Estradiol regulates gonadotropin-releasing hormone (GnRH) and its receptor geneexpression and antagonizes the growth inhibitory effects of GnRH in human ovarian surface epithelial and ovarian cancer cells.

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摘要

Abstract

In the present study, we investigated the expression of estrogen receptors (ERalpha and ERbeta) in human ovarian surface epithelial (hOSE) cells and the ovarian cancer cell line, OVCAR-3, and provided novel evidence that estrogen may have a growth regulatory effect in these cells. Expression levels of ERalpha messenger RNA (mRNA) were 1.5-fold higher in OVCAR-3 cells than in hOSE cells, as revealed by semiquantitative RT-PCR and Southern blot analysis. A significant increase (3.3-fold) in ERss mRNA levels was observed in OVCAR-3 cells compared with hOSE cells. In parallel with mRNA levels, expression levels of ERalpha and ERbeta proteins were also higher in OVCAR-3 cells compared with hOSE cells. We recently proposed that GnRH and its receptor may have an autocrine role in hOSE and ovarian cancer cells. To determine whether estrogen regulates GnRH and GnRH receptor (GnRHR), hOSE and OVCAR-3 cells were treated with various concentrations of 17beta-estradiol for 24 h. Expression levels of GnRH and GnRHR mRNA were examined using quantitative and competitive RT-PCR, respectively. Treatment with 17beta-estradiol induced a significant down-regulation of GnRH mRNA in OVCAR-3 cells, but not in hOSE cells and of GnRHR mRNA in both hOSE andOVCAR-3 cells. Tamoxifen, an estrogen antagonist, prevented the effects of 17ssestradiol, suggesting that estradiol action is mediated via the ER. Finally, the effect of estrogen on the growth of hOSE and OVCAR-3 cells was investigated. The cells were treated with various concentrations of 17ss-estradiol, and the proliferative index of cells was measured using

[(3)H]thymidine incorporation and DNA fluorometric assays. 17beta-Estradiol stimulated the growth of OVCAR-3 cells in a dose- and time-dependent manner. In contrast, 17beta-estradiol failed to stimulate the growth of hOSE cells. As estrogen down-regulated GnRH and GnRHR mRNA, we investigated whether estrogen treatment blocks the growth inhibitory effect of a GnRH agonist in OVCAR-3 and hOSE cells. Cells were treated with 17beta-estradiol (10(-7) M) together with (D-Ala(6))-GnRH (10(-7) M), and the proliferative index of cells was measured. Pre- or cotreatment of cells with 17beta-estradiol significantly attenuated the growth inhibitory effect of the GnRH agonist in OVCAR-3 cells, whereas no effect of 17ss-estradiol treatment was observed in hOSE cells. To our knowledge, these results provide the first demonstration of a potential interaction between the estradiol/ER and GnRH/GnRHR systems, which may be important in the growth regulation of normal and neoplastic hOSE cells.

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