PROGRAMMING OF NEPHRON NUMBER IN ADULT SHEEP BY MATERNAL NUTRIENT RESTRICTION IN EARLY GESTATION

G.S. Gopalakrishnan[1], D.S. Gardner[1], L.O. Kurlak[1], S.C. Langley-Evans[1], S.M. Rhind[2], M.T. Rae[2], C.E. Kyle[2], T. Stephenson[1], M.E. Symonds[1] and H. Budge[1]

[1]Centre for Reproduction and Early Life, Institute of Clinical Research, University Hospital, Nottingham, UK and [2]Macaulay Institute, Craigiebuckler, Aberdeen, UK

Maternal nutritional restriction during early gestation results in increased renal glucocorticoid sensitivity at term (Whorwood et al. 2001) and higher blood pressure in early adulthood (Gopalakrishnan et al. 2004). These adaptations may represent compensatory mechanisms as a consequence of decreased nephron number during nephrogenesis in utero (Wintour et al. 2003). In this study, it was hypothesised that maternal nutrient restriction, at the time of kidney development, would permanently reduce nephron number.

Ewes were randomly allocated to either control (C; 8.0 MJ/day) or nutrient restricted (NR; 4.0 MJ/day) diet from day 1 to 95 of gestation, with feed provision of 100% metabolisable energy requirements thereafter (Gopalakrishnan et al. 2004). Offspring delivered spontaneously at term, were ewe reared until weaning and, thereafter, fed at pasture until three years of age when they were humanely euthanased (intravenous sodium pentobarbitone, 170mg/kg) before kidney sampling. All animal procedures were performed under the UK Animals (Scientific Procedures) Act, 1986. Total renal nephron number was determined using an adaptation of an acid-hydrolysis method, renal glucocorticoid receptor abundance by RT-PCR and renal 11β-HSD2 enzyme activity by radiometric assay.

Maternal nutrient restriction in early gestation, followed by restoration of nutrient intake in mid-late gestation, resulted in a lower total nephron number in offspring at 3 years of age (C (n=7): 998 [807-1088]; NR (n=6): 350 [271-372] x 10^3 nephrons/kidney; $P<0.05$, median [interquartile ranges], Mann Whitney U-test) Although glucocorticoid receptor abundance was unaffected (C: 33.9 [27.3-54.8]; NR: 37.3 [29.7-46.4] mRNA:18S rRNA; NS), the enzyme activity of 11β-HSD2 was reduced (C: 0.54 [0.48-0.57]; NR: 0.44 [0.39-0.53] pmol/min/mg protein; $P<0.05$).

In conclusion, persistent renal effects, with a decrease in nephron number and increase in the potential sensitivity to glucocorticoids, are programmed in sheep by maternal nutrition in early fetal development. This may contribute, in part, to raised blood pressure in later life.

Gopalakrishnan GS *et al.* (2004) Am J Physiol Regul Integr Comp Physiol. **287**, R12-20.

Wintour EM *et al.* (2003) J Physiol **549**, 929-935.

Whorwood CB *et al.* (2001) Endocrinology **142**, 2854-2864.

Where applicable, the experiments described here conform with Physiological Society ethical requirements.