19

AGONISTIC AND ANTAGONISTIC EFFECTS OF ANTIESTROGENS IN TARGET CELLS.

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The biological effects of tamoxifen (TAM) were studied in two models: I) in the uterus and vagina in the perinatal period of the guinea pig; II) in the R-27 cell, a mammary cancer cell line which is resistant to TAM. TAM alone or in combination with estradiol (E_2) was administered to the pregnant or newborn guinea pigs for a long period (12 days) and uterine growth and progesterone receptor (PR) responses were explored. 24 hours after the last administration in both fetal and newborn uteri TAM provoked a significant increase in weight, protein and DNA content and did not block the effect provoked by E_2. The effect on PR was much less intense than that provoked by E_2, but TAM did not block the stimulatory action of E_2. Ultrastructural observations with electron-microscopy showed a pronounced modification of some organelles. A similar phenomenon was observed in the vagina of both fetal and newborn guinea pigs and histological examinations showed the appearance of bodies formation in the vaginal epithelium after TAM treatment. Using a monoclonal antibody against ER, in both of these tissues, it was demonstrated that ^{3}H-TAM is bound to the active form of the estrogen receptor.

In the R-27 mammary cancer cell line TAM did not block the effects provoked by E_2, estriol or estriol-3-sulfate, but ultrastructural observations after TAM treatment showed a great alteration of some organelles in relation to the non-treated cells. It is concluded that TAM is a full estrogen for uterine and vaginal growth during the perinatal periods of the guinea pig but a partial agonist for PR stimulation and in the R-27 mammary cancer cell line it does not block the action of estrogens but produces significant morphological modifications.

20

AROMATASE INHIBITORS AND THEIR POTENTIAL CLINICAL SIGNIFICANCE.

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Estrogen biosynthesis occurs not only in reproductive tissues of the female but also in such diverse sites as testes, adipose, and muscle. Our rationale for the clinical use of aromatase inhibitors is that compounds interacting with aromatase in all tissues could provide both selective and effective inhibition of estrogen production. The most potent inhibitor identified by us to date is 4-hydroxyandrostene-3,17-dione (4-OHA). This compound causes rapid competitive inhibition followed by irreversible inactivation of aromatase. Treatment of rats with 4-OHA results in inhibition of ovarian aromatase and estrogen secretion, accompanied by marked regression of carcinogen induced mammary tumors. Using rhesus monkeys, marked inhibition of peripheral aromatization by 4-OHA was also demonstrated. The first clinical study with a selective aromatase inhibitor was recently carried out using once weekly injections of 500 mg 4-OHA in 60 postmenopausal patients with advanced metastatic breast cancer and unselected for the presence of estrogen receptors. The mean serum estradiol level reduced to 36% of pretreatment values for at least 4 months. No effect of treatment on gonadotropin levels occurred indicating that the reduction in estrogen levels was due to inhibition of peripheral aromatization. In spite of the fact that all patients had relapsed from previous therapy, complete or partial tumor regression occurred in 30% of patients while 15% had static disease. Although the optimum dose of 4-OHA has not yet been established, this aromatase inhibitor appears to be of value in treating postmenopausal breast cancer and may be beneficial in other diseases associated with estrogens.