LIGHT AND ELECTRON MICROSCOPIC OBSERVATIONS IN KIDNEY OF MATERNAL AND FETAL HAMSTER AFTER MATERNAL DOSING WITH 2,3,7,8-TCDD

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ABSTRACT

In a previous paper we reported that although LD 50 values for 2,3,7,8-TCDD in rat are 2-66 ug/kg body weight and in hamster are 1,157-5,051; the toxic potency of TCDD is similar in fetal rat and hamster. In this paper we report on light and ultrastructural changes in fetal hamster kidneys following a single dose of TCDD in corn oil from 0 to 18 ug/kg p.o. to the pregnant female on gestation day 9 of a 16 day gestation cycle with sacrifice on day 15. Vascular congestion, hemorrhage, edema, mitochondrial damage and intracellular lipid droplets are described in TCDD treated animals, at 1.5 and 6.0 ug/kg maternal dosing.

INTRODUCTION

We presented findings at Dioxin '89 of similar toxic potency for reproductive effects in rat and hamster from 2,3,7,8-TCDD, despite almost a 100-fold difference in LD 50 values between these two species. Fetal mortality, hemorrhaging in the gastrointestinal tract, edema and renal congestion, and cleft palate were described in that paper, as well as dose-related decrease in fetal thymus and spleen weight/size. We noted developmental toxicity occurs at doses far below those associated with acute toxicity in mature animals. Here we present light and electron micrographs with more subtle expression of morphologic lesions consistent with dioxin sensitivity.

METHODS

Timed-pregnant Golden Syrian hamsters were obtained from Harlan Sprague Dawley, Inc. Pregnant animals were dosed at 0, 1.5, 3.0, and 6.0 ug/kg for this portion of the study. Immediately after sacrifice, tissue for electron microscopy was preserved by immersion in cold Karnovsky's fixative followed by osmium post fixation. Material was dehydrated, embedded in epoxy resin, sectioned at 500-1000 angstroms and stained with uranium and lead salts. Specimens were observed and photographed in a Philips electron

microscope at a 50 KV setting. Light micrographs were obtained from 0.5 micron sections stained with toluidine blue and photographed on a Nikon microscope.

RESULTS

Figures 1 and 2 are light micrographs of fetal kidney at doses of 1.5 and 6.0 ug/kg maternal dose. On the left of Fig. 1 can be seen numerous red cells, in an intercellular space, consistent with congestion or, more probably, hemorrhage, since endothelial cells are not seen. One glomerulus and numerous proximal and distal tubules appear relatively intact. In Figure 2, numerous red blood cells can be seen packing blood vessels, especially in the upper left and right of the micrograph. To the left, the empty intercellular space is consistent with edema, but is also characteristic of fetal tissue as compared with maternal.

Figure 3, an electron micrograph of a capillary and proximal convoluted tubule, shows swollen, sick looking mitochondria, and dilated cistrernae of the endoplasmic reticulum. The brush border is well preserved, however, as are nuclei and the blood vessel.

Figure 4 is an electron micrograph of fetal hamster kidney showing, in the glomerular podocytes or visceral epithelial cells, the round electron-dense droplets of lipid characteristic of dioxin's intracellular effects, by alteration of lipid metabolism. Rough endoplasmic reticulum, ribosomes, mitochondria and nuclei appear unremarkable in this micrograph.

CONCLUSIONS AND DISCUSSION

This paper extends the finding previously published on developmental toxicity of 2,3,7,8-TCDD to morphology of fetal hamster. It defines light and electron microscopic characteristics seen following exposure to dioxin in utero. The findings extend previously known biomarkers of exposure and sensitivity to dioxins in adults to the fetus in a species which, by LD 50 acute toxicity data, had been considered relatively insensitive to TCDD. Thus, not only TCDD-induced liver enzyme induction, as shown by Gasiewicz, is similar in hamster adults to more sensitive species, but also morphological biomarkers of exposure to dioxins are seen at relatively low doses in fetal hamster kidney.

REFERENCES

1. Olson, J. R., McGarrigle, B. P., Tonucci, D. A., Schecter, A., Eichelberger, H. Toxicity of 2,3,7,8-TCDD in the developing rat and hamster (1990) Chemosphere (In Press)

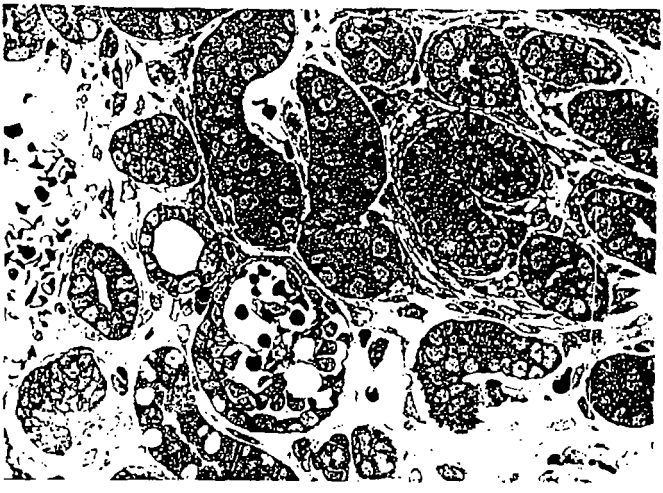

Figure 1. Light micrograph. Fetal hamster kidney, 1.5 ug/kg maternal dose of TCDD. Numerous red blood cells can be seen on the left, showing apparent hemorrhage in cortex. One glomerulus and the proximal and distal convoluted tubules appear intact.

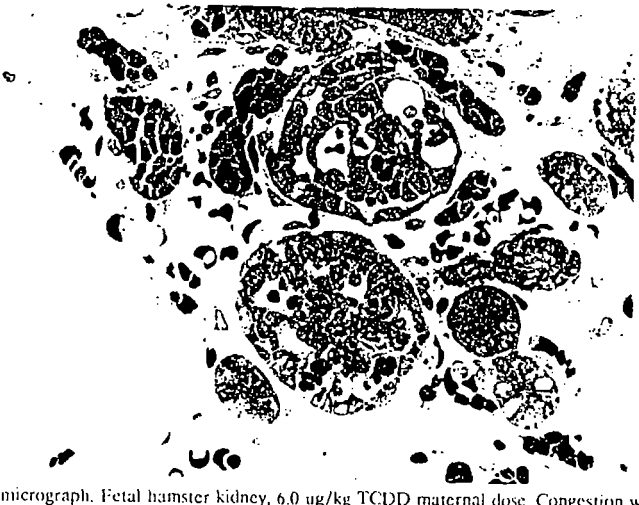

Figure 2. Light micrograph. Fetal hamster kidney, 6.0 ug/kg TCDD maternal dose. Congestion with red blood cells can be seen in capillaries in the top, middle and bottom of the micrograph. The relatively large intercellular space appears to be exaggerated beyond the usual fetal state in a fashion consistent with edema noted on gross examination.

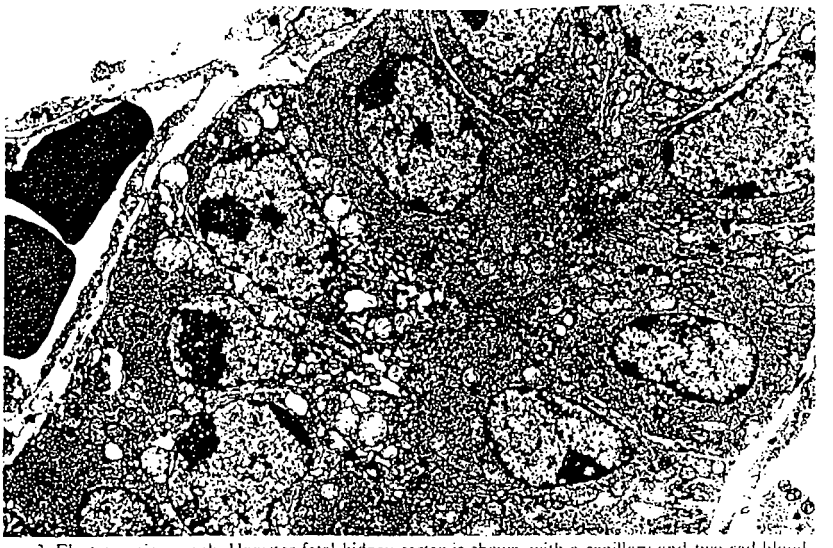

Figure 3. Electron micrograph. Hamster fetal kidney cortex is shown, with a capillary and two red blood cells on the left and a proximal convoluted tubule on the remainder. Swollen, distorted mitochondria with loss of internal structure, of cristae, matrix and granules are noted, as is swollen endoplasmic reticulum.

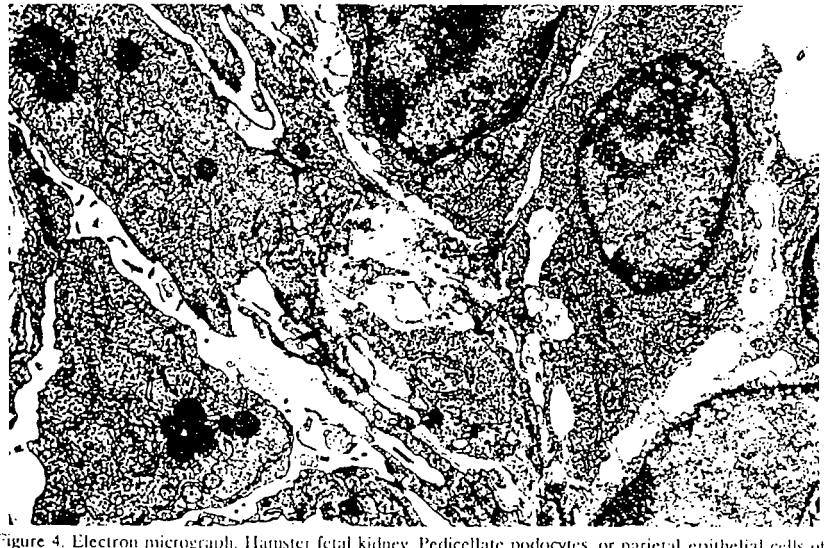

Figure 4. Electron micrograph. Hamster fetal kidney. Pedicellate podocytes, or parietal epithelial cells of the glomerulus, are seen in this view of the renal cortex. Prominent dense-staining lipid droplets characteristic of dioxin exposure are seen, especially to the left of the micrograph. Nuclei, mitochondria, and endoplasmic reticulum here are intact.