

Altered renal signalling in rat offspring born small

D.H. Hryciw, J.F. Briffa, A.J. Jeffries and M.E. Wlodek, Department of Physiology, The University of Melbourne, Parkville, VIC 3010, Australia.

Introduction. Low birth weight is associated with an increased predisposition to a number of adult diseases, including hypertension and impaired glucose tolerance. In most developed countries, being born small occurs as a result of the reduction in the delivery of nutrients and/or oxygen to the fetus due to placental insufficiency, which leads to a reduction in fetal growth. We and others have used a rat model that mimics uteroplacental insufficiency, whereby the uterine vessels are bilaterally ligated during late gestation, resulting in offspring born 10–15% lighter than those exposed to sham surgery. In this model, male offspring are more likely to present with a more severe pathophysiological phenotype, which includes hypertension, similar to born small humans. Previously we have established that in the growth restricted offspring, there are sex-specific differences in the JAK/STAT signalling pathway, which may affect proliferation of the heart. JAK/STAT proteins can be activated by the adipokine leptin, however the plasma concentrations of leptin in the control and restricted offspring generated by placental insufficiency are unknown. However, there is a clear gap in our knowledge concerning the leptin signalling pathway in the kidney in the growth restricted offspring. Therefore the aim of this study was to quantify the concentration of maternal and offspring plasma leptin as well as the expression of leptin signalling targets in the kidney of offspring born small.

Method. Animal ethics was approved by the University of Melbourne Animal Ethics committee. Female WKY rats were mated and at day 18 of pregnancy (E18: term is E22), females were randomly allocated to undergo sham surgery or bilateral ligation of the uterine vessels to induce uteroplacental insufficiency, animals were anaesthetised with a tail vein injection of mixed solution containing ketamine (50mg/kg) and ilium Xylazil-20 (10mg/kg). Post mortem of offspring was conducted at postnatal day (PN) 1. Maternal and offspring plasma and offspring kidneys were collected. Plasma leptin concentration was quantified using a Leptin ELISA and gene abundance of megalin, JAK2, STAT5, STAT3, SOCS3 AMPK and PI3K were characterized by Real Time PCR.

Results: Growth restriction was associated with a significantly decreased plasma leptin concentration in females and males at PN1 ($P<0.05$). Further, in mothers with a growth restricted pregnancy, there was a significant increase in plasma leptin concentration ($P<0.05$). Gene expression in the kidney was significantly altered in leptin signalling targets. Specifically, there was a significant difference between the gene profiles between the males and females ($P<0.05$). In males, JAK2 was reduced and AMPKb increased in the restricted offspring at PN1 ($P<0.05$). While in females, megalin and PI3K were decreased, and SOCS3 was increased in the restricted offspring at PN1 ($P<0.05$).

Conclusion: We have demonstrated that in growth restricted offspring, there are sex-specific alterations in leptin signalling targets in the kidney. Further investigation should investigate if these alterations are sustained after the completion of nephrogenesis.