Gonadotropin-releasing hormone activates mitogen-activated protein kinase in human ovarian and placental cells

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摘要

Abstract

Considering that the action of gonadotropin-releasing hormone (GnRH) may be mediated via different signaling pathways in extrapituitary tissues, in the present study we investigated the role of the human GnRH receptor (GnRHR) in activating mitogen-activated protein kinases (MAPKs), which regulate cell growth, division, and differentiation. The phosphorylation state of p44 and p42 MAPKs was examined using antibodies that distinguish phospho-p44/42 MAPK (P-MAPK, Thr(202)/Tyr(204)) from total p44/42 MAPK (T-MAPK, activated plus inactivated) in human ovarian and placental cells. Cell cultures were treated with various concentrations of a GnRH agonist, (D-Ala(6))-GnRH, for 5 min. (D-Ala(6))-GnRH stimulated a rapid activation of P-MAPK in human granulosa-luteal cells (hGLCs) and immortalized extravillous trophoblast (IEVT) cells. Interestingly, (D-Ala(6))-GnRH treatment of ovarian cancer (OVCAR-3) and placental carcinoma (JEG-3) cells induced a biphasic regulatory pattern in P-MAPK activity.In contrast, no change of T-MAPK levels was observed following addition of the GnRH agonist in the ovarian and placental cells examined. The physiological implication of MAPK activation by GnRH in the ovarian and placental cells was also investigated. Human GLCs were treated with (D-Ala(6))-GnRH for 24 h, and progesterone secretion was measured by an established RIA. (D-Ala(6))-GnRH induced a significant decrease in progesterone secretion with maximum inhibition (a 45% decrease over basal level) at 10(-7) M. This inhibitory effect was completely reversed by pretreatment with MAPK/ERK kinase 1 (MEK1) inhibitor (PD98059), suggesting the involvement of the MAPK pathway in hGLCs. Placental JEG-3 cells were treated with (D-Ala(6))-GnRH for 24 h, and betahCG mRNA level was measured using Northern blot analysis. (D-Ala(6))-GnRH stimulated the expression of betahCG mRNA to 160% of control value in JEG-3 cells. In

contrast to the ovarian cells, pretreatment of JEG-3 cells with PD98059 failed to block the stimulatory effect of GnRH on betahCG mRNA level, suggesting that other signaling pathway(s) may play a more dominant role in GnRH-induced betahCG mRNA expression. To our knowledge, this is the first demonstration that (1) GnRH induces activation of the MAPK signaling pathway in normal and carcinoma cells of the human ovary and placenta, and (2) MAPK mediates the direct action of GnRH on progesterone production in hGLCs..

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