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Editorial

Gene expression and delayed nephrogenesis in the growth-restricted rat fetus and neonate

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Gene expression in delayed nephrogenesis

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In this issue of *Acta Physiologica*, Cuffe et al. [1] explore the molecular mechanisms behind impaired nephrogenesis in a rat model of uteroplacental insufficiency and fetal growth restriction. Nephron development was delayed after growth restriction, continuing late into the postnatal period, and this was reflected in increased abundance of branching morphogenesis genes a week after birth.

The developmental origins of health and disease comprise an important field of current research. Its premise is rooted in epidemiological studies that link low birth weight to adult cardiovascular disease [2]. Low weight at birth and subsequent cardiovascular disease is also associated with reduced nephron number [3], which has focused attention on prenatal kidney development. Several animal models (sheep, rodents and primates) have been leveraged for research in the developmental origins field. Techniques to elicit fetal growth restriction are equally various and include maternal hypoxia, dietary restriction, fetal exposure to glucocorticoids and reduction of

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uterine blood flow [4]. In rats both maternal protein restriction [5] and ligation of uterine blood vessels [6] cause a reduction in glomerular number at birth. The authors of the current paper had shown previously that reduced glomerular number after uterine vessel ligation was associated with increased blood pressure at 10 weeks of age [6].

The present study explored whether those findings could be explained by altered expression of genes involved in branching morphogenesis, apoptosis, vasculogenesis and leptin signalling. Vessel ligation was performed on embryonic day 18 (E18) and kidneys harvested on day E20 or postnatal days 1 (PN1) and PN7. Male and female fetuses or offspring were analysed separately. In growth-restricted fetuses or pups, delayed kidney development was evidenced by the presence of a nephrogenic zone with immature glomeruli. Together with upregulation of the branching morphogenesis genes *Ret* and *Gdnf* at PN7 (and increased expression of GDNF protein), this suggested an extension of nephrogenesis late into the postnatal period. There were also significant changes in expression of genes associated with apoptosis, some of which persisted to PN7, which could be further evidence for immaturity of the kidneys. Accordingly, the authors concluded the nephron deficit in fetal growth restriction results from slowing or a delay in nephrogenesis.

Previous work had shown restitution of nephron number could be achieved by cross-fostering growth restricted neonates to a mother with normal lactation. Therefore, an important aspect of the study was to explore how glomerular maturation and gene expression were affected by cross-fostering. Consistent with previous findings, the width of the nephrogenic zone could be reduced by cross-fostering growth-restricted neonates to controls, although the effect was significant only in females. However, there were few clear effects on gene expression in either sex. A particular focus was on the role of leptin signalling. Maternal leptin is transferred through milk to the pup and previous work had shown that plasma leptin was reduced in the pups at PN7, but could be restored by cross-fostering [7]. The results here were rather disappointing. Although genes implicated in leptin signalling (*Megalin* and *Pi3k*) did show reduced expression at PN7, their expression could not be restored by cross-fostering.

Uterine vessel ligation approximates uteroplacental insufficiency and is pertinent to current debate on the role of the placenta in developmental programming [8]. In human pregnancy, an adequate blood supply to the placenta is ensured by extensive remodelling of the uterine spiral arteries. This in turn is dependent on invasion of the endometrium and inner myometrium by extravillous trophoblast of fetal origin. A breakdown in these processes results in inadequate perfusion of the placenta and is a prime cause of fetal growth restriction with or without preeclampsia. Although rodents use different mechanisms to increase uteroplacental blood flow, uterine vessel ligation is a

good proxy for uteroplacental insufficiency in human pregnancy. Of greater concern from a translational aspect is the short length of gestation. Completion of nephrogenesis is among many events in human prenatal development that occur postnatally in rats and mice. An alternative model might be the spiny mouse (*Acomys cahirinus*), a murid rodent with a longer gestation period that gives birth to precocial young. Nephrogenesis is completed before birth in *Acomys* [9] and partial occlusion of the uterine artery causes growth restriction [10].

There remains much to be done before we can fully understand how growth restriction impacts on nephrogenesis and adult cardiovascular disease. More needs to be discovered about the molecular mechanisms and the paper by Cuffe et al. [1] is a significant step in that direction.

Conflict of Interest

The author of this editorial has no conflict of interest to declare.

Reference List

1. Cuffe JSM, Briffa JF, Rosser S, Siebel AL, Romano T, Hryciw DH, Wlodek ME, Moritz, KM: Uteroplacental insufficiency in rats induces renal apoptosis and delays nephrogenesis completion. *Acta Physiol* Version of Record online: 6 NOV 2017 | DOI: 10.1111/apha.12982.

2. Hanson MA, Gluckman PD: Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 94: 1027-1076, 2014.

3. Brenner BM, Chertow GM: Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 23: 171-175, 1994.

4. Carter AM: Animal models of female reproduction and fetal growth and development. In *Handbook of Laboratory Animal Science Volume II Animal Models*. 3rd edition. Edited by Hau J, Schapiro SJ. Boca Raton: CRC Press;: 237-254, 2011.

5. Woods LL, Weeks DA, Rasch R: Programming of adult blood pressure by maternal protein restriction: role of nephrogenesis. *Kidney Int* 65: 1339-1348, 2004.

6. Wlodek ME, Westcott K, Siebel AL, Owens JA, Moritz KM: Growth restriction before or after birth reduces nephron number and increases blood pressure in male rats. *Kidney Int* 74: 187-195, 2008.

7. Briffa JF, O'Dowd R, Moritz KM, Romano T, Jedwab LR, McAinch AJ, Hryciw DH, Wlodek ME.: Uteroplacental insufficiency reduces rat plasma leptin concentrations and alters placental leptin transporters: ameliorated with enhanced milk intake and nutrition. *J Physiol* 595: 3389-3407, 2017.

8. Burton GJ, Fowden AL, Thornburg KL: Placental Origins of Chronic Disease. *Physiol Rev* 96: 1509-1565, 2016.

9. Dickinson H, Walker DW, Cullen-McEwen L, Wintour EM, Moritz K: The spiny mouse (Acomys cahirinus) completes nephrogenesis before birth. *Am J Physiol Renal Physiol* 289: F273-F279, 2005.

10. Dickinson H, Ellery S, Davies-Tuck M, Tolcos M, Nitsos I, Walker DW, Miller SL.: Description of a method for inducing fetal growth restriction in the spiny mouse. *J Dev Orig Health Dis* 8: 550-555, 2017.