which could be discerned histologically or physiologically, or both (3). Lithium is known to inhibit antiuretic responsiveness of the collecting duct resulting in nephrogenic diabetes insipidus (4). Before the hypothesized neural mechanism of polydipsia is accepted the direct renal effects of lead should be ruled out.

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References

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There are important implications inherent in Wedeen’s comments (1) that we attempted to address in our report (2). First, to say that we administered “massive oral doses of lead” (1) does not allow for the fact that only a portion of this dose was absorbed by the rats, as manifested by the fact that blood lead levels 24 hours after the last dose were usually between 90 and 150 μg/dl. The dose of 200 mg per day used in our model of administration to the neonate was chosen because it was the highest one at which we found no difference in body weight between treated and control rats when the animals were 60 days old (2). At the cessation of lead treatment (30 days of age), there was ample evidence of lead exposure in treated animals. Free erythrocyte protoporphyrin (FEP) values were more than doubled, and there appeared to be a small, but significant, increase in urine production and water consumption. As expected, there were large increases in blood and renal lead concentrations. Morphologically, there were increases in both numbers and size of vacuoles in the proximal convoluted tubules in the lead-treated animals, but there were no observable lead inclusion bodies.

However, within 30 to 60 days after cessation of lead treatment, these alterations disappeared, or were significantly attenuated. Basal water consumption and urine production did not differ between groups [see (2)], nor did urine protein, pH, specific gravity, or urobilinogen. FEP was still slightly elevated (about 20 percent) at 60 days as were concentrations of lead in the blood (20 μg/dl for the treated rats as opposed to 6 μg/dl for controls). Renal lead concentrations, which were 8.8 parts per million (ppm) at 30 days of age, were less than 4 ppm at 60 days of age. This is interesting because it was demonstrated (3) that aminoaciduria and renal edema do not occur until renal lead levels exceed 10 ppm.

As we reported (2), lithium administration caused greater increases in water consumption in the 60-day-old (or older) lead-treated rats, with concomitant increases in urine production. However, there were similar increases in urine protein and pH and decreases in urine specific gravity in both lead-treated and control animals. Prior to lithium administration, there were also no differences between 60-day-old (or older) lead-treated and control rats in water consumption (2), or urine production or composition. Further, light or electron microscopic evaluation of lead-treated and control animals at 60 days of age revealed no difference in renal morphology.

These data demonstrate that no alteration occurred in kidney function that would directly explain the increased lithium-induced polydipsia (LIP). The increased LIP in neonatally lead-treated rats persisted unattenuated for at least 180 days, at which time neither blood nor soft tissue lead content differed between control and treated groups (2). In contrast, in recent experiments when we administered still greater quantities of lead to older rats (lead given from postnatal days 30 to 60) we found no evidence of increased LIP when the animals were tested at 90 days of age (4). These data clearly demonstrate that the change responsible for altered LIP is permanent, and that the “lesion” must occur during early postnatal development. Further, since the 30- to 60-day exposure would also be expected to cause kidney damage, it appears that altered renal function is not the most likely mechanism. Until a precise locus for effects of lead on LIP is found, we cannot rule out the possibility that lithium administrations cause a latent kidney pathology. However, since renin secretion from the kidney is an important homeostatic step in the maintenance of fluid and electrolyte homeostasis, the fact that we found no differences in plasma renin activity (PRA) or angiotensin I or II concentrations between lead-treated and control animals, either before or after lithium challenge (2), provides further evidence that differences in kidney function were probably not the causal mechanism for our observation. Both the control and the lead-treated rats showed the expected large increases in PRA after lithium treatment (2), but they did not differ from each other.

We therefore think that our statement that “there may be permanent neural changes induced by postnatal exposure to lead” is reasonable and is the most probable explanation for our results. We are aware of the many unanswered questions related to lithium actions in the central nervous system, as well as the peripheral-central interactions involved in fluid-electrolyte homeostasis. Additional research will be necessary to answer definitively the interesting questions raised by this action of lithium in rats treated with lead as neonates.

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4. In these experiments, rats were intubated with, per kilogram of body weight, 400 mg of lead (as the acetate) from days 30 to 45. From 45 to 60 days, they had sufficient lead acetate placed in their drinking water to approximate an exposure of 400 mg/kg. These rats had blood levels greater than 400 μg/dl at 45 days and greater than 100 μg/dl at 60 days of age. In three separate experiments utilizing two litters each, no differences in LIP was found when testing was done at 90 days of age.
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