Molecular mechanisms through which 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) interferes with estrogen regulation of PRL gene expression in vivo and in vitro

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Abstract

Polyhalogenated aromatic hydrocarbon (PHAH) belongs to a group of ubiquitous environmental contaminants. Among them, 2,3,7,8-tetrachlorodibenzo- *p*-dioxin (TCDD) is one of the most toxic synthetic chemicals known. It accumulates in adipose tissues of animals and has a biological half-life estimated at 6-12 years in human. As an endocrine disruptor, TCDD affects plasma levels of pituitary hormones including gonadotropins (FSH/LH), PRL (PRL), adrenocorticotropic hormone (ACTH, corticotropin), and thyroid-stimulating hormone (TSH). Most, if not all, of these effects may be related to the ability of TCDD to exert antiestrogenic effects. Therefore the goal of this work was to first use microarrays to identify gene targets of TCDD in the pituitary gland *in vivo* and then use a pituitary-derived cell line to determine the mechanisms underlying TCDD effects on these genes. The work described in my dissertation is the first to demonstrate that TCDD acts directly on rat pituitary lactotropes and gonadotropes to interfere with E_2 regulation of genes encoding PRL and glycoprotein hormones. It is also the first to show that TCDD exerts antiestrogenic activity on the regulation of the PRL gene both *in vivo* and *in vitro,* and that this interference occurs at the transcriptional level. My findings suggest that neither activation of a putative inhibitory dioxin response element, metabolism of E_2 by CYP 1A1 and CYP 1B1 enzymes nor the down-regulation of the AhR is likely responsible for the antiestrogenicity of TCDD. Instead, I found that limitation of ERα, but not ERβ availability, after TCDD co-treatment with E_2 is responsible for the underlying antiestrogenic effects of TCDD on PRL gene expression. My findings suggest that it is likely that several pathways are involved in the ability of TCDD to limit ERα availability for PRL gene transcription. They are decreased ERα levels through down-regulation of ERα gene transcription; degradation of ERα through the ubiquitin–proteasome pathway, and direct interference with E_2-induced ERα binding to an ERE enhancer in the PRL gene promoter. Interestingly, I found that at the same time TCDD interfered with ERα binding and PRL promoter activation, liganded ER enhanced gene targets of the AhR, CYP1A1 and CYP1B1. Based on these findings, I propose a novel model of cross-talk between the AhR and ER that may explain the antiestrogenic activity of TCDD in the regulation of PRL gene transcription. In this model, ligand-activated AhR/ARNT complex may sequester liganded ERα and recruit it to DREs in AhR target genes, thereby limiting availability of liganded ERα for recruitment to ERE sequences in the PRL gene. In addition to providing a novel model to explain antiestrogenic effects of TCDD, my findings that TCDD interferes with PRL and glycoprotein hormone synthesis may explain the broad range of reproductive dysfunctions caused by TCDD exposure during development and adulthood.^

Subject Area

Toxicology

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