

The Tale of Follitropin Receptor Diversity: Is more better for integrating function?"

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The ovarian follicle and testicular Sertoli cells are dynamic structures undergoing developmental changes under hormonal stimulus or involution (apoptosis) due to lack of sustaining factors. Among many factors, follitropin exerts important regulatory effects in folliculogenesis enhancing cell division, modulating the synthesis/function of its own receptor and production of estrogen and other autocrine or intracrine modulators. The large single receptor gene exceeding 250 kbp in most species shows high propensity for alternative splicing producing the classical G protein coupled heptahelical structure (FSH-R1) and other motifs that predict different topography and functions. Following our initial studies on the recognition of several FSH-R variants from adult sheep testis we have demonstrated the existence of growth factor type I receptor in sheep and mouse ovaries. Structural studies and genomic verification clearly show that sequences from a putative Exon 11 separated by a large introns that follows the exon 10 coding for the seven transmembrane domain gives rise to two other FSH-Rs depending upon the choice of the splicing site. Focusing our attention on the growth factor type receptor called FSH-R3; we have shown that it is promptly upregulated in the immature eCG primed mouse and sheep ovaries. Temporal changes correspond to follicular growth and expansion of granulosa cells. Both mRNA and protein as detected by variant specific antibodies are upregulated in cumulus granulosa cells of the mouse ovary. None of the receptor forms are detectable in the FSH-R knockout mouse ovary confirming deletion of all variants. Extending the search to known related genomes such as the human and bovine we now find the corresponding DNA sequence allowing deduction of putative protein counterparts for verification. These studies clearly reveal high homology among the FSH-R3 structures examined thus far. By transfection studies in HEK 293 cells or receptor deficient pig granulosa cells we are able to show coupling of different FSH-R types to known signaling pathways. This demonstrates the utility of alternative splicing mechanisms to generate FSH-R motifs that can co-ordinate the action of FSH, a hormone that also exists in circulation in multiple forms subject to hormonal influences of normal physiology. Thus we can argue that having more than one receptor form accounts for functional diversity and signal integration creating a recipe for fine tuning. (Research supported by Canadian Institute of Health Research).