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Effects of Arylhydrocarbon Receptor Gene on Disposition of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin through Pregnancy and Lactation in Mice

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【 **Introduction** 】 The transplacental exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) during developmental stage of fetuses causes reproductive disorders. Arylhydrocarbon receptor (Ah-R) gene has an important role on the fetal toxicity in mice. Recently, it was shown that cleft palate was not caused in Ah-R knockout fetuses by transplacental TCDD exposure. We also observed that decrease of anogenital distance was not caused in male Ah-R -/- pups after transplacental and lactational TCDD exposure. The present study was conducted to investigate the placental and lactational transfer of TCDD to fetus/offspring among the knockout (Ah-R -/-), hetero (Ah-R +/-) and wild type (Ah-R +/+) mice.

【**Methods**】 Pregnant mice (Ah-R +/-) were given a single oral dose of 10 μg TCDD/kg body weight on gestation day (GD) 12.5. Dams were killed on GD 18.5 or at weaning (postnatal day 21), maternal and fetal tissue, or liver, adipose tissue and kidney of pups were collected. Each sample was weighed, spiked with ^{13}C-2,3,7,8-TCDD as an internal standard, and digested in 2 M potassium hydroxide solution. The digested material was extracted with n-hexane and the extract was washed with concentrated sulfuric acid. The n-hexane layer was concentrated and sequentially subjected to silica gel and active carbon impregnated-silica gel column chromatography. The GC/MS analysis was performed in the selected ion mode with a JMS 700 mass spectrometer that was coupled to an HP 6890 gas chromatograph with CP-SIL 8CB/MS column.

【**Results and Discussion**】 On GD 18.5, the greatest amount ofTCDD in the dam (Ah-R +/-) was found in the liver, followed by adipose tissue. Although TCDD level in each placenta was almost the same, the content of TCDD in fetuses were different among the genotypes (Ah-R +/+ > Ah-R +/- > Ah-R -/-). On postnatal day 21, enough number of Ah-R +/+ pups was not available. Therefore, we compared the TCDD distribution between Ah-R +/- and Ah-R -/- pups. The amount of TCDD in liver of Ah-R +/- pups was 14.3 times higher than that of Ah-R -/-. On the other hand, the amount of TCDD in adipose tissue and kidney of Ah-R -/- pups were 2.5 and 1.8 times higher than that of Ah-R +/-, respectively. Furthermore, CYP 1A1 and CYP 1A2 mRNA had been induced in liver of Ah-R +/- pups by TCDD exposure on postnatal day 21. These results indicated that fetal Ah-R gene affected the placental and lactational transfer of TCDD in mice.