Sex, drugs and developmental programming of renal, cardiovascular and metabolic dysfunction

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The nature, severity and timing of disease outcomes following an exposure to a poor in utero environment are often dependent upon the sex of the fetus/offspring. These differences cannot be simply explained by the effects of sex hormones post-puberty. Rather, it is hypothesized that males and females make sex specific adaptations to a perturbation during gestation that contribute to differential health outcomes. In animal models it is emerging that the placentas of male and female fetuses respond differently to maternal perturbations.

We have explored the effects of short term glucocorticoid (corticosterone) exposure in the mouse on the placenta during gestation and blood pressure and renal function in offspring. This stress hormone has differential effects on expression of genes controlling placental growth as well as placental transporters in the placentas of males and females. For example, VEGF-a protein levels are decreased in the placentas of males but not females during corticosterone exposure and mRNA expression of *Igf-2* and *Map2k1* is increased. This is associated with changes in placental morphology and growth in the placentas of males fetuses. In adult life, although corticosterone exposure results in offspring of both sexes having a kidney nephron deficit, only male offspring develop cardiovascular and renal dysfunction. We have investigated the effects of corticosterone on the renal renin-angiotensin system and found components of this system are altered in a sexually dimorphic manner, potentially contributing to the disease outcomes.

Secondly, we have investigated the effects of prenatal alcohol exposure using two models in rats designed to mimic human consumption patterns: chronic low dose alcohol exposure throughout pregnancy and “binge” exposure to alcohol around the time of conception. Alcohol exposure altered gene expression of growth factors and glucose transporters in the placental and caused a placental stress response. In the placentas of female fetuses exposed to alcohol around the time of conception, there was a marked deposition of glycogen and altered placental morphology. In adult life, male offspring were prone to metabolic dysfunction (including glucose intolerance and insulin resistance) and obesity. Whilst females also developed insulin resistance, they additionally developed impaired cardiac function and an inability to concentrate urine.

This research highlights the need to study males and females separately at all stages over the life-course: from fetal development to old age and further suggests that physiological outcomes depend upon the sex of the fetus and the placental responses.