Dissimilar induction of multidrug resistance (MDR) and cytochrome P450 (CYP) gene expression in the livers of Long-Evans and Han-Wistar rats by TCDD

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The toxicity of TCDD differs dramatically in the Han/Wistar (H/W) and Long-Evans (L-E) rat strains. The H/W rats can resist doses of up to 3000 μg/kg whereas the L-E rats die at the dose level of 20 μg/kg. Several physiological and biochemical parameters have been shown to behave in a similar way after TCDD administration in these rat strains, and a clear explanation for the susceptibility difference is still lacking[1].

Many of the pleiotropic effects of TCDD are mediated via the Ah (Aryl hydrocarbon) receptor. CYP1A subfamily genes are a well-established example of genes controlled by the Ah receptor[2]. TCDD is known to activate the transcription of CYP1A genes after binding to the Ah receptor. Strain and tissue-specific differences in the induction of the genes controlled by the Ah-receptor could explain the susceptibility difference between H/W and L-E rats. However, we have shown previously that the H/W and L-E rat livers contain similar amounts of the Ah receptor and that the CYP1A enzyme catalytic activities and protein levels respond in a similar way to TCDD in these strains[3].

One of the three MDR genes (MDR1b) encodes the plasma membrane-bound p-glycoprotein, which actively transports xenobiotics out of the cell, thus participating in the general detoxification process. High doses of TCDD have been shown to induce MDR genes in the rat liver, and the theory was put forward that induction of MDR gene expression is part of the TCDD-elicited pleiotropic response[4].

To study the effect of TCDD on CYP1A and MDR gene expression we performed Northern blot analysis of RNA extracted from the livers of H/W and L-E rats treated with 5 μg/kg or 50 μg/kg of TCDD. After hybridization with the rat MDR1b cDNA[5], an increased signal could be seen only in L-E rats treated with 50 μg/kg of TCDD. The amount of CYP1A1 mRNA was increased in both strains. In the L-E strain the CYP1A1 signal was weaker with the higher dose of TCDD in comparison with the lower dose. It appears therefore that the expression of MDR and CYP1A genes are dissimilarly affected by TCDD in the H/W and L-E strains.

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