disorders. Most of the known genetic causes of multiple pituitary hormone deficiency have been investigated as monogenic disorders. It can be challenging to predict clinical features from genetic data, as loss of function mutations in some genes can present with a spectrum of phenotypes ranging from craniofacial abnormalities, intellectual disability, and neurosensory and neuroendocrine defects to pituitary hormone deficiency with no other abnormalities. Although maternal exposures could be contributing factors, the contribution of rare, deleterious variation in other genes is a likely contributor. In humans, loss of function mutations in the transcription factor SIX3 cause variable, autosomal dominant holoprosencephaly with incomplete penetrance, and mouse models recapitulate some of the clinical features. Because *Six3* and *Pou1f1* gene expression patterns overlap in pituitary development, we hypothesized that doubly heterozygous mice ($Six3^{+/-}$; $Pou1f1^{+/dw}$) might have pituitary anomalies not present in singly heterozygous mice. We intercrossed $Six3^{+/-}$ and $Pou1f1^{+/dw}$ mice to produce doubly heterozygous animals. At e11.5, both $Six3^{+/-}$ and $Six3^{+/-}$; $Pou1f1^{+/dw}$ exhibited abnormal morphology of the developing infundibulum and Rathke's pouch, although ventral diencephalon expression of *Tle4, Fgf10,* and *Nkx2.1* appeared normal. Both newborn $Six3^{+/-}$ and $Six3^{+/-}$; $Pou1f1^{+/dw}$ littermates had abnormal pituitary gland morphology that resembled that of $Aes^{-/-}$. AES is a co-repressor that interacts with SIX3. Specification of vasopressin neurons and anterior lobe hormone cell types appeared normal. Mice of all genotypes were born in expected Mendelian ratios (N=144, p=0.49), and there were no significant differences in body weight at 3 wks. A portion of the $Six3^{+/-}$ and doubly heterozygous mice developed hydrocephalus, exhibited failure to thrive, and died (6-9% of N=82, 85, respectively). At 6 wks, 25% (N=61) of the $Six3^{+/-}$; $Pou1f1^{+/dw}$ animals exhibited striking pituitary dysmorphology in which the rostral aspect of the pituitary penetrated the palate. This was not observed in single heterozygotes. These results reveal that haploinsufficiency for *Six3* affects Rathke's pouch formation, resulting in pituitary gland dysmorphology in and around the stem cell niche. A significant portion of the $Six3^{+/-}$; $Pou1f1^{+/dw}$ doubly heterozygous mice have a more pronounced pituitary phenotype than $Six3^{+/-}$, supporting the possibility of digenic pituitary disease and highlighting phenotypic variability. Genetically engineered mice provide an excellent tool for assessing the possibility of gene-gene interactions that could enhance the severity of hypopituitarism and associated craniofacial development.

Reproductive Endocrinology

MALE REPRODUCTIVE HEALTH - FROM HORMONES TO GAMETES

In Vitro Effect of Different Follicle-Stimulating Hormone Preparations on Sertoli Cells

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SAT-035

Follicle-stimulating hormone (FSH) is the main regulator of spermatogenesis and plays a key role in the development and function of the reproductive system. To assess the effects of different FSH preparations in combination with testosterone on porcine pre-pubertal Sertoli cells, we performed Real Time PCR analysis of AMH, inhibin B and FSH-r, Western blotting analysis of AKT-posphoAKT, ERK1/2-posphoERK1/2, ELISA assay for AMH and inhibin B and a high-throughput proteomic analysis.We observed that all three preparations induced a reduction of AMH in terms of mRNA and secreted protein and, an increase of inhibin B in terms of mRNA in all the formulations while, only α-follitropin induced an increase of inhibin B secreted in the culture medium. Proteomic analysis permitted us to identify 46 secreted proteins.Of those, the SPARC protein was down-regulated after the treatment with testosterone associated with α-follitropin, β-follitropin and urofollitropin (vs group stimulated with T alone). 11 proteins were up-regulated by the different FSH preparations. In detail, Hemoglobin subunit beta, TPA and TPI have been observed to be up-regulated by stimulation with testosterone in addition with α-follitropin or with β-follitropin and or with urofollitropin. All preparations induced an increase in the secreted inhibin beta A chain, but in the medium after stimulation with urofollitropin we observed an higher increase in the levels of this protein. β-follitropin, associated with testosterone, specifically induces an up-regulation of 8 specific secreted proteins.Our study, showing that the three FSH preparations were associated with different effects, could offer the opportunity to shed light inside applications to personalized reproductive medicine.

Thyroid

BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID II

Monitoring Thyroid Function Tests in Patients on Lithium: Adherence to Recommended Guidelines and Comparison of Practice Patterns in a Health Care System

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