Does Diet-Induced Obesity Alter Metabolic and Reproductive Traits of Female Mice Lacking AMH Signalling?

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Obesity is closely associated with reproductive disorders, including polycystic ovary syndrome (PCOS) and infertility. Diet-induced obesity in female mice has been suggested to accelerate primordial follicle recruitment leading to premature ovarian aging. Early depletion of primordial follicle pool is also observed in mice lacking anti-Müllerian hormone (AMH) signalling, such as AMH deficient (AMHKO) mice and AMH type 2 receptor deficient (MRKI) mice. On the other hand, diet-induced obesity also results in disrupted estrous cyclicity and ovulatory failure, a phenotype resembling PCOS. To address these opposing aspects of infertility, ovarian aging and PCOS, female AMHKO and MRKI mice were exposed to a high fat high cholesterol diet (HFHCD).

Female AMH signalling deficient mice and their corresponding wild-type (WT) littermates at 30 days of age were fed a HFHCD or control diet (CD) for 14 weeks. Metabolic and reproductive parameters were assessed at the end of the treatment period.

HFHCD led to significantly increased body weight and total fat mass in WT, AMHKO and MRKI mice ($P<0.01$). Consistently, increased total serum leptin levels were observed in the HFHCD-fed mice. Serum adiponectin levels were decreased in HFHCD-fed WT mice compared to CD-fed WT mice ($P<0.05$). Interestingly, CD-fed AMHKO mice had significantly lower adiponectin levels than CD-fed WT mice ($P<0.05$), which was not further affected upon HFHCD exposure. HFHCD treatment induced glucose intolerance, as assessed by IPGTT ($P<0.01$). However, AMH signaling deficient mice did not differ from WT mice. HFHCD-fed mice had a ~15% lower respiratory exchange ratio compared to CD-fed mice ($P<0.01$). Energy expenditure (EE) was significantly increased in HFHCD-fed WT mice compared to CD-fed WT mice. Interestingly, CD-fed AMHKO mice tended to have a higher EE compared to CD-fed WT mice ($P=0.06$) - which was not further increased upon HFHCD treatment. HFHCD treatment did not affect physical activity in all groups. Estrous cyclicity was irregular in HFHCD-fed mice compared to CD-fed mice, with HFHCD-fed mice showing a ~65% reduction in number of complete estrous cycles ($P<0.01$). No genotype difference was observed. Our preliminary ovarian composition data confirmed the increased number of total growing follicles in AMHKO mice compared to WT mice. However, no dietary effect was observed among groups. In line with the disrupted estrous cycles, both HFHCD-fed WT and AMHKO mice tended to have a decreased number of corporal lutea compared to CD-fed mice. Interestingly, HFHCD-fed WT mice displayed ~50% higher serum AMH levels compared to CD-fed mice ($P<0.05$), suggestive of dysregulated granulosa cell function. Analysis of the primordial follicle pool is ongoing.

In summary, diet-induced obesity disrupts estrous cyclicity and alters granulosa cell function. AMH signalling deficiency had mild effects on studied metabolic phenotypes.