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We identified a stop-gain mutation in *eIF4ENIF1* in a family in which multiple women developed primary ovarian insufficiency (POI) at approximately age 30 years. We hypothesized that the same mutation in a mouse model would replicate POI. **Methods:** The *Eif4enif1* C57/Bl6 transgenic mouse model contains a floxed exon 10-19 cassette and a conditional knock-in cassette containing exon 10 with the c.1286C>G stop-gain mutation causing familial POI and WT exons 11-19 ($Eif4enif1^{WT/flx}$). The hybrid offspring of CMV-*Cre* mice with $Eif4enif1^{WT/flx}$ mice were designated $Eif4enif1^{WT/\Delta}$ for simplicity. Follicles were counted in fixed H&E stained ovaries from mice age days 1-5 (primordial and primary follicles), day 10, day 22 (first wave of growing follicles from small preantral to small antral follicles), week 20 (peak fertility), then every 2 months from 10 months to 26 months (follicle exhaustion). Litter frequency, pup number and genotype were recorded. Serum FSH levels were measured by the University of Virginia Ligand Assay and Analysis Core. **Results:** The heterozygotes have no outward or internal phenotypic differences compared to WT ($Eif4enif1^{WT/flx}$), with the exception of reproductive organs in females and males. A subset of female heterozygotes ($Eif4enif1^{WT/\Delta}$) had no litters for 20 weeks (2 of 18; 11%). In those with litters, the average length of time between litters was not different but the final litter was earlier (5.6±2.7 vs. 10.5±0.7 months; p=0.02). Heterozygous breeding pair ($Eif4enif1^{WT/\Delta}$ *x* $Eif4enif1^{WT/\Delta}$) litter size was 60% of WT litter size (3.9±2.3 vs. 7.2±2.1 pups/litter; 0<0.001). The genotypes were 35% $Eif4enif1^{WT/flx}$ and 65% $Eif4enif1^{WT/\Delta}$, with no homozygotes. The number of follicles in ovaries from $Eif4enif1^{WT/\Delta}$ mice was lower starting at the primordial (499±290 vs. 1445±381) and primary follicle stage (1069±346 vs. 1450±193) on day 10 (p<0.05). The preantral follicle number was lower starting on day 21 (213±86 vs. 522±227; p<0.01) and the antral follicle count was lower starting on week 20 (78±38 vs. 119±18; p<0.01). The FSH level in 12-month old mice during estrus was higher in a heterozygote compared to WT (25.0 vs. 12.1 ng/mL). **Conclusions:** Heterozygous *Eif4enif1* stop-gain mutants have follicle loss documented by day 10, decreased pup number with no homozygotes, earlier end of reproductive function and elevated FSH levels. These mice replicate the POI phenotype in women. *eIF4ENIF1* regulates protein translation by binding and storing eIF4E bound mRNA. Therefore, the unique mouse model provides a platform to study temporal and spatial regulation of protein translation across oocyte and embryo development in mammals. Further studies will determine whether follicle loss results from premature protein translation in oocytes.

Reproductive Endocrinology

RECIPROCAL EFFECTS OF OVARIAN AND METABOLIC DYSFUNCTION

MicroRNA-21 Modulates White Adipose Tissue Browning and Altered Thermogenesis in a Mouse Model of Polycystic Ovary Syndrome

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Background and Aim: Polycystic ovary syndrome (PCOS) is associated with obesity, and white adipose tissue (WAT) and brown adipose tissue (BAT) dysregulation. However, the molecular mechanisms that mediate WAT and BAT derangements in PCOS are poorly understood. Subcutaneous (SC) WAT (SC-WAT) can transition to a beige/brite adipose tissue phenotype (browning) under altered thermogenic conditions. MicroRNAs play critical functions in brown adipocyte differentiation and maintenance. We aim to study the role of microRNA-21 (miR-21) in androgen-mediated browning and beiging derangements in both SC-WAT and BAT. **Methods:** Three week-old miR-21 knockout (miR21KO) or wild type (WT) female mice were treated with dihydrotestosterone (DHT, 8 mg/silastic tube) or vehicle for 90 days (n=12/grp). Body composition was measured by EchoMRI. Energy expenditure (EE), oxygen consumption (VO2), and carbon dioxide production (VCO2) were measured by indirect calorimetry. Glucose homeostasis was measured by oral glucose tolerance test (OGTT). HOMA-IR index was calculated from fasting serum glucose and insulin levels. Gene expression for browning (UCP1, Cox7a1, Elov3, Dio2 and Cidea) and beiging (Hspb7 and Txb1) markers was quantified by RT-qPCR in SC-WAT and BAT. **Results:** DHT increased body weight (25.07 ± 0.52 vs 21.79 ± 0.47 g, p<0.05) and fat mass (4.60 ± 0.46 vs 1.98 ± 0.12 g, p<0.05), impaired OGTT (186.10 ± 5.99 vs 250.70 ± 14.76 mg·min/dL, p<0.05), and did not significantly change EE, VO2 or VCO2 in WT mice. All browning markers were downregulated by DHT in SC-WAT; however, only iodothyronine deiodinase 2 (Dio2) downregulation reached significance in both SC-WAT and BAT (by 53 and 40%, respectively) compared with the vehicle-treated mice. Beiging markers were significantly upregulated in SC-WAT and did not change in BAT. DHT-treated miR21KO mice showed attenuated DHT-mediated increase in body weight (23.84 ± 0.99 vs 25.07 ± 0.52 g, p<0.05) compared with WT mice. MiR-21 ablation did not modify DHT-mediated increase in fat mass or OGTT but worsened insulin resistance as calculated by the HOMA-IR index. Additionally, DHT-treated miR21KO mice showed a trend to reduced EE, VO2 and VCO2 values compared with DHT-treated WT. Gene expression analysis showed an exacerbation in DHT-mediated reduction in browning markers expression in the SC-WAT. Additionally, the induction in the adaptive beiging response was abolished in SC-WAT. **Conclusion and Significance:** These findings suggest that adipose tissue miR-21 may have a protective role in PCOS and ameliorate the DHT-mediated decrease in energy expenditure. Adipose tissue-specific modulation of miR-21 levels could be a novel therapeutic approach for the treatment of PCOS-associated metabolic derangements. (Supported by NIH grants NIGMS P20GM121334 to LLYC and DGR, NIDDK R21DK113500 to DGR, NIGMS P20GM104357 and NHLBI P01HL51971).