THE RETINOID RESPONSE IN 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN (TCDD)-TREATED LONG-EVANS AND HAN/WISTAR RATS

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Introduction

Long-Evans (*Turku AB*) and Han/Wistar (*Kuopio)* rats constitute an interesting model for the study of TCDD-toxicity by virtue of their remarkable differences in sensitivity to some aspects of TCDD toxicity. Genetic studies showed that the structurally aberrant aryl hydrocarbon receptor (AhR) exhibited by the Han/Wistar strain appears to be the main reason for some of these differences, in particular for acute lethality[1]. The AhR of Han/Wistar is smaller than that of the Long-Evans rat or the Sprague-Dawley rat due to a loss of 43 or 38 amino acids from the carboxyl-terminal end in the transactivation domain of the AhR protein[2].

The AhR appears to be involved in constitutive retinoid homeostasis as indicated by markedly increased levels of retinoic acid, retinol and retinyl palmitate in Ahr null mice[3]. Furthermore, studies of different AhR-ligands show a correlation between tissue retinoid levels and AhR binding affinity[4]. In this study we investigated whether the noted structural differences between the AhR of Long-Evans and Han/Wistar rats influenced retinoid concentrations in tissues of rats following subchronic TCDD dosing.

Materials and Methods

Female Long-Evans and Han/Wistar rats were given TCDD in corn oil by subcutaneous injection once per week for 20 weeks at calculated doses of 0, 1, 10, 100 and 1000 ng/kg bw/day. Control groups were similarly maintained but administered corn oil only. The method of analyses for liver and kidney retinoids has been described previously[5]. Total retinoid concentration describes the sum of retinyl esters and retinol in liver and kidney tissues. Liver TCDD concentrations have been published previously[6].

Results and Discussion

Total hepatic retinoid levels were an extremely sensitive measure of TCDD exposure in both Long-Evans and Han/Wistar rats. However, in the liver of Long-Evans rats significant effects were observed at doses 10-fold lower than those in Han/Wistar rats and the gradient of the dose-response curve was more precipitous (Figure 1a). A modeled curve of liver TCDD concentration and total retinoid content illustrated that toxicokinetic differences do not explain the differences between the two strains for retinoid effects (Figure 1b). Doses at which significant changes in retinoid levels were observed were about 14-fold lower for liver retinoids than those previously observed in a 13-week study feeding study in Sprague-Dawley rats[7]. Meanwhile, total kidney retinoid levels were also slightly, but significantly

increased at 1 ng/kg bw/day for Long-Evans rats and at 10 ng/kg bw/day for Han/Wistar rats, but levels were similar at 100 ng/kg bw/day. In addition, kidney retinol concentrations were significantly increased at 1 ng/kg bw/day for Long-Evans rats and at 100 ng/kg bw/day for Han/Wistar rats (Figure 1d). Increased kidney retinoid concentration appears to be a species specific effect and has been observed in several rat strains following single doses of TCDD, but not in other rodent species including mice, guinea pigs and hamsters[5,8]. An approximate 10-fold difference in sensitivity for the retinoid effect was comparable with other signs of toxicity including enzyme induction and bone toxicity for which up to 10-fold differences have been shown[6,9]. Previously more marked differences have been demonstrated for acute lethality, liver toxicity and bilirubin levels and these differences have been attributed to the altered transactivation domain of the Han/Wistar rat[1,2,6]. At present, it seems plausible that differences in retinoid response may stem from structurally different AhR receptors, or perhaps more probably as a result of somewhat higher concentration of AhR and ARNT in the livers of Long-Evans rats[2].

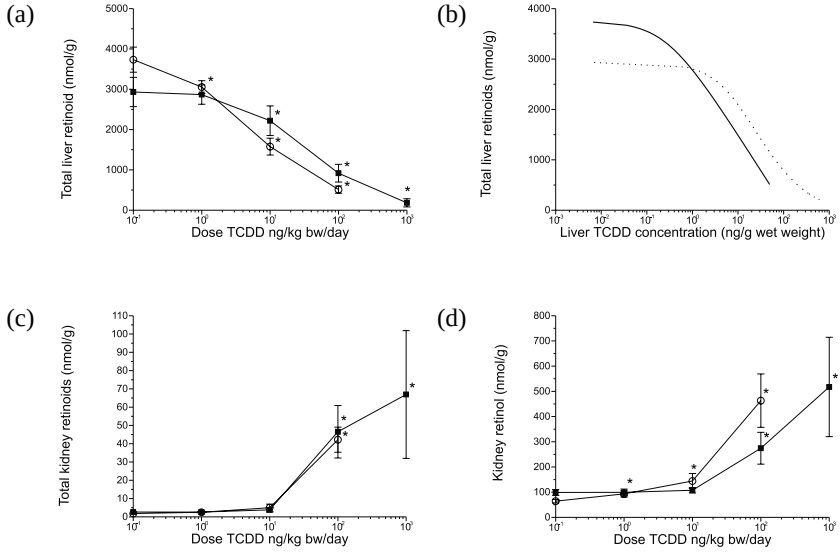

Figure 1. (a) Total retinoid concentration; (b) Total liver retinoid concentration vs liver TCDD concentration (c) Total kidney retinoid concentration (d) kidney retinol concentration for Long-Evans (○, solid line) and Han/Wistar (■, broken line) rats

In conclusion, the data show that TCDD effects retinoid homeostasis at very low doses and in multiple tissues following subchronic exposure, and further suggests the involvement of the AhR in TCDD altered retinoid homeostasis.

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