Non-Linear Dose Response Relationships for Developmental Responses: An Example with Defeminization by Estrogenic Xenobiotics

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The goal of this project is to improve our understanding of the biological basis for risk assessment for some toxic responses related to exposures to estrogenic and aromatizable androgenic compounds. We are developing a biologically based dose response (BBDR) model for a specific estrogen-related outcome, defeminization of the brain in female rats. This will allow us to evaluate the shape of the dose-response curve for this response at low doses of specific endocrine active compounds (EACs). Our hypothesis is that neonatal defeminization of the female brain has a threshold in relation to achieved concentrations of the estrogen receptor-estradiol (ER-E2) complex and its interactions with hormone responsive genes in neurons within specific regions of the hypothalamus. We have completed dosing of perinatal rats with estradiol (E2) for studies in the perinatal period and have demonstrated dose-related responses of the progesterone receptor and estrogen receptor alpha gene to low doses of estrogen (10-100 ng E2). Both of these genes are estrogen responsive. The progesterone receptor gene is upregulated by estrogen, the estrogen receptor alpha gene is downregulated by estrogen. We have developed a preliminary pharmacokinetics (PK) model for E2 action in the neonate. Since two different estrogen receptors [estrogen receptor (ER) alpha and beta] are involved in transmission of an E2 signal, we have examined the actions of ER alpha or beta selective compounds on progestin receptor (PR) expression in neonatal rats. We have determined that ER alpha is responsible for the upregulation of PR by estradiol. In addition, we have treated neonatal animals with several doses of estradiol and examined gene expression profiles in the preoptic area using microarray technology. Our analysis showed that out of 31,000 possible genes only 157 genes in males and 107 genes in females were significantly up or downregulated by 1.5 fold. Moreover, E2 upregulated only 7 (4.5%) genes in males, whereas E2 upregulated 52 (48.6%) genes in females. This dramatic sex difference in the ratio of fold change suggests that the male preoptic region responds differently to the presence of small amounts of E2 (100 ng) by mainly downregulating gene expression, whereas this was not the case in the female preoptic region. Interestingly, we found that 44 genes were similarly affected by E2 in males and females. For example, whereas E2 upregulated peroxisome proliferative activated receptor gamma and dynamin in males and females, E2 downregulated heat shock protein 70, neuroligin 2 and phosphatidylinositol 3-kinase alpha in both males and females. Currently, we are characterizing the ontogeny of these genes and verifying our results using quantitative reverse transcription polymerase chain reaction (RT-PCR). The results of these studies provide the first comprehensive examination of ER selective gene expression in the brain of the neonate. Studies are planned to determine the effect of low doses of estrogen and ER alpha or beta selective agonists delivered during the neonatal period on hormone secretory patterns and reproductive behaviors in adulthood.

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