Biology and Toxicology of Estrogen Receptor Beta

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The U.S. EPA has recommended that chemicals be screened for interaction with estrogen receptor-beta (ERβ) as part of the screening and testing guidelines for identifying endocrine-disruptive chemicals. The physiological role of ERβ is not known, and the relevance of chemical interaction with ERβ for human risk assessment remains to be determined. As a result, chemicals may be regulated based on their ability to interact with ERβ without a clear understanding of the physiological relevance of such interactions. We have identified a metabolite of the organochlorine pesticide methoxychlor, 2,2-bis (p-hydroxyphenyl)-1,1,1-trichloroethane (HPTE) that is an estrogen receptor-alpha (ERα) agonist and an ERβ antagonist in an in vitro assay system. Our results are the first to demonstrate a clear difference in activity of an environmental chemical between the two estrogen receptors. This finding gives us a tool to determine the different roles of ERα and ERβ in vivo. We plan to use HPTE and chemicals of similar structure to characterize the developmental and reproductive role of ERβ. Our hypothesis is that ERβ not only has unique cellular and molecular characteristics that lead to receptor-mediated activity that differs from ERα but also has unique tissue-specific expression during development that will play an important role in ER-mediated developmental and reproductive toxicity. We will determine the cell and promoter specificity of response, develop structure-activity relationships for differential response, and characterize chemical-specific alterations in receptor conformation as it relates to the ability of the receptor to interact with transcription-related proteins. In addition, we will use ERα knockout mice to determine the role of these two receptors in reproductive tissues. Information gained from the knockout mouse models will be used to determine the role of ERα and ERβ in ER-mediated toxicity to reproductive tissues during fetal development in the rat. Our studies will ultimately lead to a better understanding of the role of ERα and ERβ in both normal endocrine function and in endocrine disruption by environmental chemicals.

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