

Phenotypic Characterization of mice expressing a yoked hCG-LH receptor complex

Prema Narayan, Keriayn Smith, Frank Michel and Thomas P. Meehan
Department of Biochemistry and Molecular Biology, University of Georgia,
Athens, GA, USA.

The luteinizing hormone receptor (LHR) is critical in male and female reproduction. A number of mutations in LHR resulting in constitutive receptor activation have been identified in boys presenting with sporadic and familial male-limited precocious puberty. A genetically engineered yoked hormone-receptor complex (YHR), consisting of a fusion protein of single chain hCG and LHR, exhibits signaling properties of a constitutively active receptor with increases in basal levels of cAMP and inositol phosphate in cell culture studies.

To determine if YHR is functional *in vivo* and to study the effects of premature and chronic LHR activation on reproductive function, we have generated transgenic mice expressing YHR. Hormonal and histological analysis of prepubertal and adult male mice indicates that YHR expression results in increased prepubertal levels of testosterone and altered gonadal development. In addition, adult YHR male mice exhibit changes in pituitary function with differential regulation of LH and FSH levels. Female mice exhibit elevated prepubertal levels of estradiol, early degenerative changes in the ovary and are subfertile. Temporal analysis of expression of genes encoding the enzymes in the testosterone biosynthetic pathway indicated that the steady state mRNA levels of *Cyp11a1*, *Cyp 19* and *Hsd3b1* were elevated at 5 weeks in male WT mice prior to the increase in testosterone associated with puberty and declined in adult mice. The mRNA levels for these enzymes were unaltered at all ages in the YHR male mice when compared to WT controls suggesting that regulation of these mRNAs was at the post-transcriptional level. In contrast, the mRNA levels of *Cyp 17* were decreased in YHR mice at the prepubertal ages but not adult ages. The latter result suggests that the testosterone-mediated inhibition of *Cyp 17* mRNA synthesis shown in Leydig cell cultures also occurs *in vivo*.

These data indicate that the genetically engineered, constitutively active YHR is functional *in vivo* and that aberrant LHR activation results in gonadal defects and alters the regulation of the hypothalamic-pituitary-gonadal axis. Supported by NIH DK 33973 and HD044119.