

Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Compounds on the Occupied Nuclear Estrogen Receptor in MCF-7 Human Breast Cancer Cells¹

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ABSTRACT

Treatment of MCF-7 human breast cancer cells with 17β -[³H]estradiol resulted in a rapid accumulation of occupied nuclear estrogen receptor complex in which levels were maximized within 1 h and decreased after 3 h. Pretreatment of the cells with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) 6 or 12 h prior to the addition of the radiolabeled hormone resulted in a 38 and 63% reduction in the levels of the occupied nuclear estrogen receptor, respectively, whereas addition of TCDD 1 h prior to the radioligand did not cause any significant change in the levels of the occupied nuclear receptor using velocity sedimentation analysis. Moreover, it was also shown with estrogen receptor antibodies that the TCDD-mediated dose-dependent decrease in occupied nuclear receptor levels was paralleled by a comparable decrease in immunoreactive protein at concentrations of 10^{-8} to 10^{-11} M TCDD. The reduction in levels of the occupied nuclear estrogen receptor was not due to increased estradiol metabolism since a significant reduction was observed at TCDD concentrations (10^{-11} to 10^{-13} M) which do not induce cytochrome P-450-dependent monooxygenase enzyme activities in MCF-7 cells. Treatment of the MCF-7 cells with actinomycin D or cycloheximide resulted in a greater than 2-fold increase in levels of the occupied nuclear estrogen receptor, and cotreatment of the cells with both TCDD and these inhibitors significantly decreased levels of the nuclear estrogen receptor complex. The structure-activity relationships for TCDD and several congeners were similar for both the reduction of occupied nuclear estrogen receptor levels and several aryl hydrocarbon (Ah) receptor agonist activities, and these results support a role of the Ah receptor in these processes.