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# Study on the Mechanisms of a Decrease in Circulating Levels of Thyroxine in Response to 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin in Aryl Hydrocarbon Receptor-Null Mice and Transthyretin-Null Mice.

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【 **Introduction** 】 We have previously shown that the gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) perturbed thyroid hormone homeostasis, followed by hyperplasia of thyroid in offspring. The most consistent toxic effect of dioxins on thyroid hormone metabolism is a decreased level of thyroxine (T4) in serum. The increase in biliary excretion of T4-glucronide through induction of UDP-glucronosyltransferase-1 (UGT-1) by dioxins is thought to be responsible for this reduction. However, it is possible that the higher affinities of transthyretin (TTR), a major T4-binding protein, not only for PCBs but also for dioxin might contribute to reduce serum T4. To investigate the mechanism of this reduction after TCDD exposure, aryl hydrocarbon receptor (AhR)-null mice (AhR-/-) and TTR-null mice (TTR-/-) were employed.

【**Materials and Methods**】 AhR heterozygous (AhR+/-) pregnant mice were dosed at 10μg TCDD/kg bw by gavage on gestation day 12, and sera and tissues were collected from male and female offspring (AhR-/- or AhR+/-) on post-natal days (PND) 21. Male TTR-null and wild type mice (13-week-old) were dosed at 10 or 20μg TCDD/kg by gavage, and sera and samples were collected 7days after the administration. Serum levels of thyroxin (T4) and triiodothyronine (T3) were determined with radioimmunoassay. Thyroid stimulating hormone (TSH) was determined by enzyme-linked immunoassay. Induced levels of dioxin-responsive genes, UDP-glucuronosyltransferase-1A6 (UGT1A6) and cytochrome P4501A1 (CYP1A1) in the liver were semiquantified by RT-PCR.

【**Results and Discussion**】 TCDD administration significantly decreased serum total T4 (TT4) and free T4 (FT4) levels but not total T3 (TT3) in AhR+/- mice. In these mice induction of hepatic UGT-1 mRNA and CYP1A1 mRNA was also observed. In contrast, TCDD had no effects on serum TT4, FT4 and TT3 levels and hepatic UGT1A6 gene expression in AhR-/- mice. Interestingly, TT4 levels in TTR-/- mice were approximately 50% of TTR+/+ mice. TCDD administration resulted in a decrease in TT4 and TT3 levels concomitant with induction of hepatic UGT1A6 mRNA in both TTR-/- and TTR+/+ mice. From the present results, we conclude that the reduction of circulating serum TT4 levels by TCDD was caused mainly by an enhanced biliary excretion of T4-glucronide mediated by the AhR, and that TTR was minimally responsible for the reduction by TCDD.