Abstract

Obesity is a prevalent disease worldwide, recurrently associated with infertility. Expansion of adipose tissue leads to endocrine imbalance, particularly increased circulating leptin levels, which potentially affects ovarian function. Although systemic leptin resistance was demonstrated in various organs like hypothalamus, liver or muscles, no previous study characterized putative changes in leptin signalling in the ovary in the course of obesity. Importantly, leptin is a key regulator of ovarian function, with known dose- dependent effects on ovarian cells. Indeed, leptin was shown to regulate steroidogenesis, control follicular reserve, as well as oocyte maturation and ovulation. Thus, we used diet- induced obese (DIO) and pharmacologically hyperleptinemic (LEPT) mice protocols to characterize leptin signaling in the ovary during obesity progression and study the effects of leptin on cumulus and theca cells function.

Mice were subjected to high- fat diet (HFD) or chow diet (CD) for 4 or 16 weeks (wk), and treated with leptin or saline for 16 days. We initially observed after 4 wk HFD the hyperactivation of leptin signalling in the ovary, measured by increased phosphorylation of tyrosine 985 of leptin receptor (Tyr985ObRb) and its conserved inhibitor the suppressor of cytokine signalling 3 (SOCS3). On the other hand, after 16 wk HFD treatment leptin signalling was repressed, evidenced by decreased phosphorylation of Janus kinase 2 (pJAK2) with parallel upregulation of SOCS3 protein levels, supporting the establishment of leptin resistance. Transcriptome analysis of cumulus cells (CCs), the somatic companions of the oocyte, showed dramatic changes which correlated with maternal body weight. Furthermore, in early obesity (4 wk HFD) the hyperactivation of leptin signalling was linked to increased glucose metabolism but decreased epigenetic regulation and cytoskeleton organization. Conversely, during late obesity (16 wk HFD) changes in gene expression pointed to maintenance of inflammatory pathways and morphological rearrangement.

The present study revealed for the first time the establishment of leptin resistance in the ovary of obese mice, and characterized temporally changes in CCs gene expression during obesity progression, highlighting the specific role of increased leptin signalling. These results represent a potential tool in assisted reproductive clinics, helping characterizing levels of disease progression and ovarian failure throughout obesity.

Finally, the effects of maternal obesity and changes in local leptin signalling on folliculogenesis and oocyte maturation were described in the review. Potential outcomes for oocyte quality and early embryo development were characterized. Interestingly, we used transcriptome of oocyte and GC isolated from different stages of folliculogenesis in women by Zhang's, to characterize leptin signalling component expression. It is suggested that decreased leptin signalling during obesity might contribute to accelerated follicle loss, disturbed antral follicle formation or improper oocyte maturation.