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Influence of Cadmium on Two-Kidney Goldblatt Hypertension in Dahl Rats[1] (40194)

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Cadmium has been implicated in the etiology of "essential" hypertension in man (1). Experimental studies have indicated that cadmium administered intraperitoneally induces persistent hypertension in rats (2), and that the feeding of cadmium has a synergistic effect on renal ischemic hypertension (3). In this laboratory we have evolved two unique lines of rats, by selective inbreeding, from a common pool of Sprague–Dawley ancestors. They are designated Dahl hypertension-resistant (R) and hypertension-sensitive (S) lines according to their resistance or susceptibility to developing hypertension in response to the following: excess NaCl ingestion; deoxycorticosterone acetate (DOCA) plus NaCl; uninephrectomy without NaCl; adrenal regeneration with NaCl; cortisone without NaCl; psychic stress; and cadmium (4–6). Since S rats were found to respond to unilateral renal artery constriction (two-kidney Goldblatt procedure) without additional dietary NaCl by showing severe hypertension, whereas R rats respond only mildly (7), it appeared desirable to investigate the effect of intraperitoneal cadmium injection on the course of two-kidney Goldblatt hypertension in Dahl rats.

Materials and methods. All the rats used in this experiment were from the two Dahl lines described above. Details on care, housing, and blood pressure measurements as well as the rationale for defining "hypertension" have been published (8); therefore, only pertinent items relevant to the current study are included. Seven-week-old male rats were used, 12 R and 12 S. After their systolic blood pressures were measured under light ether anesthesia by tail plethysmography, a sterling silver clip with an internal diameter of 0.2 mm was applied on the exposed right renal artery (9), the left kidney and its circulation being left intact. The rats were then divided into two groups as follows: (a) cadmium (6 R and 6 S) and (b) control (6 R and 6 S). The rats in the cadmium group were injected ip with 2 mg of cadmium (as the acetate) per kg of body weight at a concentration of 1 mg cadmium/ml 0.9% aqueous NaCl (saline), and the controls were injected ip with the same volumes of saline. Specially ordered low salt (0.4% NaCl) food (0.08 μg cadmium/g wet weight) and tap water (0.0006 mg cadmium/liter) were allowed *ad libitum*. At weekly intervals, blood pressure measurements were repeated and weights were measured, since weight loss is a sensitive index of ill health in these rats (8).

Autopsies were done on rats that died or were sacrificed, and body, renal, and hepatic weights were recorded. Cadmium concentrations in renal and hepatic tissues were assayed by atomic absorption spectrophotometry (Perkin-Elmer) after wet ashing (10). Statistical analysis for difference of means was made by Student's t test or by analysis of variance where applicable. The values shown represent the mean ± SEM. A P value < 0.05 was considered significant.

Results. Systolic blood pressure. The data are plotted in Fig. 1. An analysis of variance revealed the anticipated difference, with S rats exhibiting significantly higher ($P < 0.001$) blood pressure than R rats before (0 weeks) and after (1–8 weeks) unilateral renal artery clipping. This confirms our previous findings (7).

Two weeks after clipping and cadmium injection, S rats showed marked elevation of blood pressure, significantly higher ($P < 0.01$) than that of their S controls. This difference continued through the 8th week. No significant difference ($P > 0.05$) in blood pressure was observed between R cadmium rats and their R controls throughout the experiment.

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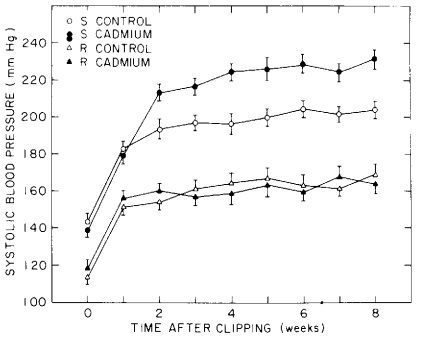

FIG. 1. Effect of cadmium injection on blood pressure in R and S rats with a clipped renal artery. Each symbol represents the mean ± SEM of six animals.

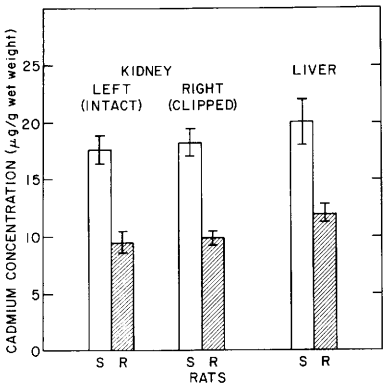

FIG. 2. Cadmium in kidneys and liver of R and S rats injected with cadmium. Each bar represents the mean ± SEM of six animals.

Mortality. Mortality among S cadmium rats started the 9th week after clipping, and there was only one survivor by the end of the week; no apparent cause of death was detected at autopsy. Conversely, R cadmium rats and R and S controls were all alive and healthy when the experiment terminated at the end of the 9th week.

Body, kidney, and liver weights. At autopsy, body weights of the 6 R and the 6 S rats (about 16 weeks old) in the cadmium group (379 ± 6.2 and 383 ± 7.5 g, respectively) and their 6 R and 6 S controls (384 ± 8.1 and 380 ± 6.5 g, respectively) did not differ statistically ($P > 0.05$). The weights of left (intact) and right (clipped) kidneys and of the liver in both lines, regardless of cadmium treatment, were similar ($P > 0.05$), being 0.41 ± 0.03, 0.34 ± 0.02, and 3.8 ± 0.7 g per 100 g body weight ($n = 24$), respectively. Reduction of renal mass in the right kidney was indicated by mean weights only 24–29% of those of the left.

Cadmium in kidneys and liver. In the control group, both lines ($n = 12$) showed the same extent of accumulation of small amounts of cadmium in their left and right kidneys and liver: 0.48 ± 0.21, 0.61 ± 0.32, and 0.53 ± 0.27 μg/g wet weight, respectively. The daily ingestion of food and water containing some cadmium (see Materials and Methods) probably accounted for the presence of cadmium in these tissues. In the cadmium group, the cadmium levels in the kidneys and liver were considerably higher ($P < 0.001$) for S rats than for R rats (Fig. 2).

Discussion. From this study of the effect of cadmium injection on two-kidney Goldblatt hypertension in R and S rats the following conclusions emerge: (a) The rate and degree of hypertension development and the mortality were dramatically increased by cadmium in S but not in R rats. (b) Cadmium concentrations in renal and hepatic tissues were significantly higher for S rats than for R rats.

In observations that seem relevant to ours, Schroeder and associates (3) found that 5 ppm of cadmium in drinking water acted as an accessory factor augmenting ischemic renal hypertension in Long-Evans rats, but they had no explanation for the mechanism involved.

In previous experiments on hypertension due either to high NaCl intake (11) or to renal manipulations including the two-kidney Goldblatt procedure (7), we found that S rats produced a humoral hypertensinogenic factor which was transmitted to R rats in parabiosis and induced hypertension in the latter. We surmised that this factor plays an important role in evoking the fulminating salt or renal hypertension characteristically observed in nonparabiotic S rats (7).

The results of our earlier acute (12) and chronic (6) cadmium studies can be summarized as follows: (a) S rats had greater vascular hyperreactivity to intra-arterially injected cadmium than did R rats; (b) cadmium failed to render the vascular system more sensitive to the pressor action of intra-arterially injected angiotensin II or norepinephrine in both lines; and (c) following ip injections of cadmium, S rats developed sustained hypertension associated with renal vascular changes characteristic of renal hypertension

of moderate degree whereas R rats remained normotensive. These findings indirectly suggested that cadmium may act directly on vascular smooth muscle to cause hypertension in S rats (6).

The results of these parabiosis and cadmium studies combined with those of the current study led us to the following hypothesis: Cadmium, in addition to its hypertensive effect in S rats, accelerates the pathogenesis of hypertension in these rats by enhancing the production and/or release of the humoral hypertensinogenic factor in response to the two-kidney Goldblatt procedure. Since no conclusive evidence is yet available to substantiate such a thesis, further speculation at present would not be rewarding.

It is difficult to explain the difference in cadmium content of renal and hepatic tissues between R and S rats. However, since previous work showed that metallothionein, a cadmium-binding protein of low molecular weight first identified by Kägi and Vallee (13), is synthesized in mammalian tissues following acute or chronic exposure to cadmium (14), it seems reasonable to assume that the difference in cadmium accumulation between the two lines of rats was due to the difference in cadmium-binding properties of their renal and hepatic metallothioneins.

Summary. In Dahl hypertension-resistant (R) and hypertension-sensitive (S) lines of rats, an ip cadmium injection exacerbated two-kidney Goldblatt hypertension and mortality in S but not in R rats. Renal and hepatic cadmium concentrations of S rats were markedly higher than those of R rats. These observations imply that the genetic background critically affects the adverse effects of cadmium on two-kidney Goldblatt hypertension in Dahl rats.

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