ASAS CELL BIOLOGY SYMPOSIUM: LONG-TERM CONSEQUENCES OF MATERNAL AND NEONATAL NUTRITION FOR PREGNANCY AND POSTNATAL OUTCOMES

0106 Lactocrine programming of postnatal reproductive tract development. F. F. Bartol[*1] and C. A. Bagnell[2], [1]*Auburn University, AL,* [2]*Rutgers University, New Brunswick, NJ.*

Lactocrine signaling occurs when bioactive factors are communicated from mother to offspring as a consequence of nursing. In the pig (*Sus scrofa*), relaxin was identified as a prototypical lactocrine-active factor in colostrum. Administration of exogenous relaxin from birth [postnatal day (PND) = 0] increased neonatal uterine estrogen receptor-α (ESR1) expression. Using multispectral immunofluorescence imaging, expression of ESR1 is detectable in nascent endometrial glandular epithelium and stroma within 2 d of birth, and supports uterine gland genesis. Imposition of a lactocrine-null condition for 2 d from birth by substitution of porcine milk replacer for colostrum retarded endometrial development and uterine gland genesis. Compared with nursed gilts, replacer feeding from birth reduced stromal ESR1 expression and endometrial cell proliferation, and increased endometrial relaxin receptor expression by PND 2. Effects of transient imposition (48 h) of the lactocrine-null state on endometrial morphology were pronounced by PND 14, when cell proliferation, reflected by patterns of proliferating cell nuclear antigen immunostaining, and development of nascent endometrial glands were markedly reduced. Collectively, the observations suggested a lactocrine-driven mechanism regulating establishment of the uterine developmental program and endometrial adenogenesis in the neonatal pig. The lactocrine hypothesis for maternal programming of reproductive tract development predicts that neonates deprived of colostrum will have reduced uterine capacity to support conceptus development as adults due to disruption of the uterine developmental program shortly after birth. Results of a retrospective study involving 381 gilts indicated that lifetime fecundity (number of piglets born alive over ~4 parities per gilt) was reduced in animals that consumed minimal amounts of colostrum as indicated by low serum immunocrit values on PND 0. To the extent that the first 2 d of neonatal life constitute a critical period for establishment of the uterine developmental program, effects of replacer feeding for 2 d from birth on global patterns of uterine gene expression were evaluated using whole uterine transcriptome analysis via RNA sequencing (RNA-seq). Analyses were performed on uteri (n = 4/group) obtained on PND 2 from gilts that were either nursed (PND 2N) or fed porcine milk replacer from birth (PND 2R). Using RNA-seq, 896 genes were determined to be differentially expressed (> twofold) between the PND 2N and PND 2R groups. Thus, disruption of lactocrine signaling has profound effects on neonatal uterine gene expression. The results indicate that lactocrine support is required to establish a normal uterine developmental program in the neonatal pig.

Key Words: development, lactocrine programming, neonate

0107 Long-term consequences of maternal and neonatal nutrition for pregnancy and postnatal outcomes. D. G. Burrin[*1] and B. Stoll[2], [1]*USDA-ARS Children's Nutrition Research Center, Houston, TX,* [2]*Baylor College of Medicine, Houston, TX.*

The nutritional environment during fetal and neonatal life is a key determinant affecting the risk for adult-onset diseases, such as diabetes and obesity. Studies show that preterm infants experience increased risk for glucose intolerance as adolescents and young adults. Preterm infants often receive parenteral nutrition for several days or weeks after birth as a lifesaving form of clinical support. Considerable evidence shows that the normal and dysfunctional secretion of gut hormones play a key role in metabolic health and diseases, including diabetes and obesity. We have used the model of parenterally fed neonatal pig to test whether the modality of nutritional support (enteral vs. parenteral) significantly impacts both the pattern of gut hormone secretion and metabolic function. We first showed (J. Nutr.140:2193) that chronic parenteral (PN) compared with enteral (EN) nutrition in neonatal pigs for 2 wk leads to an adverse metabolic phenotype marked by increased glucose intolerance, insulin resistance, body fat deposition, and reduced pancreatic β-cell proliferation. We also showed (JPEN.36:538) that the pattern of enteral nutrition (intermittent vs. continuous) is a stronger determinant than modality of nutrition to optimize glucose utilization and insulin sensitivity. We also showed that the secretion of gut incretin hormones, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide 1 (GLP-1) correlated closely with glucose utilization and insulin sensitivity. An important question is whether the adverse metabolic phenotype that results from that chronic PN during the first 2 wk of neonatal life persists into late infancy and adolescence. We recently tested this in newborn pigs by feeding either PN or EN for 2 wk, followed by ad lib feeding of a high-fat (30%) and sucrose (20%) diet for 5 mo. We measured body composition by dual-emission X-ray absorptiometry at 2 and 8 wk, and 5 mo, and performed an IVGTT at 5 mo. Our results showed that PN during the neonatal period increased adiposity transiently into early infancy, but PN-induced glucose intolerance, adiposity, pancreatic β cell number, and hepatic steatosis were not sustained into adolescence, even when challenged with an obesogenic diet. This presentation will highlight the link between enteral nutrition as a key trigger for gut hormone secretion and function, and how these hormone-signaling pathways may be relevant to domestic animal growth.

Key Words: nutrition, pregnancy, signaling pathways

0108 The epigenetic landscape of the β-cell in IUGR rats. S. Pinney and R. A. Simmons*, *Perelman School of Medicine, University of Pennsylvania, Philadelphia.*

The abnormal intrauterine milieu of intrauterine growth retardation (IUGR) permanently alters gene expression and function of pancreatic b-cells, leading to the development of diabetes in adulthood. Expression of the pancreatic transcription factor Pdx1 is permanently reduced in IUGR and epigenetic modifications are responsible for this decrease. The Pdx1 encodes a homeobox transcription factor, critically important for β-cell function and development. The fetal IUGR state is characterized by loss of USF-1 binding at the proximal promoter of Pdx1, with deacetylation of histones H3 and H4, due to recruitment of the histone deacetylase (HDAC1) and the co-repressor Sin3A. After birth, H3K4 is demethylated and H3K9 is methylated. During the neonatal period, the reduction in Pdx1 expression and these epigenetic changes can be reversed by HDAC inhibition. Finally, once diabetes occurs, DNA methylation of the CpG-island in the proximal promoter ensues, resulting in permanent silencing of the Pdx1 locus. Exendin-4 (Ex-4), a long-acting glucagon-like peptide 1 (GLP-1) analog, given on d 1 to 6 of life increases Pdx1 expression and prevents the development of diabetes in the IUGR rat. The Ex-4 increases USF-1 and PCAF association at the proximal promoter of Pdx1, thereby increasing histone acetyl transferase (HAT) activity, which leads to a permanent increase in histone H3 acetylation and H3K4 methylation. Normalization of these histone modifications precludes DNA methylation, thereby preventing silencing of Pdx1 in islets of IUGR animals. These studies demonstrate a novel mechanism whereby a short treatment course of Ex-4 in the newborn period prevents diabetes in adulthood by restoring Pdx1 promoter chromatin structure, thus preserving Pdx1 transcription. Finally, using the HELP assay, we generated the first DNA methylation map of the rat genome in normal and IUGR β-cells. We validated candidate dysregulated loci with quantitative assays of cytosine methylation and gene expression. The IUGR changes cytosine methylation at 1400 loci in male rats at 7 wk of age, preceding the development of diabetes and thus representing candidate loci for mediating the pathogenesis of metabolic disease that occurs later in life. Epigenetic dysregulation occurred preferentially at conserved intergenic sequences, frequently near genes regulating processes known to be abnormal in IUGR islets, such as vascularization, β-cell proliferation, insulin secretion, and cell death, associated with concordant changes in mRNA expression. These results demonstrate that epigenetic dysregulation is a strong candidate for propagating the cellular memory of intrauterine events, causing changes in expression of nearby genes and long-term susceptibility to type 2 diabetes.

Key Words: diabetes, epigenetic, programming