The effects of maternal renal insufficiency on glomerular haemodynamics and tubuloglomerular feedback in the ovine fetus

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Maternal renal insufficiency, caused by subtotal nephrectomy (STNx) of the ewe prior to mating, resulted in a number of fetal effects suggestive of fetal volume expansion (Gibson *et al*., 2007). Since we have previously shown that tubuloglomerular feedback (TGF) is operative in fetal life, and that volume expansion causes a decrease in fetal TGF sensitivity (measured as an increase in the turning point (TP) of the fetal TGF curve; Brown *et al*. (2005)), we hypothesized that TP would be increased in fetuses of STNx ewes.

At least two months prior to mating, STNx was carried out under general anaesthesia (1 g sodium thiopentone i.v. followed by 1-3% halothane in oxygen). The right kidney was removed and a branch of the left renal artery (supplying at least one third of the kidney) was ligated. At 137-141 days (term = 150 days) fetuses of both STNx ewes (STNxF) and intact ewes (IntF) were prepared for either renal micropuncture or blood flow measurements. Ewes were anaesthetised with i.v. thiopentone and maintained with 2-4% isoflurane in 100% oxygen via a ventilator. Maternal jugular and carotid vessels were catheterized. After exposure of the uterus via a midline abdominal incision, the fetal lower body was exteriorized and catheters inserted into both tarsal veins, a femoral artery and suprapubically into the bladder. Fetuses were delivered into a water bath (39°C) with care taken to maintain umbilicoplacental blood flow. Vecuronium (0.1 mg/kg i.v.) was administered to the ewe and fetus as needed. In eight IntF and seven STNxF, the left kidney was prepared for micropuncture. In six IntF and eight STNxF, transonics flow probes were positioned around the abdominal aorta and left renal artery for measurement of blood flows. TGF activity was assessed by measuring proximal tubular stop-flow pressure (P_{SF}) in response to various perfusion rates of the loop of Henle.

Although renal blood flow was similar in STNxF and IntF, glomerular filtration rate (GFR, measured as clearance of endogenous creatinine) was higher in STNxF (7.2 ± 0.7 *vs.* 4.6 ± 0.5 (SE) ml/min, $p < 0.01$). Despite this higher GFR, net filtration pressure (NFP) was lower in STNxF than IntF (19.2 ± 0.4 *vs.* 24.4 ± 0.9 mmHg $p < 0.001$). Consequently the calculated filtration coefficient was higher in STNxF ($p < 0.001$). While the maximal change in P_{SF} (ΔP_{SF}; a measure of TGF reactivity) was reduced in STNxF (5.8 ± 0.2 *vs.* 7.1 ± 0.4 mmHg, $p < 0.05$), the turning point (TP) was similar in the two groups (15.0 ± 1.4 *vs.* 16.0 ± 1.3 nl/min).

Contrary to our prediction, TP was not increased in STNxF. However, these STNxF were ~ 10 days older than those we had previously studied (aged 126-128 days). Furthermore, a number of the findings that were suggestive of volume expansion in the younger STNxF (*e.g.*, reduced haematocrit and depressed fractional reabsorption of sodium by the proximal tubule) were not present in this older cohort. Since younger STNxF had GFRs that were similar to IntF (3.6 ± 0.6 *vs.* 2.9 ± 0.5 ml/min, Gibson *et al.*, 2007), the higher GFR in the older STNxF compared to IntF, may indicate that with age, STNxF have managed to adapt their renal function to compensate for the altered maternal fluid and electrolyte balance.

Gibson KJ, Boyce AC, Karime BM & Lumbers ER. (2007) *American Journal of Physiology - Regulatory, Integrative, and Comparative Physiology*, **292:** R1204-R1211.

Brown RD, Turner AJ, Persson AEG & Gibson KJ. (2005) *32nd Annual Meeting of the Fetal and Neonatal Physiological Society*, 07.