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Mutations of Constitutive Activation and Mutations That Impair Signal Transduction Modulate the Agonist-stimulated Internalization of the Lutropin/Choriogonadotropin Receptor

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The lutropin/choriogonadotropin receptor (LHR) is a member of the rhodopsin-like subfamily of G protein coupled receptor (GPCRs), that has been shown to mediate the internalization of its two naturally occurring agonist, lutropin and choriogonadotropin (CG). The clustered agonist-receptor complex is internalized by a dynamin-dependent pathway and traverses the endosomal compartment without agonist dissociation. Dissociation of the agonist-receptor complex occurs in the lysosomes, where both the agonist and receptor are degrade. Recently, constitutively activating mutations of the receptor have been identified that are associated with familial male-precocious puberty (FMPP). A FMPP is a form of sexual precocious puberty in boys in which testosterone levels are elevated independent of changes in luteinizing hormone-releasing hormone and serum luteinizing hormone levels.

We have now analyzed two naturally occuring, constitutively active mutants of the human LHR. These mutations were introduced into the rat LHR (rLHR) and are designated L435R and D556Y. Cells expressing rLHR-D556Y bind human choriogonadotropin (hCG) with normal affinity, exhibit a 25-fold increase in basal cAMP and respond to hCG with a normal increase in cAMP accumulation. Cells expressing rLHR-L435R also bind hCG with normal affinity, exhibit a 47-fold increase in basal cAMP, and do not respond to hCG with a further increase in cAMP accumulation. This mutation enhances the internalization of the free and agonist-occupied receptors ~2- and ~17-fold, respectively. We conclude that the state of activation of the rLHR can modulate its basal and/or agonist-stimulated internalization. Since the internalization of hCG is involved in the termination of hCG actions, we suggest that the lack of responsiveness detected in cells expressing rLHR-L435R is due to the fast rate of internalization of the bound hCG, The finding that membranes expressing rLHR-L435R respond to hCG with an increase in adenylyl cyclase activity supports this suggestion. Autonomous Leydig cell activity in FMPP is caused by a constitutively activating LH/CGR.

Key words) *LH/CG receptor, signal transduction, internalization*