

Loss of Estrogen Receptor Activity: Consequences in Endocrine Physiology

Kenneth Korach¹

¹ Laboratory of Reproductive & Developmental Toxicology, NIEHS/NIH, Research Triangle Park, NC USA

Estrogen receptors (ER) are thought to play a crucial role in development, reproduction and normal physiology. Even though the concept of ER gene mutations was thought to be lethal. Gene targeting allowed us to produce lines of mice with disrupted ER-alpha (aERKO) and ER-beta genes (bERKO) as well as a compound abERKO. Comparable levels of ERb mRNA in tissues of aERKO mice suggesting that ERb expression is not dependent on ERa. aERKO mice were totally unresponsive to uterotrophic assays, to estrogen, EGF or IGF-1 treatments. Progesterone receptor mRNA was detected in aERKO mice, but not stimulated by estrogen in the uterus, mammary gland and ovary, indicating an estrogen dependent and independent gene regulation. aERKO females are infertile, have loss of negative feedback and have hypoplastic uteri, hyperemic ovaries and no corpora lutea. bERKO females show arrested folliculogenesis and subfertility. Ovarian analyses indicate differential gene expression related to ovulatory stimulation. Mammary glands of adult aERKO females showed a primitive ductal rudiment rather than the fully developed ductal tree seen in WT or bERKO mice. Findings from the mice suggest that the absence of estrogen and functional ER is not lethal and results in significant effects on a number of organs systems affecting physiological processes allowing determination of consequences of ER mediated actions and the specific roles of the two different forms of ER.