by the mid-cycle surge of luteinizing hormone (LH). The CL is a transient ovarian endocrine structure that maintains pregnancy in primate during the first trimester and in rodents during the entire pregnancy by producing steroid hormone progesterone (P4). CL growth and differentiation are tightly regulated by both survival and cell death signals, including endocrine (LH), intra-ovarian regulators, and cell-cell interactions. Neuregulin-1 (NRG1) is a member of the epidermal growth factor-like factor family that mediates it's effect through the erythroblastoma (ErbB) family. However, the detailed mechanisms associated with the interplay of NRG1 and its receptors in CL function is not known. Therefore, we examined the role and action of NRG1 and its receptors in the gonadotropin signaling pathway that impacts CL functions. Immunocolocalization of NRG1 and ErbB2/3 in pregnant rat CL on day 14 and 21 suggest that both NRG1 and ErbB2/3 are differentially expressed in CL. Moreover, both NRG1 and ErbB2/3 are highly expressed in rat CL on day 14 compared to day 21. Furthermore, *in vitro* studies revealed that rat luteal cells (LCs) treated with exogenous tumor necrosis factor-α (TNFα, an inflammatory cytokine) promoted apoptosis in LCs in a dose and time-dependent manner. However, the effects of TNFα was attenuated in presence of exogenous NRG1. Under these experimental conditions, immunoblot analysis indicated that exogenous TNFα treatment in the presence of NRG1 inhibits apoptosis through increased levels of the anti-apoptotic proteins Bcl2 and Bclxl, and activation of ErbB2-ErbB3-PI3K-Akt signaling pathway. Collectively, these studies provide new insights on the NRG1-mediated anti-apoptotic mechanism in LCs through ErbB3-ErbB2-PI3K-Akt→Bcl/Bcl-xL pathway and may have important clinical implications.

**Acknowledgements:** This study was supported in part by National Institutes of Health Grants 1 SC1 GM130544-01A1, 1SC3GM113751 and G12RR03034. This research was conducted in a facility constructed with support from the Research Facilities Improvement Grant C06RR018386 from the National Institutes of Health National Center for Research Resources.

## Reproductive Endocrinology

### OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

***Hepatic Dysregulation of Bile Acid Homeostasis in Hyperandrogenemic Female Mouse Model of Polycystic Ovary Syndrome***

*Alexandra M. Huffman, MS, Samar Rezq, PhD, Jelina Basnet, MS, Licy L. Yanes Cardozo, MD, Damian G. Romero, PhD.*
University of Mississippi Medical Center, Jackson, MS, USA.

**Introduction and Purpose**: Polycystic Ovary Syndrome (PCOS) is recognized as the most common endocrine disorder in women of reproductive age. Notably, PCOS women with hyperandrogenism have a pronounced increased risk for cardio-metabolic comorbidities compared with healthy individuals. Bile acids are endocrine signaling molecules that modulate hepatic lipid, glucose, and energy metabolism by aiding in absorption of lipids. Alteration of bile acid homeostasis affects overall metabolic homeostasis and contributes to pathogenesis of an array of metabolic diseases, although the molecular mechanisms of this have not been studied in PCOS. **Methods:** Four-week old C57BL/6N female mice were implanted subcutaneously with dihydrotestosterone (DHT, 8.0 mg) or vehicle silastic tubes (n=8/grp). Weekly body weight, food intake, and body composition was assessed. Fasting serum was obtained and the oral glucose tolerance test (OGTT) was performed in the last week of treatment. Animals were euthanized on treatment day 90 and livers were harvested. Expression levels of mRNA were assessed using RT-qPCR. **Results:** DHT treated females had significantly higher liver mass (1,387 ± 51 vs 1,197 ± 29 g, $p<0.05$), increased lean mass (21.25 ± 0.27 vs 19.58 ± 0.23 g, $p<0.05$) and increased fat mass (4.83 ± 0.47 vs 3.59 ± 0.36 g, $p<0.05$) compared to the vehicle counterparts. These hyperandrogenemic females additionally showed altered glucose homeostasis, having increased fasting glucose (201.10 ± 11.11 vs 152.80 ± 9.23 mg/dL, $p<0.05$) and an increased area under the curve (209.2± 11.0 vs 160.8± 3.5 mg.min/dL, $p<0.05$) following OGTT. Hepatic expression of both classic (Cyp8b1, 1.4 ± 0.1-fold, $p<0.05$) and alternative (Cyp7b1, 2.0 ± 0.3-fold, $p<0.05$) bile acid synthesis cytochrome P450 enzyme genes were significantly upregulated in DHT treated animals. Additionally, expression of sulfotransferase Sult2a2 was completely abolished in DHT treated animals compared with vehicle animals, indicating the possibility of androgen regulation of the sulfonation of bile acids marked for elimination. Liver expression of both the bile acid receptor G-protein coupled bile acid receptor 1 and the androgen receptor were both significantly downregulated (Gpbar1: 0.68 ± 0.08-fold, AR: 0.46 ± 0.04-fold, $p<0.05$) in DHT treated animals. **Conclusions:** Bile acid synthesis, transport, and elimination are tightly controlled processes in the liver to maintain a constant bile acid pool and limit reabsorption. Together, our results highlight the potential role of androgens in DHT-treated female mice in the dysregulation of bile acid homeostasis and its potential contribution to influence metabolic dysfunction. (Supported by NIH grants NIGMS P20GM-121334 to LLYC and DGR, and NIH NIDDK R21DK-113500 to DGR and the Mississippi Center of Excellence in Perinatal Research.)

## Reproductive Endocrinology

### OVARY, TESTES, AND IMPACT OF HORMONES ON METABOLIC FUNCTION

***Involvement of BMP-15 in Glucocorticoid Actions on Ovarian Steroidogenesis by Rat Granulosa Cells***

*Chiaki Kashino, MD, Toru Hasegawa, MD, PhD, Yasuhiro Nakano, MD, Nahoko Iwata, PhD, Koichiro Yamamoto, MD, Yasuhiko Kamada, MD, PhD, Hisashi Masuyama, MD, PhD, Fumio Otsuka, MD, PhD.*
Okayama University Grad School, Okayama, Japan.

Glucocorticoid receptor (GR) are known to be expressed in the ovary and glucocorticoids are shown to exert direct effects on granulosa cell functions. In the clinical setting, menstrual abnormality, amenorrhea and hypermenorrhea can be shown in patients with glucocorticoid excess. On the other hand, glucocorticoids can also be used for the treatment of PCOS with hyperandrogenism. However, the effects of glucocorticoids on the reproductive system have not been fully elucidated. In the present study, we investigated the