THE THYROID DISRUPTOR 1,1,1-TRICHLORO-2,2-BIS(*P*-CHLOROPHENYL)-ETHANE APPEARS TO BE AN UNCOMPETITIVE INVERSE AGONIST FOR THE THYROTROPIN RECEPTOR

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In this study, we aimed at establishing whether two previously identified thyroid disruptors, the insecticide 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) and Aroclor-1254 (a complex mixture of polychlorinated water), may inhibit thyrotropin (TSH) receptor (TSHr) activity. DDT and Aroclor-1254 were shown to inhibit both the basal and bovine TSH (bTSH)-stimulated accumulation of cAMP in Chinese hamster ovary (CHO)-K1 cells stably transfected with the TSHr. Furthermore, both DDT and Aroclor-1254 did indeed prevent cAMP accumulation, as induced by the constitutive activity of a point mutant TSHr(I486M) transiently transfected in African green monkey kidney fibroblast (COS)-7 cells. Neither trypsin digestion of the extracellular domain (ECD) nor deletion of the ECD in a mutant TSHr trunk transiently transfected in COS-7 cells counteracted the inhibitory activity of DDT and Aroclor-1254. DDT exerted a weak inhibitory activity against forskolin in both CHO-K1 and COS-7 cells, whereas it was nil against the agonists dopamine and 5'-(*N*-ethyl-carboxamido)-adenosine (NECA) in CHO cells stably transfected with the dopamine D1 receptor and in COS-7 cells transiently transfected with the adenosine type 2a receptor (A_{2a}) receptor. Furthermore, DDT was inactive against the stimulation by isoproterenol of the endogenously expressed β_2 adrenergic receptor in COS-7 cells. Conversely, Aroclor 1254 inhibited completely forskolin activity in CHO-K1 cells but not in COS-7 cells. Furthermore, it did not prevent accumulation of cAMP as induced by NECA in A_{2a} transfected cells. The analog of DDT, diphenylethylene, was inactive against bTSH-induced increase in cAMP in CHO-K1 cells stably transfected with the TSHr. We interpreted these results as indicating that DDT and possibly Aroclor-1254 may have an uncompetitive inverse agonist activity for the TSHr. While these data were in publication in (Rossi et al., 2007 Journal of Pharmacology and Experimental Therapeutics) we discover that other steroids inhibit glycoprotein hormone receptors, and finally that β-estradiol is the most powerful of the inhibitors, with an IC_{50} in the low nM range. These findings rise the intriguing possibility that steroid inhibition of glycoprotein hormone receptors might reflect a physiological mechanism of regulation for these receptors.