Role of mitogen-activated protein kinase in prostaglandin F2 alpha action in human granulosa-luteal cells

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摘要

Abstract

In the ovary it has been demonstrated that PGF2 activates the phospholipase C (PLC)/diacylglycerol/protein kinase C pathway. However, little is known about the downstream signaling events that mediate subsequent cellular responses such as steroidogenesis. The present study was designed to examine the effect of PGF2 on activation of the mitogen-activated protein kinase (MAPK) signaling pathway and its physiological role in human granulosa-luteal cells (hGLCs). Human GLCs, obtained from women undergoing in vitro fertilization-embryo transfer, were treated with increasing concentrations of PGF2 (10 nmol/L to 10 μmol/L) for 5 min. For time-course experiments, hGLCs were treated with 1 μmol/L PGF2 for 1, 5, 10, or 20 min. Western blot analysis, using a monoclonal antibody that detected the phosphorylated forms of extracellular signal-regulated kinases 1 and 2 (p42mapk and p44mapk, respectively), demonstrated that PGF2 activated MAPK in hGLCs in a dose- and time-dependent manner. Treatment of the cells with neomycin (10 mmol/L; a PLC inhibitor), bisindolylmaleimide I (5 μmol/L; a PKC inhibitor), or PD98059 (50 μmol/L; a MEK inhibitor and a MAPK kinase inhibitor) significantly attenuated the PGF2-induced activation of MAPK. In contrast, MAPK activation was not significantly affected by pertussis toxin (200 ng/mL; a Gi inhibitor) pretreatment. To determine the role of MAPK in steroidogenesis, hGLCs were treated with PGF2 (1 μmol/L), hCG (1 IU/mL), or PGF2 plus hCG in the presence or absence of PD98059. Progesterone levels in the culture medium were examined by RIA. Treatment of hGLCs with PGF2 significantly inhibited hCG-induced progesterone production. The presence of the MEK inhibitor, PD98059, reversed the inhibitory effect of PGF2 on hCG-induced progesterone production. To our knowledge, it is the first demonstration of PGF2-induced activation of the MAPK signaling pathway in the human ovary. These results indicated that PGF2 activated MAPK subsequent to PLC and PKC activation through pertussis toxin-insensitive G protein in hGLCs. Further, we demonstrated that PGF2-induced MAPK activation is associated with modulation of progesterone production.

These results support the idea that the MAPK signaling pathway is involved in mediating PGF2 actions in the human ovary.