Maternal stress during pregnancy in growth restricted females programs sex-specific metabolic outcomes in second generation male and female rats

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Introduction: Intrauterine growth restriction increases the risk of adult metabolic diseases, with males exhibiting more severe phenotypes than females. These disease risks are not limited to the first, directly exposed generation (F1) but may be transmitted to the next generation (F2). Stress is increasingly prevalent in today's society and exposure of mothers to stress during pregnancy adversely impacts fetal development. However, the effects of a stressful pregnancy on offspring of mothers that were born small are not well understood. We characterised the metabolic phenotype of F2 male and female born to growth restricted F1 mothers and determined if maternal stress during late pregnancy exacerbated the phenotype.

Methods: Late gestation uteroplacental insufficiency was induced on embryonic day 18 by bilateral uterine vessel ligation (Restricted) or sham (Control) surgery in F0 females. Rats were anaesthetised with 4% isoflurane and 650ml.min-1 oxygen flow (reduced to 3.2% isoflurane and 250ml.min-1 oxygen flow when suturing). F1 females (Control, Restricted) were mated with a normal male Wistar Kyoto rat and randomly allocated to Unstressed or Stressed groups. Physiological stressors (24h metabolic cage, tail cuff blood pressure, glucose tolerance test) were introduced during late pregnancy of F1 females in the Stressed group while their Unstressed counterparts were unhandled. F2 body weights were measured from birth and metabolic function characterised by fasting intraperitoneal glucose tolerance test (IPGTT) and insulin challenge at 6 and 12 months (mo). All data were analysed by two-way ANOVA.

Results: F2 males and females from mothers exposed to maternal stress had reduced birth weight (−5%, $P<0.05$). Body weights were not different across groups at all subsequent ages. At 6mo, Control and Restricted F2 males from Stressed mothers had increased area under the glucose curve during IPGTT (+27%, $P<0.05$). F2 Control and Restricted females from Stressed mothers had lower area under the glucose curve during IPGTT (−11%, $P<0.05$) at 12mo compared to their Unstressed counterparts. Insulin sensitivity and secretion were not altered at either ages in males or females.

Conclusions: Mothers exposed to modest stress during late pregnancy, independent of maternal birth weight, reduced F2 birth weight. We have demonstrated that there are sex specific effects of maternal stress on offspring metabolic health. F2 males that were born to Stressed mothers had impaired glucose tolerance that was subsequently normalised. F2 females from mothers exposed to stress during pregnancy were protected and had better glucose tolerance compared to their Unstressed counterparts at 12mo. These effects were all independent of maternal birth weight and these offspring may be predisposed to differential responses when challenged with second-hits including unhealthy diets and sedentary lifestyles.