

Summary

The glycoprotein hormones, luteinizing hormone (LH), human chorionic gonadotropin (hCG), follicle stimulating hormone (FSH) and thyroid stimulating hormone (TSH) participate in reproduction, pregnancy and in the regulation of thyroid metabolism. This thesis summarizes, investigates and expands our understanding of the physiopathology, genetics and therapy. We summarize the current knowledge about glycoprotein hormones. We then discuss different clinical models of hyper and hypo-secretion of glycoprotein hormones in human pathology.

The first chapter of this thesis is focused on the description of a series of pituitary adenomas that over-secrete TSH. This study of 43 cases, the largest at the moment of its publication, documents in addition to hyperthyroidism, the different hormones over-secreted by these tumors, namely prolactin, growth hormone and the alpha subunit. We assess the diagnostic value of modern radiological tools such as Octreoscan, PET scan and consider the role of petrosal sinus catheterization in difficult cases. Genetic studies contributed to increasing our understanding of tumorigenesis in these rare tumors. Finally, we document the effectiveness in these patients of surgical treatment and medical treatment with somatostatin analogues, alone or in combination.

The second chapter of this thesis is devoted to the syndrome, familial isolated pituitary adenomas (FIPA) that we contributed to describe and focus in detail on cases of gonadotroph adenomas and thyrotroph adenomas with a familial presentation.

The third chapter of this thesis describes a novel cause of male hypogonadism. We study the consequences of the absence or failure of LH secretion in man. We describe a homozygous Gly36Asp mutation in the β LH gene and clarify a particular phenotype of hypogonadism in humans. These data let us to recognize an important role of LH in male fertility, which was previously attributed mainly to FSH. Patients with LH deficiency present with a pubertal delay, hypoandrogenism, elevated FSH and delayed or absent maturation of spermatogenesis. *In vivo* hormonal studies, *in vitro* and genetic studies were performed. This case and other reported since, highlight the sequential role of placental hCG and fetal LH in testicular maturation. This work demonstrates the critical role of alpha-beta subunit hetero-dimerization for LH function. We demonstrate, for the first time in this type of patients, that assisted fertility is feasible and that spermatogenesis is restored by hCG treatment. The phenotype of the heterozygote mutation phenotype has been studied in the son of the initial case at birth.

Papers related to the Ph D Thesis

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4. **Valdés-Socin H**, Salvi R, Daly AF, Gaillard RC, Quatresooz P, Tebeu PM, Pralong FP, Beckers A. Hypogonadism in a patient with a mutation in the luteinizing hormone beta-subunit gene. *N Engl J Med.* 2004;351(25):2619-25. **Impact factor: 54,4**

5. **Valdés-Socin H**, Salvi R, Thiry A, Daly A, Pralong F, Gaillard R and A Beckers. Testicular effects of isolated luteinizing hormone deficiency and reversal by long-term human chorionic gonadotropin treatment. *Clin Endocrinol Metab.* 2009;94 (1):3-4. **Impact factor: 6,5**