

## Introduction to the Special Issue

### *Current Topics in Gonadotropin Biology and Medicine*

This special issue of *Endocrine* is dedicated to the theme of Gonadotropins; it highlights recent developments and emerging trends in this field. Pituitary and placental gonadotropins along with thyrotropin have long been considered to be classical glycoprotein hormones in Endocrinology, a view that will change with the discovery of new ligands and receptor members of this class. Our knowledge of the structural features and sequences of gonadotropins gained well before the advent of cDNA cloning techniques has eventually extended to many other species including lower vertebrates. However, the revelations of the structures of their receptors that began in the late 1980s and early 1990s provided the impetus to uncovering receptor-related fertility disorders or aberrations that are of clinical significance.

A major advance published in January 2005 records the first impressions of the three-dimensional structure of the follitropin–receptor hormone complex as gleaned from X-ray crystallographic studies. No doubt this lays down the path to future studies directed at the much larger and complex member with transmembrane topography. The theme of gonadotropin–receptor interactions is discussed in articles in this issue capturing the proposed features of the follitropin receptor. Hendrickson and his colleagues discuss how the hormone interacts with the extracellular domain of the follitropin receptor, essential features of which need to be confirmed and extended to the whole receptor with its seven transmembrane domains. Moyle and his colleagues present another view based on more traditional approaches of probing including detailed considerations of interspecies comparisons, while Campbell et al. discuss aspects of gonadotropin pharmacology that will have significant impact on their clinical applications for the burgeoning field of assisted reproductive technologies. Gonadotropins optimized for improving oocyte quality and enhancing sperm characteristics would help improve pregnancy rates and successful completion.

Next are four contributions that demonstrate how receptor/hormone gene cloning data have been used successfully to discover the effect of mutations or deletions in both of these genes and their implications for normal or abnormal

functions and generation of animal models. Huhtaniemi and Themmen provide a current update of all human mutations paving the way for additional function-related studies. Two papers, one by Danilovich and Sairam and another by Kumar recount the interesting and varied phenotypes in mice where each receptor gene or the individual hormone  $\beta$  subunit genes have been deleted. These mice as well as several transgenic animals outlined by Allan and Handelsman provide a glimpse of more interesting studies to come. Opportunities abound here to investigate pathologies relevant to several human disorders related to loss of hormone function during aging including menopause and andropause.

There are three articles addressing issues related to gonadotropin action. The article by Dias et al. discusses potential interactions that manifest during postreceptor recognition by the hormone. Examples of protein interactions found for follitropin in model systems could serve as starting points to elucidate events in gonadotropin target cells in their varied states of development and differentiation. Their understanding might help devise strategies for postreceptor activation options for potential treatment of deficiencies. Whether this will be possible in the case of complex interactions such as gonadotropins and receptor systems remains a challenge for the future. As for all receptors, gonadotropin receptors are dynamic entities subject to a variety of modifications on their way to initiate signaling. Menon et al. discuss various posttranslational modifications that affect receptor function and propose new modes of controlling mRNA levels in the ovary. Will the evidence from studies on the LH receptor in the corpus luteum that implicate a metabolic enzyme in such a process be applicable for follitropin receptor too in a similar fashion? Next Sarit et al. discuss the potential for discovering new genes related to gonadotropin action by examining the ovarian transcriptome in granulosa cells from hormone-stimulated women.

The next two articles introduce the reader to new and somewhat unexpected findings. The article by Park et al. reviews recent data on the evolutionary significance of the conservation of glycoprotein hormone subunit family and new leucine-rich repeat containing GPCR members. Determining their functional roles in reproduction or other events is an interesting challenge that will be addressed in due course. The article by Kaiser and Kuohung highlights the spate of recent findings from basic as well as clinical studies implicating the Kiss-1 peptide and the orphan receptor GPCR54 as novel players in gonadotropin regulation of puberty. The

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recognition that this system plays a significant role as a gate keeper for the GnRH control of the pituitary will open a whole new chapter in reproductive endocrinology.

Two articles cover the vexing topic of ovarian hyperstimulation syndrome (OHSS) that is a complication during gonadotropin treatment and perimenopause, states during which there is elevated follitropin, either administered or secreted. The article by Delbaere et al. is a nice attempt to explain OHSS by relating molecular aberrations found in the follitropin receptor to promiscuous action by rising concentrations of hCG that occur in early pregnancy and remain high in the first trimester. These studies provide yet another example of the power of molecular medicine to explain clinical findings. The article by Prior discusses ovarian aging and perimenopausal transition and considers a paradox of endogenous ovarian hyperstimulation.

The last two topics dwell on emerging issues with importance to ovarian biology and aspects of health during aging. The article by Bukovsky et al. on oogenesis in the adult highlights observations that follicular renewal exists in adult rodent and human ovaries and the reserve of primary follicles is not a static set entity, but a very dynamic event, and that increased chromosomal aberrations may cause their demise. The final article in this series, by Meethal et al., tries to reconcile well-known observation of elevated gonadotropins during menopause (and andropause) and the higher incidence of Alzheimer's disease in women. In particular, attempts are made to correlate high LH levels (rather than steroid hormone deficiency) with neurodegeneration. In this regard the expression of putative LH receptors in the brain and their interaction with high LH levels deserves meticulous scrutiny in future studies. The presence of extragonadal receptors for gonadotropins is not solely confined

to LH, as other studies seem to imply the presence of follitropin receptors in bone as a potential contributor to the well-established occurrence of osteoporosis in post-menopausal women (Devleta, B., Adem, B., and Senada, S. (2004). *J. Bone Miner. Metab.* **22**, 360–364.) It is expected that some of these contentious issues will be resolved as we learn more about the hormones and receptors in their forms and different signaling pathways.

It is hoped that the collection of articles presented which address selected topics will serve as an example of issues that will likely be at the forefront of investigations in gonadotropin and receptor biology and medicine. It will help the reader appreciate the diversity of opinion on matters of controversy and help interpret observations in the literature. During the efforts to assemble this issue in early 2005 I became aware of the demise of Dr. Om P. Bahl, Professor in the Department of Biological Sciences, at the State University of New York, Buffalo at the age of 77. He was a long-standing contributor to the determination of structure and function of hCG including the carbohydrate moieties and the LH/CG receptor. Many contributors to this special issue including this author who interacted with him in different capacities pay a special tribute to his reputation for research and development.

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