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Intrarenal Distribution of Mercury in the Rat: Effect of Administered Dose of Mercuric Chloride

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We recently observed that the distribution of mercury in the hypertrophied remnant kidneys of uninephrectomized rats was different from that in the kidneys of sham-operated rats when given the same non-toxic dose of mercuric chloride ($HgCl_2$; 0.5 μmol/kg) (Zalups and Diamond, 1986). In the hypertrophied remnant kidneys, twice as much mercury (percent of dose/gram tissue) accumulated in the outer medulla than in the cortex, whereas in the kidneys of the sham-operated rats, similar amounts of mercury accumulated in the cortex and outer medulla. These observations are quite significant, since the altered intrarenal distribution of mercury in uninephrectomized rats may cause uninephrectomized rats to develop more severe tubular necrosis in the outer medulla than sham-operated rats. The implication is that animals which have experienced and adapted to a reduction of renal mass may be more vulnerable to the nephrotoxic effects of mercury.

In the experiments described above, the mercury burden of the hypertrophied remnant kidneys from the uninephrectomized rats was approximately twice that of each of the kidneys from the sham-operated rats. Thus, the altered intrarenal distribution of mercury in the uninephrectomized rats may be, in part, the result of the remnant kidney being exposed to more mercury. Implicit in this hypothesis is the idea that the manner in which the kidney accumulates mercury is dependent on the amount of mercury it is exposed to. If this is the case, then one would predict that the intrarenal accumulation of mercury in rats with two kidneys would change as the administered dose of $HgCl_2$ is increased from the dose of 0.5 μmol/kg. The principal aim of this study was to test this hypothesis.

MATERIALS AND METHODS

Fifteen male Long Evans hooded rats weighing 225–275 g were used. The rats were divided equally into three groups of five. Each group was given one of three doses of $HgCl_2$ intravenously. One group received 0.5 μmol $HgCl_2$/kg, a second group received 1.5 μmol

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$HgCl_2$/kg and the third group received 2.5 μmol $HgCl_2$/kg. The respective doses of $HgCl_2$ were given in the form of a solution (2 ml/kg) containing 0.9% NaCl, radioactive $HgCl_2$(1μCi/ml), non radioactive $HgCl_2$ and equimolar cysteine (0.25 μmol/ml, 0.75 μmol/ml or 1.25 μmol/ml). Twenty-four hours after the injections of $HgCl_2$ were given, the content of mercury in liver, blood, right and left kidneys and samples of renal cortex, outer medulla and inner medulla were determined by gamma counting the excised tissues in a well-type gamma counter.

Statistical differences between means of each parameter measured at the three doses of $HgCl_2$ were determined by using one-way analysis of variance followed by Newman-Keuls multiple comparison test. Differences between means were regarded statistically significant when p was less than 0.05.

RESULTS AND DISCUSSION

As the intravenous dose of $HgCl_2$ was increased from 0.5 μmol/kg to 2.5 μmol/kg, the absolute amount of mercury in the kidneys, liver and blood of the treated rats increased significantly (Table 1).

Table 1. Content of Mercury in Kidneys, Liver and Blood of Rats 24 Hours After Single Intravenous Injections of $HgCl_2$

	Mercury in Tissue		
Dose of Administered $HgCl_2$ (μmol/kg)	Total Renal Mass (nmol)	Liver (nmol)	Blood (nmol/g)
0.5	76.7± 4.2	6.4 ± 1.1	0.13 ± 0.04
1.5	208.1 ± 18.6[a]	14.7 ± 2.5[a]	0.34 ± 0.05[a]
2.5	246.3 ± 17.4[ab]	36.8 ± 6.5[ab]	1.31 ± 0.20[ab]

Values are mean ± S.D. of 5 animals.
a = Statistically different ($p < 0.05$) from the corresponding value obtained with the 0.5 μmol/kg dose of $HgCl_2$.
b = Statistically different ($p < 0.05$) from the corresponding value obtained with the 1.5 μmol/kg dose of $HgCl_2$.

The content of mercury in the kidneys, after each dose of $HgCl_2$, was far greater than that in the liver and blood, which is in agreement with the prevailing assertion that the kidney is the major site for the accumulation of mercury (Clarkson, 1972; Rothstein and Hayes, 1960). The increases in the content of mercury in the kidneys, liver and blood, however, were not proportional to the increases in the administered dose of mercury. As shown in Figure 1,

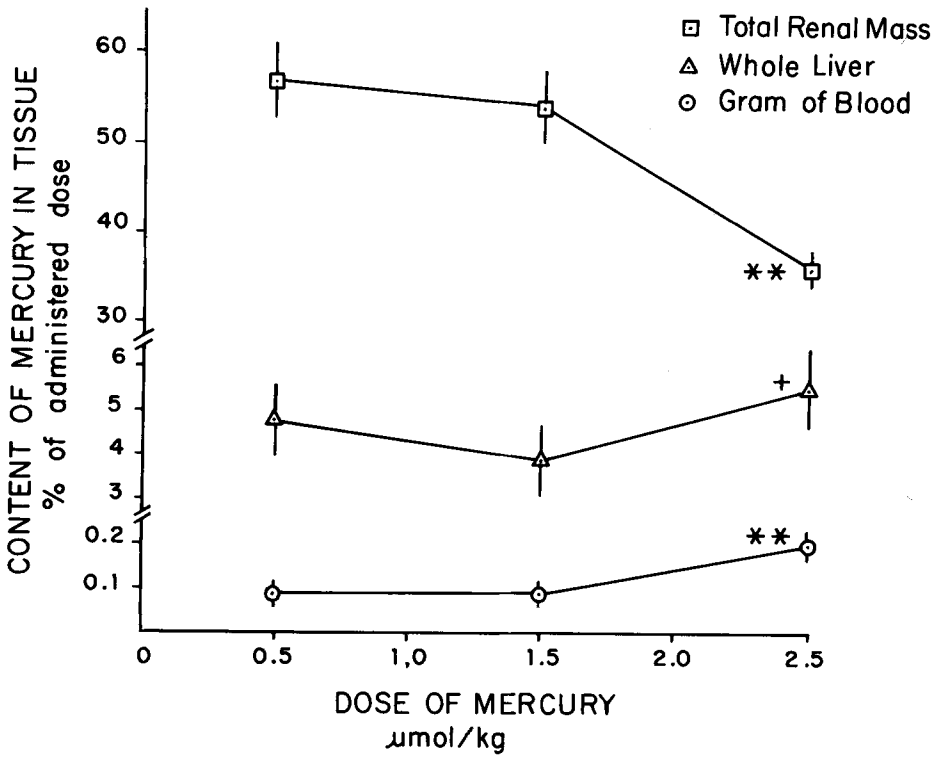

Figure 1. Accumulation of mercury in the kidneys, liver and blood of rats 24 hours after single intravenous injections of 0.5, 1.5 or 2.5 µmol/kg $HgCl_2$. Values are mean ± S.D. ** = significantly different than the corresponding mean value obtained with the 0.5 µmol/kg and 1.5 µmol/kg dose of $HgCl_2$. + = Significantly different than the corresponding mean value obtained with the 1.5 µmol/kg dose of $HgCl_2$.

the percent of the administered dose of mercury that accumulated in the kidneys decreased as the dose of mercury was increased, whereas the opposite appears to have been the case for liver and blood. Similar findings for the kidney have also been reported by Taugner et al., 1966. Thus, as less of the administered dose of mercury accumulated in the kidneys with larger doses of mercury, it appears that more mercury was made available for other sites of accumulation, such as the liver and blood.

Profound changes also occurred in the intrarenal distribution of mercury as the dose of mercuric chloride was increased (Figure 2).

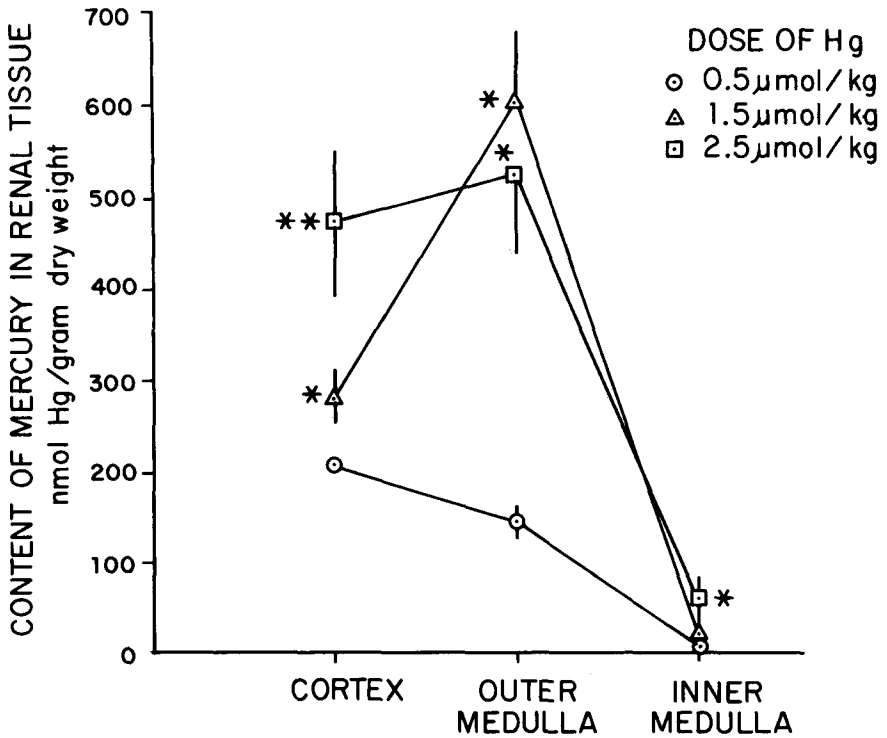

Figure 2. Distribution of mercury in the kidneys of rats 24 hours after the administration of single intravenous injections of 0.5, 1.5 or 2.5 µmol/kg dose of $HgCl_2$. Values are mean ± S.D. * = significantly different than the corresponding mean value obtained with the 0.5 µmol/kg dose of $HgCl_2$. ** = Significantly different than the corresponding mean value obtained with the 0.5 µmol/kg and 1.5 µmol/kg dose of $HgCl_2$.

At the 0.5 µmol/kg dose of $HgCl_2$, slightly more mercury accumulated in the cortex (205 ± 11 nmol/g, mean ± S.D.) than in the outer medulla (142 ± 14 nmol/g), and very little mercury accumulated in the inner medulla, which is consistent with that observed previously in sham-uninephrectomized rats given the same dose of mercury (Zalups and Diamond, 1986). When the administered dose of mercury was increased to 1.5 µmol/kg, twice as much mercury accumulated in the outer medulla (603 ± 81 nmol/g) than in the cortex (280 ± 28 nmol/g), despite the fact that the amount of mercury in the cortex was significantly greater than the amount of mercury found in the renal cortex of rats treated with 0.5 µmolHg/kg. As with the lowest dose of $HgCl_2$, comparatively little mercury accumulated in the inner medulla (18 ± 11 nmol/g). It is

particularly interesting that the hypertrophied remnant kidneys in uninephrectomized rats given a 0.5 μmol/kg dose of $HgCl_2$ also accumulated twice as much mercury in the outer medulla than in the cortex (Zalups and Diamond, 1986). This similarity in findings indicates that the altered intrarenal distribution of mercury in uninephrectomized rats may be due, in part, to the remnant kidney being exposed to a greater amount of mercury than either of the two normal kidneys in the control animals. Finally, in rats given the highest dose of $HgCl_2$ (2.5 μmol/kg), the amount of mercury localized in the outer medulla (550 ± 86 nmol/g) was slightly less than that found at the 1.5 μmol/kg dose of $HgCl_2$. However, the amount of mercury in the cortex (471 ± 76 nmol/g) was almost two-fold greater than that found at the 1.5 μmol/kg dose of $HgCl_2$. The content of mercury in the inner medulla (57 ± 23) was small, but was significantly greater than that found with either of the two lower doses of mercury.

Dose-dependent changes in the intrarenal accumulation of injected mercury have also been reported by Taugner et al., 1966, although their findings are somewhat different from those of the present study. They observed that 24 hours after rats were given single intramuscular injections of $HgCl_2$ at doses of 0.5 - 2.5 μmol/kg, mercury accumulated primarily in the cortex, whereas at doses of 5.0 - 50.0 μmol/kg, mercury accumulated similarily in both the cortex and outer medulla. In one experiment, mercury accumulated mainly in the outer medulla when the 5.0 μmol/kg or 50.0 μmol/kg dose of $HgCl_2$ was administered by means of an intraperitoneal injection rather than an intramuscular injection. This finding of Taugner et al. indicates that the route for the administration of mercury may also be a factor that affects the intrarenal distribution of mercury. Differences in the manner by which mercuric chloride was injected may also account for the disparity in findings between the study by Taugner et al. and the present study. One point that is in common with both the study by Taugner et al. and the present study, is that as the dose of $HgCl_2$ was increased, mercury accumulation in the outer medulla increased.

To recapitulate, the renal mercury burden and the intrarenal distribution of mercury changed markedly as the administered dose of $HgCl_2$ was increased from 0.5 to 2.5 μmol/kg. Increasing the dose of $HgCl_2$ from 0.5 to 1.5 μmol/kg caused the renal mercury burden to increase from 77 ± 4 nmol Hg to 208 ± 18 nmol Hg, and caused the pattern of mercury accumulation to shift from one in which more mercury accumulated in the cortex than outer medulla to a pattern in which twice as much mercury accumulated in the outer medulla than cortex.

Incorporating the present findings with the results from our previous study (Zalups and Diamond, 1986), it appears that associated with raising the renal mercury burden, by either increasing the dose of $HgCl_2$ or by uninephrectomy and compensatory renal growth, the renal handling of mercury changes in a manner such that a greater fraction of the mercury burden of the kidney is accumulated in the outer medulla.

Changes in the intrarenal accumulation of mercury may be highly significant to the expression of mercury-induced nephrotoxicity. Injections of $HgCl_2$ primarily result in damage to the pars recta segment of the proximal tubule (Cuppage and Tate, 1967; Gritzka and Trump, 1968; Verity and Brown, 1970), which is located mainly in the outer medulla. Thus, an increased mercury burden in the outer medulla could reflect increased exposure of the pars recta segments of proximal tubules to mercury and might result in enhanced toxicity to this region of the kidney. In support of this hypothesis, we have determined that the severity of mercuric chloride-induced damage to the pars recta segments of proximal tubules is increased in rats following unilateral nephrectomy and a period of compensatory renal growth. A more thorough understanding of the mechanisms that determine the renal accumulation of mercury may yield a better understanding of the mechanisms of mercury-induced nephrotoxicity.

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