normal pregnancies to term. Thus, Pdyn-Cre/Kiss$^{fl/fl}$ KO females have complete infertility. Ongoing studies of male fertility data suggest that Pdyn-Cre/Kiss$^{fl/fl}$ KO males are subfertile, in accordance with their variable spermatogenesis phenotype - some KO males sired pups when paired with proven, WT females, whereas other KO males are infertile. Future experiments include assessing the capability of Pdyn-Cre/Kiss$^{fl/fl}$ KO mice to respond to chronic, exogenous kisspeptin and GnRH administration to rescue abnormal LH pulsatility and estrous cyclicity in females, as well as the impaired fertility in both sexes.

Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY BASIC RESEARCH ADVANCES

MIF Inhibition Suppresses Cell Viability and Induces Apoptosis via the ATF4-CHOP Pathway in Mouse Pituitary AtT-20 Cells

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Cushing's disease (CD) is characterized by cortisol overproduction due to ACTH hypersecretion from a pituitary tumour (PT). With an incidence of approximately 1.2 to 2.4 cases per million per year, CD patients have higher rates of morbidity and mortality than the general population. Surgical management is currently the first therapeutic option. However, remission rates vary between studies, and patients may suffer from complications caused by hormonal abnormalities from remnant PT tissues, the surgery itself, as medical treatment options are limited. Macrophage migratory inhibitory factor (MIF) is a cytokine expressed in various tumors, including ACTH-producing PTs, and has been found to play a crucial role in tumorigenesis. Previous studies demonstrate that MIF regulates cell growth via the signal transducer and activator of transcription 3 (STAT3) pathway, the mammalian target of rapamycin (mTOR) pathway, and autophagy. Together, these indicate MIF as a potential therapeutic target for PTs. However, the role of MIF in ACTH-producing PTs remains unknown. Using mouse ACTH-producing PT cells, AtT-20 cells as a model, we established that MIF overexpression led to increased cell growth. In contrast, pharmacological MIF inhibition by 4-iodo-6-phenylpyrimidine (4-IPP) and (S,R)-3-(4-Hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid (ISO-1) and genetic MIF downregulation by siRNA both suppressed cell viability and induced apoptosis, suggesting an anti-apoptotic role of MIF. Genetic MIF downregulation also increased the expression of apoptosis-inducible genes such as activating transcription factor 4 (ATF4) and C/EBP homologous protein (CHOP), and reduced ACTH production. However, pharmacological MIF inhibition had no effect on ACTH production, which suggests that the mechanism of pharmacological MIF inhibition may be different from MIF downregulation. Neither MIF upregulation nor downregulation affected cell signalling pathways such as the STAT3 pathway, the mTOR pathway, or autophagy. Our findings suggest that MIF inhibition can be a viable therapeutic approach for ACTH-producing PTs.

Neuroendocrinology and Pituitary

NEUROENDOCRINOLOGY AND PITUITARY BASIC RESEARCH ADVANCES

Mild Maternal Undernutrition Results in a Premature Neonatal Leptin Surge that Promotes Resistance in Male Offspring to a High Fat Diet

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Malnutrition alters leptin signaling, resulting in dysregulation of pituitary somatotropes that may be sex-specific. We reported sex differences in acute fasting responses with reductions in serum leptin in males, but not females (1). Maternal undernutrition can also alter the neonatal leptin surge by blunting with 50% food deprivation (2), causing a premature surge with 30% food deprivation (3), and resulting in metabolic dysfunction in adulthood (2,3). We developed a milder undernutrition model to relate more closely to society's nutritional challenges and to test the hypothesis that a shift in the neonatal leptin surge would result in sex-specific metabolic changes. Compared to paired *ad libitum* (Fed) dams, we studied pups from undernourished dams that were calorically restricted by 20% (CR20) from embryonic day 15 until postnatal day (PND) 21.

We tested 216 offspring from 11 Fed dams and 13 undernourished dams (CR20), detecting a leptin surge in control fed progeny at PND11. CR20 offspring of both sexes had an early surge (PND8) that was 62% ($P<0.0001$) higher compared to offspring of Fed dams and was maintained at high levels until PND11. Interestingly, GH levels at PND1 were 354% ($P<0.0001$) higher in the CR20 progeny compared to controls. By PND16, serum IGF-1 levels in underfed pups were lower than levels in control pups (111364±71 vs 244145±135 pg/ml; $P=0.0277$). CR20 male weights were 13.1% lower ($P<0.0001$) and lengths were 8.4% shorter ($P=0.0002$) than controls by 8 weeks of age and did not recover. CR20 female weights were lower by 11% ($P=0.0013$) and lengths were shorter up to 3 weeks of age.

At 3 months of age, offspring were exposed to a 45% HFD for 16 weeks, testing 54 pups from 3 dams per nutrient status. Fed mice from both sexes responded to the HFD with an average weight gain of 12.3g ($P<0.0001$) in females and 12.6g ($P<0.0001$) in males. Females from CR20 dams also gained weight (8.74g, $P<0.0001$) on the HFD, but was significantly lower than females from Fed dams ($P=0.0362$). Surprisingly, male progeny from CR20 dams did not respond to weight gain by HF feeding when compared to control fed males, appearing to be protected from impact.

Sex-specific changes in pituitary *Gh*, *Ghrhr*, and *Ghsr* mRNA levels were as follows. Among CR20 males exposed