An Estrogen Receptor Paradox: Why Do Estrogen and Tamoxifen Antagonize Each Other’s Activity?

The thought-provoking review by Nilsson et al. on the β estrogen receptor (ERβ) raises the possibility of resolving some of the unsolved problems of estrogen action. In the hope of stimulating suggestions and experiments by readers of Trends in Endocrinology and Metabolism, we restate a troubling paradox. It has long been known that in ovariec-tomized, or immature, rat uteri, tamoxifen acts as an agonist but antagonizes the activity of exogenous estrogen. The extent of this phenomenon is emphasized by the data in Fig. 1.

**Mutual Annihilation of Agonistic Action**

In prepubertal rat diaphysis, epiphysis and uterus (Fig. 1), tamoxifen stimulates the estrogen-induced marker enzyme creatine kinase B (CKB) to a peak activity no less than that induced by 10 nmols (2.7 μg) 17β-estradiol per rat. When a 30-fold molar excess of tamoxifen is injected simultaneously with estrogen, no stimulation of CKB activity is seen. Therefore, tamoxifen is a full agonist when injected alone, but a complete antagonist to a super-physiological dose of estrogen. That excess tamoxifen prevents the action of estrogen is expected, but that the agonist activity of tamoxifen is abolished by 30 times less estrogen, leading to mutual annihilation of their action, is a phenomenon without an obvious explanation in terms of estrogen receptor types or classic pharmacology of competitive inhibition. This phenomenon is not limited to tamoxifen, for example, both tamoxifen methiodide and raloxifene show this effect in bone-derived cells. The same mutual annihilation of activity of estradiol and tamoxifen is seen in cultured human Saos2 osteoblast-like cells and Ishikawa endometrial cancer cells, as well as in ROS17/2.8 osteoblast-like cells.

**A Highly Speculative Model**

The combination of α and β receptors in the presence of two different ligands might result in a heterodimer between estrogen-liganded and tamoxifen-liganded monomers, whose resulting conformation would be inactive but have sufficient increased affinity for DNA to block agonist activity at the creatine kinase estrogen-response element. Changes in the specific receptor surface induced by the different ligands would therefore lead to interactions with a different set of co-repressors, co-activators, and integrators, which might provide the basis of an explanation of the mutual annihilation phenomenon.

Perhaps the solution to this paradox could contribute to an understanding of the practical problem of why tamoxifen, after long-term use, becomes an agonist for breast cancer rather than an effective antagonist.

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