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## Intergenerational programming of nephrogenesis and hypertension following feeding of a low-protein diet in rat pregnancy

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Epidemiological associations between birth weight and CVD in adult life are supported by rodent experiments showing that undernutrition in fetal life programmes adult blood pressure<sup>(1)</sup>. In rats the feeding of a maternal low-protein (LP) diet during gestation programmes hypertension<sup>(2)</sup>. Given current interest in the role of epigenetic modification of gene expression, the present study assesses the potential for a nutritional insult to impact across several generations.

Pregnant female Wistar (F0) rats were fed a control (Con; *n* 10) or low-protein (LP) diet (*n* 10) throughout gestation. At delivery all animals were fed the same standard laboratory chow diet. At approximately 10 weeks of age F1-generation offspring were mated to produce a second generation (F2) without any further dietary change. The same procedure was followed to produce the F3 generation. Blood pressure was determined at 8 weeks of age and nephron number was determined at 10 weeks of age<sup>(3)</sup>. Data were analysed using a mixed model ANOVA, with gender and maternal diet as main factors, with adjustment for litter of origin. F1- and F2-generation LP-exposed offspring exhibited raised systolic blood pressure (SBP) compared with Con rats ( $P < 0.001$ ; Table). This intergenerational transmission in the F2 generation occurred via both the maternal and paternal lines. Reduced total nephron number per kidney was observed in F1 ( $P < 0.001$ ) and F2 ( $P < 0.05$ ) animals either subjected to protein restriction during gestation or derived from breeding crosses in which the parents were originally subjected to protein restriction during fetal life.

Generation	Maternal diet and cross†	<i>n</i>	Males				Females				
			SBP (mmHg)		Nephrons per kidney		SBP (mmHg)		Nephrons per kidney		
			Mean	SE	Mean	SE	Mean	SE	Mean	SE	
F1	Con	31	131	3	19 053	1643	29	135	4	21 430	970
	LP	28	139*	5	12 752*	2158	29	137*	4	13 936*	1081
F2	Con × Con	33	121	3	21 187	912	33	126	2	19 367	883
	Con × LP	24	136*	3	13 396*	939	24	131*	5	11 740*	1811
	LP × Con	23	133*	4	12 407*	1176	26	135*	4	13 329*	1825
F3	LP × LP	35	129*	3	11 327*	768	29	130*	3	13 356*	1237
	Con × Con	31	144	3	11 503	1344	29	148	3	13 805	1214
	LP × LP	23	146	3	11 530	915	24	143	3	10 954	1263

Mean values were significantly different from those of Con rats of same gender and generation: \* $P < 0.05$ . †For F2 and F3 crosses the dietary origin of the male parent is shown before the female parent.

The data are consistent with previous findings relating to the effects of an LP diet on blood pressure and renal development in the F1 generation<sup>(4)</sup>. For the first time, it has been shown that fetal protein restriction may play a critical role in determining blood pressure and overall disease risk in a subsequent generation. It is clear from the data that both males and females can transmit their phenotype to a subsequent generation. This finding suggests that maternal diet can influence the nature of epigenetic markers in germ line cells.

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