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JOURNAL ARTICLE

Mechanism of action of gonadotropin-releasing hormone-stimulated Leydig cell steroidogenesis. I. The stimulatory effect is calcium dependent and not mediated by cyclic nucleotides

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The present study was designed to elucidate mechanisms responsible for gonadotropin-releasing hormone (GnRH)-stimulated testosterone formation. Purified Leydig cells from adult Sprague-Dawley rats were incubated with varying concentrations of GnRH agonist (des-Gly10, (D-Ala6) GnRH N-ethylamide), hCG, 8-bromo cAMP or pregnenolone; testosterone, cAMP, cyclic GMP (cGMP) and cAMP-dependent protein kinase activity were measured after various time periods. Basal testosterone levels were 2.54 +/- 0.13 ng/10(5) cells, increasing to 3.18 +/- 0.14, 4.32 +/- 0.08, and 4.63 +/- 0.12 ng within 1 hour after the addition of 10(-9), 10(-8), and 10(-7) M GnRH agonist, respectively. After a 3-hour incubation a 10(-7) M dose of GnRH agonist increased testosterone production four-fold above control. GnRH agonist potentiated hCG-stimulated testosterone formation, but had no significant effects on cGMP levels and cAMP-dependent protein kinase activity. Cyclic AMP levels in the incubation medium increased slightly. GnRH agonist also enhanced 8-bromo-cAMP and pregnenolone-induced testosterone formation. Furthermore, GnRH agonist increased testosterone formation both in the absence and presence of phosphodiesterase inhibitor. These results suggest that the major effect of GnRH agonist is probably beyond the cAMP step. When purified Leydig cells were incubated in a calcium-free medium, the stimulatory effects of GnRH agonist on testosterone formation were completely abolished, but could be restored by the addition of calcium to the incubation medium. GnRH agonist-induced testosterone formation was also blocked by the addition of nifedipine (a calcium channel blocking agent, 0.1 to 10 micrograms/ml). Finally, GnRH antagonist in a concentration of 10 micrograms/ml completely inhibited GnRH agonist-stimulated testosterone formation. In conclusion: GnRH agonist stimulated Leydig cell testosterone formation in short-term incubations. The stimulatory effect is calcium dependent and not mediated by cyclic nucleotides.