

Partial Antagonism of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin-Mediated Induction of Aryl Hydrocarbon Hydroxylase by 6-Methyl-1,3,8-trichlorodibenzofuran: Mechanistic Studies

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SUMMARY

6-Methyl-1,3,8-trichlorodibenzofuran (MCDF) binds with moderate affinity to the aryl hydrocarbon (Ah) receptor protein (4.9×10^{-8} M) but is a weak Ah receptor agonist. Cotreatment of male Long Evans rats with MCDF (50 μ mol/kg) and a dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) that causes a near-maximal induction of hepatic microsomal aryl hydrocarbon hydroxylase and ethoxyresorufin *O*-deethylase activities resulted in a significant inhibition of these activities for up to 96 hr. Comparable results were obtained with MCDF (10^{-7} M) and TCDD (10^{-8} M) in rat hepatoma H-4-II E cells in culture over 36 hr. TCDD treatment of rats resulted in an initial decrease of hepatic cytosolic Ah receptor within 6 hr and this was followed by a subsequent 138% increase in cytosolic receptor levels 72 hr after treatment. Although MCDF (50 μ mol/kg) did not significantly alter rat hepatic cytosolic Ah receptor levels in animals cotreated with TCDD plus MCDF, the latter compound significantly inhibited TCDD-mediated replenishment of the cytosolic Ah receptor. In contrast,

treatment of rat hepatoma H-4-II E cells with TCDD (10^{-8} M) resulted in the rapid (within 1 hr) depletion of cytosolic Ah receptor, which remained undetectable for up to 36 hr; cotreatment of the cells with MCDF (10^{-7} M) and TCDD (10^{-8} M) resulted in cytosolic Ah receptor levels that were similar to those observed after treatment with TCDD alone. The effects of MCDF on the uptake and persistence of nuclear [3 H]TCDD-Ah receptor complex levels were also determined in rat liver and rat hepatoma H-4-II E cells in culture. MCDF did not significantly decrease levels of occupied nuclear Ah receptor complexes in the rat or rat hepatoma cells. Moreover, using the sucrose density gradient assay procedure, the sedimentation coefficients of the cytosolic and nuclear TCDD-Ah receptor complexes in the presence or absence of MCDF were comparable. The results of these and other related studies with 6-substituted-1,3,8-trichlorodibenzofurans suggest that MCDF may act as a partial TCDD antagonist by competing with TCDD for nuclear binding sites.