Effects of Aqueous and Dietary Cadmium on Rat Growth and Tissue Uptake

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Various effects of chronic cadmium exposure on laboratory rats have been reported. SCHROEDER and BALASSA, (1963), found that 5 ppm cadmium salts in aqueous solution caused increased body weight at 60 days, but not thereafter. DECKER, et al., (1958), found that concentrations of cadmium ranging from 0.1-10 ppm in aqueous solution did not significantly alter growth patterns. Significant stunting was observed when cadmium was fed as a dietary supplement in concentrations of 31 ppm (WILSON, et al., 1941). The same effect was noted when dietary concentrations were increased to 100 ppm (BANIS, et al., 1969).

Investigations concerning the effect of dietary cadmium at the FDA/WHO maximum limit (5 ppm) have not been performed. Also, the possibility that aqueous cadmium might constitute a different hazard to human health than does dietary cadmium has not been investigated.

This investigation was undertaken to answer these questions.

MATERIALS AND METHODS

Sixty weanling brown rats (O.S.U. strain) were randomly divided into three groups, 10 males and 10 females each. The animals were maintained individually in galvanized cages in an air conditioned room. Lighting was on a 12 hour cycle (12 on, 12 off). Food and water were available ad libitum.

Group 1 (BASAL) was fed a ground commmercial laboratory chow[1] and distilled water. Group 2 (CAD) was fed the same basal ration, but 5 mg cadmium (as $CdCl_2$)/liter was added to the distilled water. The third group of animals (CDDIET) was fed the basal ration, which contained 5 mg cadmium (as $CdCl_2$)/kg, and distilled water. Weekly records of body weights were kept for 10 weeks. Growth curves slopes were computed using linear regression analysis.

Composite samples of the basal ration were periodically analyzed for cadmium content. Samples were dried, weighed,

[1] Purina Laboratory Chow®, Ralston Purina Company, Checkerboard Square, St. Louis, Missouri.

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and then wet-ashed in 5 ml HNO_3 and 3 ml $HCLO_4$. The samples were dried, redissolved in 2 ml 0.1 N HCL, and analyzed by atomic absorption spectrophotometry[2] (Jarrell-Ash sensitivity for cadmium = .005 ppm.)

Tissue Concentration Studies. Four animals from each of the above groups were sacrificed at six month intervals and their tissues and fluids analyzed for cadmium content. Sample times (after being placed on the respective diets) were 0, 6, 12, and 18 months. Tissues and fluids analyzed included liver, kidney, heart, blood and urine.

Analytical procedures were the same for tissues as for diet samples. Since only the liver and kidney showed any definite accumulation patterns for the metal, the values for other organs are not reported. Tissue accumulation rates were computed by regression analysis and reported as slopes of the resulted regression lines.

RESULTS

Growth Studies. The magnitudes of the regression line slopes of the growth curves are shown in TABLE 1. The growth rate of CAD males (23.97±1.14 gm/wk, R^3=.90) was significantly less than the growth rate of BASAL animals (27.48±0.73 gm/wk, R=.98) and CDDIET (28.81±0.94 gm/wk, R=.96) of the same sex ($p<0.75$ and $p<.025$, respectively). Although the growth rate of CDDIET males exceeded that of BASAL males, the difference was not significant. No difference in growth was observed among any test group of females.

Tissue Accumulation Studies. The magnitudes of the regression slopes for tissue accumulation of cadmium are shown in TABLE 1 for liver tissues and kidneys. In the liver, CAD animals accumulated cadmium at a rate which was nearly two and one-half times greater than that of the CDDIET animals (1.34±0.25 µgm Cd/gm dry wt/mo, R=.81 as compared to 0.57±0.08 µgm Cd/gm dry wt/mo, R=.87) ($p<.001$). BASAL animals also accumulated the metal (0.02±0.01 µgm Cd/gm dry wt/mo, R=.62) principally from the 0.2 ppm cadmium present in the basal ration.

Cadmium retention rate in the kindey of both CAD and CDDIET rats far exceeded the rates found for their livers. The rate for accumulation in the kidneys of CAD animals (5.23±0.58 µgm/gm dry wt/mo, R=.92) was more than two and one half times the rate for CDDIET animals (2.00±0.25 µgm/gm dry wt/mo, R=.90) ($p<.001$).

Animals on basal ration accumulated cadmium at the rate of 0.08±0.02 µgm/gm dry wt/mo, with a regression coefficient (R) of 0.72. No sex differences were observed in the accumulation rates of the experimental animals.

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[2] Jarrell-Ash Company, 590 Lincoln Street, Waltham, Massachusetts.

[3] R = regression coefficient.

TABLE 1.

Magnitudes of regression slopes for rat growth rates for 10 weeks and tissue accumulation rates for 18 months (± std. error).

	Growth rate[a] (gm/week)	Cadmium accumulation rate (µgm cd/gm dry wet/mo)	
		Liver[b]	Kidney[c]
BASAL	27.48±0.73	0.02±0.01	0.08±0.02
Cadmium in diet (5 mg Cd/kg) (CDDIET)	28.81±0.94	0.57±0.08	2.00±0.25
Cadmium in water (5 mg Cd/liter) (CAD)	23.97±1.14	1.34±0.25	5.32±0.58

[a] BASAL > CAD ($P < .075$), CDDIET > CAD ($P < .025$), NSD between BASAL and CDDIET.

[b] CAD > CDDIET ($P < .001$), CAD > BASAL ($P < .001$), CDDIET > BASAL ($P < .001$).

[c] CAD > CDDIET ($P < .001$), CAD > BASAL ($P < .001$), CDDIET > BASAL ($P < .001$).

DISCUSSION

The relative differences between the growth rates of animals fed aqueous cadmium and control diets shown in this study conflict with the results of previous studies. SCHROEDER, et al, (1), have shown that the growth rate of test animals relative to control animals was increased by aqueous cadmium. However, much of the observed difference could be attributed, as discussed by that author, to the slow growth rate of the control animals.

DECKER, et al., (2), reported no difference when comparing the growth curves of animals on diets of aqueous cadmium ranging from 0 to 10 ppm cadmium. It should be recognized, however, that the values reported were body weights and not growth rates. Also, the initial weights of the animals of 100 grams is heavier than the weanling rats usually used for growth studies. The task of discerning growth differences for the very young rat, who might be most affected, would be extremely difficult.

One feature which both studies had in common was the high protein diets fed. Although the diets were not identical, the protein content in each was similar. Since low protein diets have been shown to enhance cadmium toxicity (SUZUKI, et al., 1969) perhaps a high protein diet has the opposite effect.

More important than differences between different studies, is the observation that when cadmium is administered at the same level as a solid supplement or as an aqueous supplement, a difference in toxicity occurs within groups of rats even though they are fed the same basic food and water, are maintained the same, and are genetically similar.

That cadmium supplementation affected the growth of males, but not females, indicates that the physiological differences of the two sexes has some effect on the toxicities of the metal. The difference in observed effects may be attributable to hormone differences or, possibly, to the shorter growth period of the female. Perhaps a threshold body burden is necessary before growth depression can be observed. Since females have a smaller weight gain differential from weaning to adult than males, the threshold dose may not have been achieved. The accumulation rate of the metal, however, would not be effected by such an occurrence. The female, being smaller, would eat less than the male, thus, the intake of the metal would be a function of size. The reduction in food intake by the females is compensated for by smaller tissue weights, affecting a rate of accumulation comparable to that of the males.

The relative toxicity of aqueous to solid cadmium is demonstrated by the increased accumulation rate of the metal in the liver and kidney of the animals in the CAD group over that of the animals in the CDDIET group. Since the toxicity of the metal is related to the accumulation rate which in turn is dependent upon the absorption rate, it may be concluded that some process within the intestine of the test animals is discriminating against cadmium which is ingested simultaneously with solid food.

One possible explanation is that, gram for gram, more water is consumed than is solid food over the same period of time. Food and water measurements over a period of time showed that 1.5 times as much water was consumed by these rats as was solid food. This, however, does not sufficiently explain the two and one-half fold difference in accumulation rates in the livers or kidneys of the two test groups of animals.

A second explanation concerns the physical state of the digestive tract during the time of ingestion. If cadmium were ingested simultaneously with solid food, many large organic molecules would be present which might serve as ligands and bind much of the cadmium present. If these molecules are not absorbed due to size or some other consideration, the cadmium attached to the molecule will be passed through the body and eliminated.

Since water intake does not necessarily coincide with solid food intake, the number of large molecules in the digestive tract would be much less, thus less cadmium would be bound, allowing more cadmium to be absorbed by the intestine.

It is likely that neither explanation is entirely correct, but rather, a combination of factors accounts for the differential absorption of the metal.

This study has shown that the growth rates and tissue cadmium accumulation rates differ between aqueous and solid cadmium salts. Since most of the work correlating cadmium to hypertension has employed water as the cadmium carrier, the resulting hypertension may be the result of both the method of administration and the level of cadmium fed rather than just the latter. Since man's greatest source of cadmium is through ingestion of contaminated foodstuffs (SCHROEDER and BALASSA, 1961), the development of hypertension should be investigated using solid foods as the cadmium vehicle.

This study has also implied that dietary levels of cadmium at the FDA/WHO maximum permissible concentration may result in an accumulation rate which would greatly increase the body burden of cadmium over that of the present standard man. More uptake and retention studies on various species should be performed and the resulting information might then be utilized to re-evaluate the FDA/WHO maximum limit for cadmium in foodstuffs.

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