

Human adrenal LH/hCG receptors and what they could mean for adrenal physiology and pathology.

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Human adrenals are complex endocrine organs, consisting of three outer concentric cortex layers and inner medulla. ACTH is a primary regulator of glucocorticoid secretion by zona fasciculata and DHEAS secretion by zona reticularis. However, the DHEAS secretion is elevated without any changes in ACTH levels in chronic anovulatory women with or without PCO, who have increased LH levels. Moreover, hCG can stimulate fetal human adrenal DHEAS secretion. These observations, coupled with the common embryologic origin of adrenals and ovaries, prompted us to test the hypothesis that normal adult human adrenals contain functional LH/hCG receptors. The results revealed that indeed the receptors are present, primarily in the deeper part of zona fasciculata and entire zona reticularis, both which can secrete DHEAS. Functional studies on surrogate H295R human adrenal cortical carcinoma cells, which retain many features of normal adrenal cortical cells, showed that hCG can stimulate DHEAS secretion in a dose, time dependent, hormone and steroid specific manner. The increase was not due to de novo steroid synthesis, but it is rather due to an increase in DHEA sulfotransferase levels. hCG uses cAMP/PKA signaling and was totally ineffective in the absence of its receptors. These data suggest that functional adrenal LH/hCG receptors could explain increased adrenal androgen secretion in chronic anovulatory women, with or without PCO, during adrenarche when ACTH levels are normal and increased androgen levels can be suppressed by GnRH treatment. They may also explain increased cortisol secretion during early pregnancy when ACTH levels are normal and hCG is rapidly increasing. The decreased DHEAS levels when LH levels are increasing during aging appear to be due to a decreased zona reticularis thickness and DHEA sulfotransferase levels. Adrenal LH/hCG receptors appear to play a role in ACTH independent Cushing syndrome due to bilateral macronodular adrenal hyperplasia, adenomas and carcinomas, some virilizing and aldosterone producing adrenal adenomas. However, it has not been proven whether the receptors involved could be eutopic, which became activated due to some molecular change.