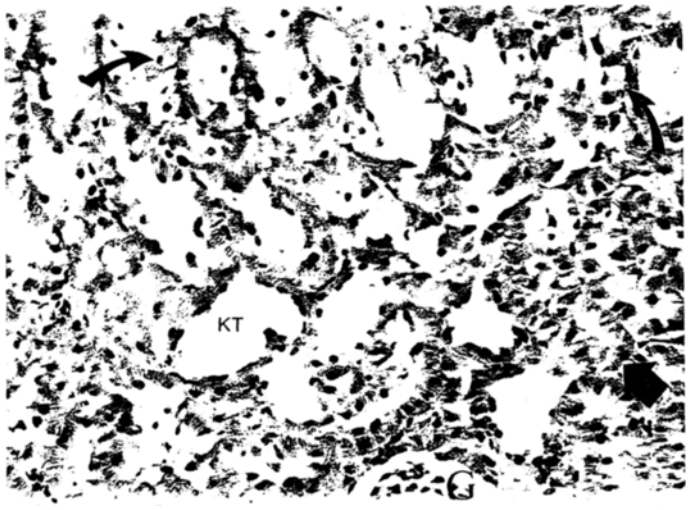

Fig. 2. Cystic dilatations of cortical tubuli (KT), albumin (thick arrow) and hydropic degeneration (thin arrows), and glomerulus (G) in kidney at the end of 13th mo. Hematoxylin-eosin stain × 150.

Tissue Distribution of Cadmium

The distribution of cadmium (depending on exposure period) in kidneys, liver, and testis is shown in Table 1. At the end of the 13th mo of exposure, it was observed that cadmium accumulated mainly in the kidneys and liver. Cadmium was not detected in testis above the detection limit (0.1 μg/mL).

Sugawara and Sugawara (*6*) detected cadmium in testis in concentrations of only 1/20 of that of kidney and of 1/10 of that of liver after subcutaneous administration of cadmium to mice. In general, the cadmium level in the testis is much lower than in the kidney and liver in animals given cadmium parenterally. The detection limit of our analytical method was evidently insufficient to permit the determination of cadmium in the testis of the experimental animals.

Effect of Cadmium Intake on Fertility

In the control group, all the female rats in all cages became pregnant and delivered. In the cadmium-exposed group, rats in 7 cages (total 18 cages) lost their reproduction capacities, and no pregnancy or delivery was observed (38.89%). Our result showed that the reproductive function of male rats was reduced after chronic exposure to cadmium. Huang et al. (*14*) have found that ip cadmium-treated male mice lost their reproductive abilities. Our results confirm this finding.

Table 1
Tissue Cadmium Levels of Rats (μg Cadmium/g Wet Wt)[a]

Experimental groups	Liver	Kidney	Testis
1 Controls (n = 3)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
2 Fertile cadmium treated (n = 5)	0.139 ± 0.003	0.976 ± 0.070	0.000 ± 0.000
3 Infertile cadmium treated (n = 5)	0.213 ± 0.014	1.009 ± 0.034	0.000 ± 0.000
Significance[b]	$P < 0.001$	$P > 0.05$	

[a]Means ± SE.
[b]Difference between groups 2 and 3.

In conclusion, the effect of cadmium in testis on chronic exposure with diet needs more detailed studies. Further studies must focus on the effects of duration on chronic exposure and concentration of cadmium in the diet, and on the elucidation of the biochemical mechanisms of cadmium-induced testicular damage.

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