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Activation of estrogen signaling by dioxins-induced association of Ah receptor with estrogen receptor.

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Dioxins are typical environmental pollutants that are thought to exert diverse biological effects including estrogen-mimicking and esrrogen-disruptive activities. The transcription factors dioxin (Ah) receptor/Arnt heterodimer are considered to mediate the actions of dioxins, whereas estrogen receptors (ERs) α and β mediate those of estrogen. In the present study, we examined the functional cross-talk between AhR- and ER-mediated signaling pathways by in vitro cell culture and in vivo animal systems.

We found that 3-methylcholanthrene(3MC)-liganded AhR/Arnt activated ERE-mediated transcription by direct association with unliganded ERα or ERβ in several lines of cultured cells. 3MC exhibited estrogenic actions in the uterine weight increase, with induction of estrogen-responsive target genes in the ovariectomized mice. Such estrogenic actions of 3MC were abolished in the mice deficient of AhR (AhR-/-) and ERα (ERα-/-), suggesting that AhR and ER α mediates estrogenic actions of 3MC in animals. TCDD and the other AhR-Ligands also activated estrogen pathway in reporter assays and mouse uterus.

Thus, these findings suggest that 3MC-liganded AhR/Arnt activates the transcription of estrogen target genes by complex fortmation of AhR/Arnt with ERα/β. This mechanism may partly account for the dioxin effects on the estrogen signaling pathway.