2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) AS AN ANTIESTROGEN IN HUMAN BREAST CANCER CELLS: MECHANISTIC STUDIES

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ABSTRACT

The MCF-7 and T-47D human breast cancer cell lines have been characterized as aryl hydrocarbon (Ah)-responsive, whereas the MDA-MB-231 cells are Ah-nonresponsive. Treatment of the MCF-7 and T-47D cells with [^{3}H]-17β-estradiol in the presence or absence of TCDD showed that TCDD caused a downregulation of occupied nuclear estrogen receptor (ER) levels in both cell lines. TCDD also inhibited the 17β-estradiol-induced secretion of the 52-kDa protein in MCF-7 cells but did not effect the secretion of this protein in MDA-MB-231 cells.

INTRODUCTION

TCDD exhibits antiestrogenic effects in rats and mice (1-3) and in long-term feeding studies it was reported that TCDD caused a dose-dependent decrease in the formation of spontaneous mammary and uterine tumors in female Sprague-Dawley rats (4). Gierthy and coworker have shown that TCDD inhibits the 17β-estradiol-induced secretion of tissue plasminogen activator activity (5) and also increases the rate 17β-estradiol hydroxylation in MCF-7 human breast cancer cells (6). This paper briefly summarizes our current research on the mechanism of action of TCDD as an antiestrogen in human breast cancer cell lines.

RESULTS AND DISCUSSION

TCDD causes a concentration-dependent induction of aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin-O-deethylase (EROD) activity in MCF-7 and T47-D cells but

does not significantly induce these enzyme activities in MDA-MB-231 cells (7). Similar results were also observed using 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 1,2,4,7,8-pentachlorodibenzo-p-dioxin (pentaCDD) as inducers and the order of induction potencies (2,3,7,8-TCDD $\geq$ 2,3,7,8-TCDF > 1,2,4,7,8-pentaCDD) were similar to the Ah receptor binding affinities of these congeners (Table 1). In addition, the Ah receptor was identified in the Ah responsive MCF-7 and T47-D cells and the Ah non-responsive MDA-MB-231 cells.

Table 1. Effects of 2,3,7,8-TCDD, 2,3,7,8-TCDF and 1,2,3,7,8-PentaCDD as Inducers of AHH and EROD Activity.

Congener	EC_{50} Values (M)			
	T47-D Cells		MCF-7 Cells	
	AHH	EROD	AHH	EROD
2,3,7,8-TCDD	0.55×10^{-9}	1.5×10^{-9}	3.8×10^{-10}	0.94×10^{-10}
2,3,7,8-TCDF	0.66×10^{-9}	0.15×10^{-9}	1.9×10^{-9}	2.2×10^{-9}
1,2,3,7,8-pentaCDD	1.5×10^{-7}	2.6×10^{-8}	5.1×10^{-8}	7.1×10^{-9}

Treatment of MCF-7 or T47-D cells with [^{3}H]-17β-estradiol resulted in the rapid accumulation of occupied nuclear estrogen receptor (ER) complexes with maximum levels observed one hour after the addition of the radiolabeled hormone (8). Treatment of the cells with TCDD six or twelve hours prior to the addition of [^{3}H]-17β-estradiol, resulted in a concentration-dependent decrease in the nuclear ER levels in both cell lines (8). Moreover, in the MCF-7 cells, the relative potencies of various congeners as antiestrogens paralleled their competitive binding affinities for the Ah receptor (8). These results strongly support a role for the Ah receptor in mediating the downregulation of the nuclear estrogen receptor in Ah-responsive human breast cancer cell lines.

The effects of 2,3,7,8-TCDD and related compounds on several other 17β-estradiol-induced responses have also been investigated in human breast cancer cell lines. The results in Table 2 summarize the concentration-dependent inhibition by TCDD of the 17β-estradiol-induced secretion of the 52-kDa protein (procathepsin D) in MCF-7 cells (9). Similarly, TCDD also inhibited the 17β-estradiol-induced growth and the secretion of the 160- and 34-kDa proteins in MCF-7 cells. In contrast, the inhibitory effects of 2,3,7,8-TCDD were not observed in the Ah non-responsive MDA-MB-231 cell line. These data confirm that the antiestrogenic activity of 2,3,7,8-TCDD and related compounds are mediated through the Ah receptor and the molecular mechanism of this process will be discussed.

Table 2. Effects of 2,3,7,8-TCDD on the 17ß-Estradiol-Induced Secretion of the 52-kDa Protein in MCF-7 Cells[a].

Treatment		Relative Concentration of the
TCDD	17ß-Estradiol	52-kDa Protein (% of Control)
0.1 nM	-	102 ± 4.35
0.01 nM	-	93.1 ± 15.5
0.001 nM	-	87.7 ± 4.89
0.0001 nM	-	103 ± 6.63
-	1 nM	225 ± 27.8
0.0001 nM	1 nM	163 ± 20
0.001 nM	1 nM	126 ± 4.60[b]
0.01 nM	1 nM	103 ± 4.39[b]
0.1 nM	1 nM	94.4 ± 3.80[b]

[a]determined by autoradiographic analysis
[b]significantly lower ($p < 0.01$) than values for the 17β-estradiol-treated cells.

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