Prenatal and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) impairs renal development in offspring of rhesus monkeys

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Introduction

Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) results in wide variety of effects including immunological dysfunction, teratogenicity and carcinogenesis1-4. In utero and lactational exposure to TCDD induces developmental abnormality in the brain and reproductive tissue of female offspring5, 6. Renal involvement by TCDD toxicity has been reported in rodents, horses, and cats7. Prenatal exposure to a high dose of TCDD is known to induce hydronephrosis in the mouse8. Considering the pronounced difference between species observed in some previous studies, effects of low dose of TCDD on development of the kidney in non-human primate were investigated in the present study after subcutaneous administration of TCDD into rhesus monkeys during pregnancy and lactation. The results showed a peculiar form of interstitial and peripelvic fibrosis with tubular and glomerular dysgenesis in the kidney of rhesus monkey offspring.

Materials and Methods

TCDD was purchased from Wellington Laboratories Inc., Guelph, Ontario, Canada) and was dissolved in a mixture of toluene/dimethylsulfoxide (DMSO;1:2, v/v) at Kanto Kagaku Co., Ltd. (Tokyo, Japan). Final concentrations were confirmed by gas chromatography. Colony bred adult female rhesus monkeys (age, 3-10 years; weight, 4-7kg) were purchased from China National Scientific Instruments & Materials Import/Export Corporation (Beijing, China).

TCDD (0, 30, 300ng/kg of body weight) was subcutaneously administrated to pregnant female monkeys on gestation day 20 (GD20), followed by injection with 5% of the initial dose every 30 days during pregnancy and lactation until GD90. Offspring that died by postnatal day (PND) 1100 were necropsied and examined macroscopically and histopathologically. Electron microscopic observation was also done. Renal tissue specimens were examined with quantitative image analysis (Win Roof, Mitani Corporation, Fukui, Japan) for fibrosis after picrosirius red stain. Immunohistochemical staining was performed on paraffin-embedded renal tissues using MAX-PO kitt (DakoCytomation, Glostrup, Denmark) and anti-vimentin (DakoCytomation), anti-alpha-smooth muscle actin (SMA) (DakoCytomation), anti-lymphocyte common antigen (LCA)(DakoCytomation) antibodies.

Results and Discussion

Numbers of dams in each group (0, 30, 300ng/kg) were 23, 20, and 20, respectively; live births, 18, 15, and 16; postnatal deaths, 6, 3, and 9. The cause of postnatal death included pneumonia in one monkey and renal failure in two. Renal interstitial and peripelvic fibrosis with or without atrophic papilla (Figure 1,2) was found in 5 (56%) of 9 offspring of dams exposed to relatively high dose of TCDD (300ng/kg), which were alive until PND1 to 465. The renal lesion was associated with renal tubular damage and function failure. Tubular and glomerular dysgenesis was also indicated. Electron microscopic observation showed interstitial collagen deposition and loss of renal tubuli. Quantitative image analysis disclosed significant increase in sirius-red positive areas within the renal cortex, medulla, and hilus. An immunohistochemical study revealed predominant proliferation of vimentin-positive fibroblasts, not SMA-positive myofiboblast, in these lesions. LCA-posive lymphocyte infiltration was minimal. No remarkable abnormalities were detected in the kidneys of 6 offsping of controls and 3 offspring of dams exposed to

relatively low dose (30ng/kg) of TCDD.

Although it has been reported that low doses of TCDD cause myocardial fibrosis in marmosets[9], severe renal fibrosis found in offspring of rhesus monkey in the present study might not be directly induced by TCDD transferred from dams into offspring via placental blood or breast milk[10]. But it might be rather a secondary change which might follow abnormal renal differentiation including dysgenesis or loss of nephrons because it is known that TCDD induces hydronephrosis without severe fibrosis in offspring of mice and, in addition, both renal dysgenesis and hydronephrosis without severe fibrosis is evident in kidneys of transgenic mouse models with developmental anomaly[11-13]. This study is ongoing. We will be able to examine renal changes in still alive offspring in the near future.

In conclusions, this is the first report that describes a peculiar form of renal interstitial and peripelvic fibrosis with nephron dysgenesis developed in offspring of rhesus monkeys exposed during prenatal and lactational period to TCDD. The renal lesions developed exclusively in offspring of dams exposed to relatively high dose (300ng/kg) of TCDD.

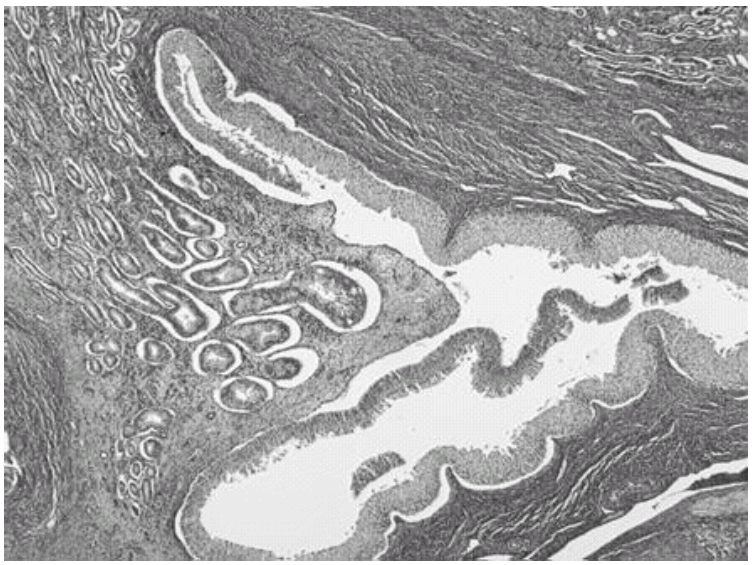

Figure 1. Interstitial and pericalyceal fibrosis with atrophic papilla in the kidney of rhesus monkey offspring.

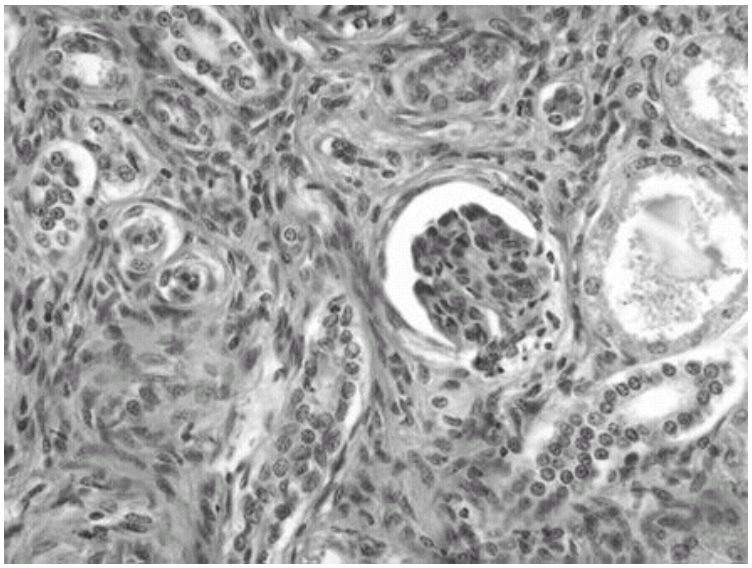

Figure 2. Interstitial fibrosis with sclerosing glomeruli and destruction or loss of renal tubuli in the kidney of rhesus monkey offspring.

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