Differential regulation of two forms of gonadotropin-releasing hormone messenger ribonucleic acid in human granulosa-luteal cells

戴承杰

Kang Sk;Tai CJ;Nathwani PS;Leung PC

摘要

Abstract

Until recently, the primate brain was thought to contain only one form of GnRH known as mammalian GnRH (GnRH-I). The recent cloning of a second form of GnRH (GnRH-II) with characteristics of chicken GnRH-II in the primate brain has prompted a reevaluation of the role of GnRH in reproductive functions. In the present study, we investigated the hormonal regulation of GnRH-II messenger RNA (mRNA) and its functional role in the human granulosa-luteal cells (hGLCs), and we provided novel evidence for differential hormonal regulation of GnRH-II vs. GnRH-I mRNA expression. Human GLCs were treated with various concentrations of GnRH-II, GnRH-II agonist (GnRH-II-a), or GnRH-I agonist (GnRH-I-a; leuprolide) in the absence or presence of FSH or human CG (hCG). The expression levels of GnRH-II, GnRH-I, and GnRH receptor (GnRHR) mRNA were investigated using semiquantitative or competitive RT-PCR. A significant decrease in GnRH-II and GnRHR mRNA levels was observed in cells treated with GnRH-II or GnRH-II-a. In contrast, GnRH-I-a revealed a biphasic effect (up- and down-regulation) of GnRH-I and GnRHR mRNA, suggesting that GnRH-I and GnRH-II may differentially regulate GnRHR and their ligands (GnRH-I and GnRH-II). Treatment with FSH or hCG increased GnRH-II mRNA levels but decreased GnRH-I mRNA levels, further indicating that GnRH-I and GnRH-II mRNA levels are differentially regulated. To investigate the physiological role of GnRH-II, hGLCs were treated with GnRH-II or GnRH-II-a in the presence or absence of hCG, for 24 h, and progesterone secretion was measured by RIA. Both GnRH-II and GnRH-II-a inhibited basal and hCG-stimulated progesterone secretion, effects which were similar to the effects of GnRH-I treatment on ovarian

steroidogenesis. Next, hGLCs were treated with various concentrations of GnRH-II, GnRH-II-a, or GnRH-I-a; and the expression levels of FSH receptor and LH receptor were investigated using semiquantitative RT-PCR. A significant down-regulation of FSH receptor and LH receptor was observed in cells treated with GnRH-II, GnRH-II-a, and GnRH-I-a, demonstrating that GnRH-II and GnRH-I may exert their antigonadotropic effect by down-regulating gonadotropin receptors. Interestingly, GnRH-II and GnRH-II-a did not affect basal and hCG-stimulated intracellular cAMP accumulation, suggesting that the antigonadotropic effect of GnRH-II may be independent of modulation of cAMP levels. Taken together, these results suggest that GnRH-II may have biological effects similar to those of GnRH-I but is under differential hormonal regulation in the human ovary.