Maternal diets rich in fat programme obesity, hypertension and altered sympathetic nervous system activity in adult offspring

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The prevalence of obesity and related disease are rising rapidly worldwide. The majority of Australian adults are overweight or obese and the cardiovascular and metabolic consequences are predicted to have high financial and social costs. Adult risk factors, genetic predisposition and socioeconomic factors all contribute to the development of obesity and obesity related hypertension however there is compelling evidence that the early life environment also contributes to disease progression. This process is termed "developmental programming" and it is hypothesized that maternal dietary imbalance in pregnancy results in fetal and neonatal adaptations including redistribution of blood flow, altered organogenesis and growth in response to altered nutritional availability later in life (Barker 2001; Armitage, Taylor & Poston, 2005). Maternal obesity, maternal essential fatty acid deprivation (Weisinger *et al.*, 2001), or high fat consumption in pregnancy can programme obesity and hypertension in the offspring (Khan *et al.*, 2003). This programmed obesity related hypertension has been associated with dysfunction of the peripheral vascular, metabolic and renal systems (Armitage *et al.*, 2004). We hypothesized that the hypertension and obesity seen in offspring of fat fed mothers was associated with elevated sympathetic nerve activity and altered hypothalamic responses to peripheral appetite controlling peptides and hormones including leptin and ghrelin, and developed an animal model to test the hypothesis.

Female New-Zealand White rabbits were fed either a control (3.5% fat) or high fat diet (HFD, 13.5% fat) for 3 weeks prior to mating and throughout gestation and lactation. After weaning, all offspring were fed a calorie controlled 3.5% fat diet. At 4 months of age all rabbits were instrumented with intracerebroventricular (icv) cannulae and renal nerve electrodes under isoflurane anaesthesia (Prior *et al.*, 2010). The central ear artery was catheterized and arterial pressure, heart rate and sympathetic nerve activity recorded under basal conditions and in response to a stressful stimulus; a jet of air blowing at 100 L/min was directed at the face for 10 minutes. The cardiovascular and renal sympathetic nerve responses to increasing doses of leptin (recombinant murine leptin Peprotech USA, 5-100ng delivered icv) and ghrelin (human ghrelin Auspep, Melbourne 1-5 nMol, icv) on separate days. Body weight was similar between groups, however HFD offspring (n = 9) had heavier visceral white adipose tissue compared with control offspring (n = 8, $p < 0.05$). Rabbits from fat fed mothers demonstrated greater mean arterial pressure (+7%, $p < 0.05$) tacchycardia (+11%, $p < 0.05$) and elevated renal sympathetic activity (+17%, $p < 0.05$) compared with control offspring. The cardiovascular and sympathetic responses to acute stress were similar between groups. Interestingly, although icv administration of ghrelin reduced the pressor, tachycardic and RSNA response to stress in both groups, this reduction in stress responses was abrogated in offspring of fat fed rabbits, compared with controls ($p < 0.05$).

Maternal high fat feeding during pregnancy and suckling results in the development of obesity related hypertension in the offspring. Our results indicate that elevated renal sympathetic activity is associated with the hypertension and that perturbations of the leptin and ghrelin systems in the hypothalamus may underlie the phenotype. Further understanding of which hypothalamic nuclei are affected are the subject of ongoing work.

Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. (2004) *Journal of Physiology* **561(2):** 355-377.

Armitage JA, Taylor PD, Poston L. (2005). *Journal of Physiology* **565(1):** 3-8.

Barker DJ. (2001). *British Medical Bulletin* **60**: 69-88.

Khan IY, Taylor PD, Dekou V, Seed PT, Lakasing L, Graham D, Dominiczak AF, Hanson MA, Poston L. (2003). *Hypertension* **41(1):** 168-175.

Prior LJ, Eikelis N, Armitage JA, Davern PJ, Burke SL, Montani JP, Barzel B, Head GA. (2010.) *Hypertension* **55(4):** 862-868.

Weisinger HS, Armitage JA, Sinclair AJ, Vingrys AJ, Burns PL, Weisinger RS. (2001). *Nature Medicine* **7(3):** 258-259.