The effect of prenatal diet and glucocorticoids on growth and systolic blood pressure in the rat

David S. Gardner[1]*, Alan A. Jackson[1] and Simon C. Langley-Evans[2]
[1]*Division of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton SO16 7PX, UK*
[2]*Department of University Medicine, Level D South Block, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK*

Hypertension is a major cardiovascular risk factor for stroke and CHD in Westernized societies (Thom *et al.* 1992). Whilst many factors contribute towards elevated blood pressure, such as low physical activity, obesity, saturated fat, salt and alcohol intake (Ward, 1993), they only explain a proportion of cardiovascular risk. Since adult systolic blood pressure (SBP) tracks growth from infancy, i.e. SBP increases in proportion to the increase in growth from infancy (Law *et al.* 1993) and is related to the rate of increase in SBP in childhood (Lever & Harrap, 1992), then factors that influence SBP in early life may determine future cardiovascular risk. Barker and colleagues (Law *et al.* 1991) have identified a negative relationship between birth weight and SBP in childhood. The relationship remains into adult life and, furthermore, is amplified (Barker *et al.* 1989). Thus, determinants of intrauterine growth leading to an asymmetric or a proportionately-small baby at term also influence future cardiovascular risk (Barker, 1994).

Cross-fostering and sibling studies have clearly shown that the maternal environment, rather than genetic factors, largely accounts for variations in birth weight (Walton & Hammond, 1938; Milner & Gluckman, 1996). Intrauterine growth is primarily substrate driven (Karlberg *et al.* 1994) and, thus, the supply of substrate may influence the intrauterine growth process. Indeed, low birth weight in man is associated with a reduced maternal intake of protein coupled with a high intake of carbohydrate (Godfrey *et al.* 1996 and indices of poor maternal nutritional status, such as reduced skinfold thickness (Godfrey *et al.* 1994) and reduced maternal Fe stores (Godfrey *et al.* 1991).

SBP in childhood and adult life is inversely related to the same indices of poor maternal nutritional status, i.e. maternal anaemia (Law *et al.* 1991) and reduced maternal skinfold thickness (Godfrey *et al.* 1994). A low intake of protein coupled with a high intake of carbohydrate during gestation is associated with an elevated SBP in the offspring when measured 40 years later (Campbell *et al.* 1996). The propensity towards hypertension and thus towards CHD, therefore, is partially determined *in utero* by nutritional factors. The underlying physiological processes relating maternal nutrition, intrauterine growth patterns and adult hypertension are as yet unknown.

Research using animal models has provided some insight into the mechanism of intrauterine programming of adult hypertension. Whilst hypertension can be experimentally produced in animal models through reno-vascular manipulations such as Goldblatts or aortic coarctation (Wilkinson, 1994), or steroid-induced using deoxycorticosterone acetate or dexamethasone (Kenyon & Morton, 1994), these methodologies do not account for an early origin of adult hypertension. Steroid-induced hypertension associated with reduced birth weight can be reproduced, however, by either dexamethasone (Benediktsson *et al.* 1993; Levitt *et al.* 1996) or carbenoxolone (Lindsay *et al.* 1996) injections during pregnancy in the rat.

Maternal glucocorticoids (GC) are metabolized by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (*EC* 1.1.1.146; 11-HSD2; Seckl, 1997*a*). Placental 11-HSD2 is inhibited by carbenoxolone and has weak activity towards dexamethasone. Thus, increased fetal exposure to excess maternal GC reduces birth weight and renders the resultant offspring hypertensive. Importantly, hypertension associated with carbenoxolone injections requires a product of the maternal adrenal gland, since carbenoxolone injections to adrenalectomized dams have no effect on birth weight or SBP of the resultant offspring (Lindsay *et al.* 1996). The activity of placental 11-HSD2 is positively correlated with birth weight in rats (Benediktsson *et al.* 1993) and man (Stewart *et al.* 1995), and activity at term predicts birth weight (Benediktsson *et al.* 1995). Thus, Edwards *et al.* (1993) contend that placental 11-HSD2 has an important role in determining birth weight and, through maternal GC influence, may mediate the fetal origins of

Abreviations: GC, glucocorticoids; 11-HSD2, 11β hydroxysteroid dehydrogenase type 2; MLP, maternal low-protein isoenergetic diet; SBP; systolic blood pressure

***Correponding author:** D. S. Gardner, present address: Department of Physiology, University of Cambridge, Downing Street, Cambridge CB2 3EG, UK; fax 01223 333840, email dsg22@cam.ac.uk

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press

adult cardiovascular disease. Nutritional factors are clearly important, however, in determining future cardiovascular risk (Barker & Osmond, 1986; Barker *et al.* 1993).

Nutritional programming of adult hypertension has been demonstrated in the rat. Reductions in either food intake (Woodall *et al.* 1996) or maternal Fe stores (Crowe *et al.* 1995) throughout pregnancy render the resultant adult offspring hypertensive. Similarly, a maternal low-protein isoenergetic (MLP) diet both reduces birth weight and elevates the SBP of the resultant offspring (Langley & Jackson, 1994; Isherwood-Peel *et al.* 1997). The greater SBP exhibited by the offspring of MLP dams is of early onset and apparently lifelong (for review, see Langley-Evans *et al.* 1997).

Pharmacological blockade of GC synthesis throughout the first 2 weeks of rat pregnancy prevents the development of MLP-induced hypertension (Langley-Evans, 1997*a*). In addition, MLP-induced hypertension is associated with a reduction in both the activity (Langley-Evans *et al.* 1996*c*; DS Gardner, unpublished results) and expression (CB Whorwood and SC Langley-Evans, upublished results) of placental 11-HSD2 from mid to late gestation. Thus, exposure to excess maternal GC during gestation in the rat may represent a common factor between MLP-induced hypertension and steroid-induced hypertension (Seckl, 1997*b*). Indeed, injections of carbenoxolone to protein-replete rat dams reduces the birth weight and elevates the SBP of the resultant offspring as effectively as maternal protein restriction (Langley-Evans, 1997*b*).

Exposure to MLP diet during gestation leads to patterns of disproportionate fetal growth that appear to favour maintenance of brain growth (Langley-Evans *et al.* 1996*a*). Thus, whilst growth of the fetal brain over late gestation was maintained in proportion to body weight, the growth of the liver, lungs and trunk was retarded (Fig. 1).

In association with deficits in organ growth, the offspring from MLP dams exhibit long-term programming of the hypothalamic–pituitary–adrenal axis. Specific elevations in the activities of central and peripheral GC-inducible enzymes, despite similar circulating corticosterone concentrations, indicate a hypersensitivity to GC action in adult life (Langley-Evans *et al.* 1996*b*). Disproportionate fetal growth patterns and hypersensitivity to GC action may represent a manifestation of a common phenomenon. Thus, the fetuses from MLP dams enter the third week of gestation on an accelerated growth curve (Langley-Evans *et al.* 1996*a*). Undernutrition has a greater impact on rapidly-growing fetuses (Harding *et al.* 1992). In response to a nutritional challenge, blood supply is preferentially diverted to organs necessary for continued survival under conditions of stress, such as the brain, heart and adrenal glands (Rudolph, 1984). Consequently, somatic (trunk) and peripheral (liver, lung) organ growth is reduced such that, at term, the control pups either exceed or match the birth weight of MLP pups (Langley & Jackson 1994).

Changes in circulatory dynamics and organ growth rates are likely to be mediated by hormones, and particularly GC. GC influence cellular differentiation and growth (McEwen *et al.* 1986), the fetal cardiovascular system (Tangalakis *et al.* 1992) and additionally serve to mobilize fuel molecules, maintaining the glucose supply to the brain (Dallman *et al.*

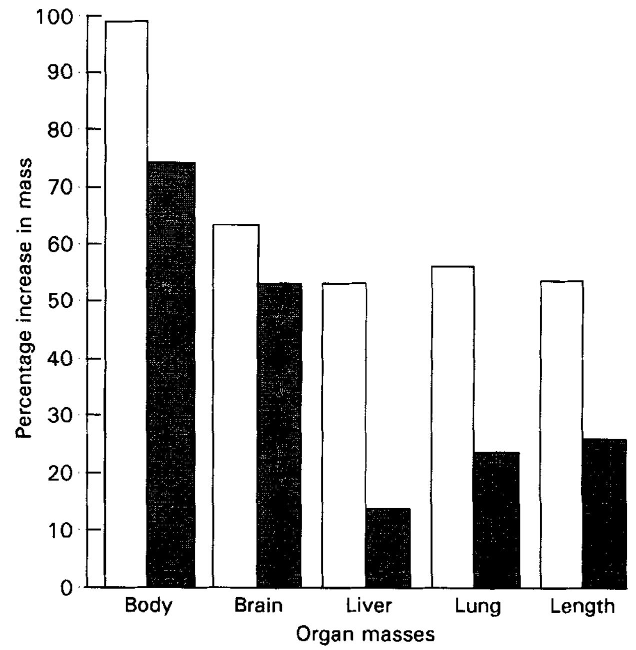

Fig. 1. The percentage increase in mass and length between day 20 and full term in rat fetuses exposed to either a control (□) or low-protein (MLP; ■) maternal diet. Values are expressed as a percentage of the fetal mass or length as determined at day 20 gestation. A total of twenty rat dams were fed on either 180 g casein/kg (control; *n* 10) or 90 g casein/kg (MLP; *n* 10) for 2 weeks before mating and throughout gestation. At day 20 gestation, five dams from each dietary group were killed and fetal body and organ masses recorded. The remaining pregnancies proceeded to term. Offspring were killed within 12 h of the dam giving birth and organ weights determined. (Redrawn from Langley-Evans *et al.* 1996*a*.)

1989). Reduced placental 11-HSD2 function in mid-late gestation, as a consequence of maternal undernutrition, may allow an increased flux of maternal GC into the fetal environment and facilitate fetal adaptation to undernutrition. The fetal hypothalamic–pituitary–adrenal axis assumes independence from maternal GC at about day 16 in the rat (Chatelain *et al.* 1980), and increased GC action during this period, whilst facilitating metabolic changes, may promote inappropriate expression of GC-inducible genes that in adult life increase the propensity towards hypertension. If maternal GC concentrations are reduced during gestation, either by pharmacological (Langley-Evans, 1997*a*) or surgical adrenalectomy (Fig. 2), then MLP-induced hypertension is prevented. Furthermore, replacement of corticosterone to either pharmacologically (Langley-Evans, 1997*a*)- or surgically (DS Gardner, unpublished results)-adrenalectomized rat dams restores the hypertensive state of MLP offspring. Exposure to maternal GC, therefore, appears essential for programming of hypertension in MLP rats.

Virtually all recognized effects of GC are mediated by GC receptors (McEwen *et al.* 1986) and GC receptor expression is demonstrable in the developing fetal rat brain from as early as embryonic day 15 (Kitraki *et al.* 1996). MLP-induced hypertension, therefore, may be mediated by alterations to GC receptor densities in central and peripheral regions, as has been observed in the present

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press

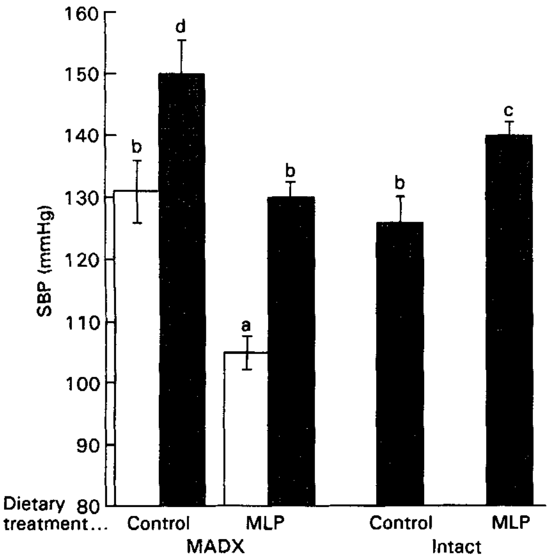

Fig. 2. Systolic blood pressures (SBP) of 6-week-old offspring from maternally adrenalectomized (MADX) rats fed on either a control or low-protein (MLP) diet during pregnancy. Twelve rats were bilaterally adrenalectomized 2 months before mating. On conception rats received either a control (180 g casein/kg; *n* 6) or MLP (90 g casein/kg; *n* 6) diet throughout pregnancy. At birth the diet was substituted for standard chow and litters culled to eight pups (four male and four female). Offspring were weaned onto chow at 4 weeks of age. SBP was determined at 6 weeks of age on male (□) and female (■) pups using the indirect tail-cuff method and compared with age-matched offspring from adrenal-intact control dams. Values are means with their standard errors represented by vertical bars. Two-way ANOVA indicated a significant effect of diet ($F=11{\cdot}99$, $P=0{\cdot}002$) and sex ($F=16{\cdot}21$, $P=0{\cdot}0001$) on the SBP of the offspring. a,b,c, Values with unlike superscript letters were significantly different (*post hoc* analyses by Student's *t* test; $P<0{\cdot}01$).

animal model (Langley-Evans *et al.* 1996*b*) and in others (Mulay *et al.* 1982; Meaney *et al.* 1988). In central regions, increased GC action may 'imprint' the immature fetal hypothalamus, resulting in altered function in adult life. Elevated central activities of GC-inducible enzymes and an acyclic secretion pattern of adrenocorticotrophic hormone suggest programming at the central level (Langley-Evans *et al.* 1996*b*). Altered central metabolism of glutamate, indicated by increased glutamine synthetase (*EC* 6.3.1.2) activity in MLP (Langley-Evans *et al.* 1996*b*), may influence blood pressure control, since glutamate is excitatory in the nucleus tractus solitarus (the cardiovascular control centre in the medulla; Talman *et al.* 1984). Interestingly, transplantation of hypothalamic tissue grafts from day 16 spontaneously-hypertensive rat embryos to normotensive adult Wistar-Kyoto rats significantly elevates the SBP of the Wistar-Kyoto rats (Eilam *et al.* 1991), indicating that hypothalamic factors underlie hypertension in spontaneously-hypertensive rats. Later menarche in women is associated with reduced birth weight (Cooper *et al.* 1996), and growth hormone secretion in adulthood is related to growth in infancy (C Fall, P Hindmarsh, E Dennison, S Kellingray, D Barker and C Cooper, unpublished results). Both are suggestive of centrally-orientated programming in early life.

In the periphery, redistribution of blood flow causing shifts in haemodynamic loads are known permanently to alter the structural properties of vascular smooth muscle (Berry 1978). In fetal vascular tissues, elevated GC receptor densities may facilitate increased SBP and the redistribution of blood flow in MLP, since GC have many hypertensionogenic actions in the vasculature (Walker & Williams, 1992; Whitworth *et al.* 1995). In postnatal life an increased sensitivity to GC action in MLP may predispose towards elevated SBP. Adrenalectomy of 6-week-old male rats from MLP dams significantly reduced SBP to yield pressures similar to controls (Gardner *et al.* 1997). No effect of adrenalectomy on SBP of control rats were observed. Furthermore, the hypotensive effect of adrenalectomy in MLP rats was prevented by corticosterone replacement (Table 1). Thus, maintenance of MLP-induced hypertension in adult life is dependent on an intact adrenal gland and, in particular, corticosterone.

However, maintenance of hypertension in MLP rats does not appear to be entirely through GC receptors, since blockade of GC receptors using RU486, an antiGC, has no

Table 1. The effect of postnatal adrenalectomy on the systolic blood pressure of animals exposed to either a maternal control or low-protein (MLP) diet‖ (From Gardner *et al.* 1997)

(Mean values with their standard errors for five to six observations (control) and four to five (MLP) rats in each treatment group)

	Systolic blood pressure (mmHg)											
Dietary group†...	Control						MLP					
	Initial		7 d		14 d		Initial		7 d		14 d	
Treatment group	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
SV	147	4	149	5	137	7	161*	7	168*	10	153	11
AV	142	5	149	2	137	10	162*	12	143	9	131§	6
SC	146	8	166†	6	146	7	175*	9	165*	4	171*	5
AC	143	7	174†	3	168†	4	165*	6	202*†‡	8	185*†‡	9

* The effect of diet was significant (ANOVA; $F=29{\cdot}85$, $P<0{\cdot}0001$).
† The effect of corticosterone replacement was significant (ANOVA; $F=50{\cdot}67$, $P<0{\cdot}0001$).
‡ The interaction between diet and corticosterone replacement was significant (ANOVA; $F=3{\cdot}47$, $P<0{\cdot}06$).
§ Mean value was significantly different from the initial value for MLP–AV rats (Bonferroni/Dunn test; $P<0{\cdot}05$).
‖ A total of twenty-four male offspring from control (180 g casein/kg) or MLP (90 g casein/kg, *n* 20) dams were either bilaterally adrenalectomized (A) or sham-operated (S) under pentobarbitone anaesthesia at 47 ± 1 d of age. Corticosterone (C) replacement (20 mg/kg in 0·1 ml arachis oil) or vehicle replacement (V; 0·1 ml arachis oil) began the following day (subcutaneously twice daily for 14 d). The systolic blood pressure of rats was determined by the indirect tail-cuff method before surgery (initial) and subsequently at days 7 and 14 following either adrenalectomy or sham operation (day 0).

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press

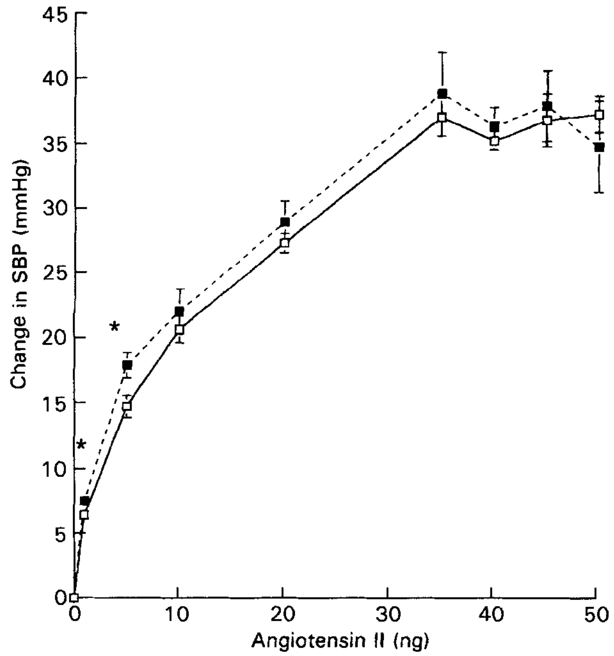

Fig. 3. A curve illustrating the maximal pressor response to angiotensin II of female rats exposed to either a maternal control (□) or low-protein (■) diet. At 10 weeks of age, offspring from control or low-protein dams (five rats per dietary group at each dose of angiotensin II) were administered sodium pentobarbitone anaesthetic (72 mg/kg body weight) intraperitoneally. Angiotensin II was delivered intravenously, through a femoral catheter, dissolved in a total volume of 0·1 ml, 9 g NaCl/l maintained at 37°. Increasing doses (0, 1, 5, 10, 20, 40 ng) of angiotensin II were administered, allowing a period of at least 5 min between each injection. Systolic blood pressure (SBP) was recorded directly through a carotid cannula. Values are means with their standard errors represented by vertical bars. Two-way ANOVA indicated a significant effect of diet ($F=5{\cdot}54$, $P=0{\cdot}02$) and angiotensin II dose ($F=195{\cdot}4$, $P=0{\cdot}0001$). Mean values for MLP rats were significantly different from those for control rats: $^{*}P<0{\cdot}05$.

effect on the SBP of MLP rats (DS Gardner, unpublished results). This is unsurprising, since hypertension is classically multifactorial. A more likely mechanism is through a permissive effect of GC on vasoconstrictors such as angiotensin II. GC modulate the pressor responsiveness of vascular tissue to angiotensin II (Whitworth *et al.* 1995) and in SHR rats, upregulate the expression of angiotensin II (AT1) receptors (Provencher *et al.* 1995). Indeed, inhibition of angiotensin-converting enzyme normalizes SBP in MLP rats (Langley-Evans & Jackson, 1995), and vascular tissue of MLP-female rats is more responsive to the pressor action of angiotensin II in physiological doses (Fig. 3). At doses of angiotensin II between 1 and 40 ng the pressor response curve to angiotensin II was shifted to the left, indicating an increased physiological sensitivity to angiotensin II action. The dose of angiotensin II which produced the maximal pressor response was established to be significantly lower in MLP rats than controls (MLP 37 (SE 1) ng angiotensin II, *n* 5; controls, 44 (SE 2) ng angiotensin II, *n* 5; $P=0{\cdot}01$).

In adult life, MLP-induced hypertension is, therefore, a consequence of a steeper rise in SBP due to centrally-programmed factors and a synergistic interplay between peripheral hypothalamic–pituitary–adrenal activity, the renin–angiotensin system and the kidney. With regard to the kidney, the MLP diet consistently impairs renal growth as a whole (Langley-Evans *et al.* 1996*d*) and more specifically, the formation of nephrons (SJM Welham, unpublished results). A reduced nephron complement at birth is associated with an increased susceptibility to hypertension (Mackenzie & Brenner, 1995). In the periphery, the combination of altered blood-flow profiles *in utero*, increased vascular sensitivity to pressors and increased pressor action, which perhaps are mediated by GC, may comprise the initial stimulus leading to primary hypertension. Postnatally, these exaggerated responses persist, facilitating structural cardiovascular adaptations that predispose to higher blood pressure and secondary hypertension (Folkow, 1978). Structural adaptation within baroreceptor sites may reset the 'barostat' function of baroreceptors at a higher level, further contributing to the hypersensitive state (Sleight *et al.* 1975).

In conclusion, increased maternal glucocorticoid exposure, therefore, may primarily facilitate fetal peripheral adaptation to an MLP diet. A consequence of the increased GC exposure is programming or imprinting of the immature fetal hypothalamus. Fetal physiology is thus programmed *in utero* towards an increased propensity for SBP to rise. Postnatally, summation of the central and peripheral programmed alterations result in a greater rate of increase of SBP in early life, leading towards hypertension in later life. If the mechanisms, e.g. angiotensin II, facilitating secondary structural adaptation in postnatal life are prevented, then hypertension does not develop (Sherman *et al.* 1997). Furthermore, the early rise in SBP is exacerbated by conditions of nutritional excess. The effects of early exposure to a low-protein diet on SBP followed by exposure to a cafeteria diet in later life are cumulative (Petry *et al.* 1997).

Acknowledgements

The support of the Medical Research Council and British Heart Foundation is gratefully acknowledged.

References

Barker DJP (1994) *Mothers, Babies and Disease in Later Life.* London: BMJ Publishing Group.

Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA & Robinson JS (1993) Fetal nutrition and cardiovascular disease in adult life. *Lancet* **341**, 938–941.

Barker DJP & Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet* **i**, 1077–1081.

Barker DJP, Osmond C, Golding J, Kuh D & Wadsworth MEJ (1989) Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *British Medical Journal* **298**, 564–567.

Benediktsson R, Lindsay R, Noble J, Seckl JR & Edwards CRW (1993) Glucocorticoid exposure *in utero*: A new model for adult hypertension. *Lancet* **341**, 339–341.

Benediktsson R, Noble J, Calder AA & Seckl JR (1995) 11β-Hydroxysteroid dehydrogenase activity in intact dually-perfused fresh human placenta predicts birth weight. *Journal of Endocrinology* **144**, Suppl., 161.

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press

Berry C (1978) Hypertension and arterial development: long term considerations. *British Heart Journal* **40**, 709–717.

Campbell DM, Hall MH, Barker DJP, Cross J, Shiell AW & Godfrey KM (1996) Diet in pregnancy and the offspring's blood pressure 40 years later. *British Journal of Obstetrics and Gynaecology* **103**, 273–280.

Chatelain A, Dupouy J-P & Allaume P (1980) Fetal–maternal adrenocorticotrophin and corticosterone relationships in the rat: Effects of maternal adrenalectomy. *Endocrinology* **106**, 1297–1303.

Cooper C, Kuh D, Egger P, Wadsworth M & Barker D (1996) Childhood growth and the age at menarche. *Journal of Obstetrics and Gynaecology* **103**, 814–817.

Crowe C, Dandekar P, Fox M, Dhingra K, Bennet L & Hanson MA (1995) The effects of anaemia on heart, placenta and body weight, and blood pressure in fetal and neonatal rats. *Journal of Physiology* **488**, 515–519.

Dallman MF, Darlington DN, Suemaru S, Cascio CS & Levin N (1989) Corticosteroids and homeostasis. *Acta Physiologica Scandinavica* **136**, Suppl. **S583**, 27–34.

Edwards CRW, Benediktsson R, Lindsay RS & Seckl JR (1993) Dysfunction of placental glucocorticoid barrier: link between fetal environment and adult hypertension. *Lancet* **341**, 355–357.

Eilam R, Malach R, Bergmann F & Segal M (1991) Hypertension induced by hypothalamic transplantation from genetically hypertensive to normotensive rats. *Journal of Neuroscience* **11**, 401–411.

Folkow B (1978) Cardiovascular structural adaptation: its role in the initiation and maintenance of primary hypertension. *Clinical and Scientific Molecular Medicine* **55**, 3s–22s.

Gardner DS, Jackson AA & Langley-Evans SC (1997) Maintenance of maternal diet-induced hypertension in the rat is dependent upon glucocorticoids. *Hypertension* **30**, 1525–1530.

Godfrey KM, Forrester T, Barker DJP, Jackson AA, Landman JP, Hall JSE, Cox V & Osmond C (1994) Maternal nutritional status in pregnancy and blood pressure in childhood. *Journal of Obstetrics and Gynaecology* **101**, 398–403.

Godfrey KM, Redman CWG, Barker DJP & Osmond C (1991) The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight. *Journal of Obstetrics and Gynaecology* **98**, 886–891.

Godfrey KM, Robinson S, Barker DJP, Osmond C & Cox V (1996) Maternal nutrition in early and late pregnancy in relation to placental and fetal growth. *British Medical Journal* **312**, 410–414.

Harding J, Liu L, Evans P, Oliver M & Gluckman P (1992) Intrauterine feeding of the growth retarded fetus: Can we help? *Early Human Development* **29**, 193–197.

Isherwood-Peel SG, Houghton FD & Leese H (1998) Effect of a low protein maternal diet on energy metabolism during organogenesis. *Proceedings of the Nutrition Society* **57**, 77A.

Karlberg J, Jalil F, Lam B, Low L & Yeung CY (1994) Linear growth retardation in relation to the three phases of growth. *European Journal of Clinical Nutrition* **48**, S25–S44.

Kenyon CJ & Morton JJ (1994) Experimental steroid-induced hypertension. In *A Textbook of Hypertension*, pp. 494–503 [JD Swales, editor]. Oxford: Blackwell.

Kitraki E, Alexis MN, Papalopoulou M & Stylianopoulou (1996) Glucocorticoid receptor gene expression in the embryonic rat brain. *Neuroendocrinology* **63**, 305–317.

Langley-Evans SC & Jackson AA (1994) Increased systolic blood pressure in adult rats induced by fetal exposure to maternal low protein diets. *Clinical Science* **86**, 217–222.

Langley-Evans SC (1997*a*) Hypertension induced by fetal exposure to maternal low-protein diet, in the rat, is prevented by pharmacological blockade of maternal glucocorticoid synthesis. *Journal of Hypertension* **15**, 537–544.

Langley-Evans SC (1997*b*) Maternal carbenoxolone treatment lowers birth weight and induces hypertension in the offspring of rats fed a protein replete diet. *Clinical Science* **93**, 423–429.

Langley-Evans SC, Gardner DS & Jackson AA (1996*a*) Association of disproportionate growth of fetal rats in late gestation with raised systolic blood pressure in later life. *Journal of Reproduction and Fertility* **106**, 307–312.

Langley-Evans SC, Gardner DS & Jackson AA (1996*b*) Evidence of programming of the hypothalamic–pituitary–adrenal axis by maternal protein restriction during pregnancy. *Journal of Nutrition* **126**, 1578–1585.

Langley-Evans SC, Gardner DS & Jackson AA (1998) Intrauterine programming of cardiovascular disease by maternal nutritional status. *Nutrition* **14**, 39–47.

Langley-Evans SC & Jackson AA (1995) Captopril normalises systolic blood pressure in rats with hypertension induced by fetal exposure to maternal low protein diets. *Comparative Biochemistry and Physiology* **110**, 223–228.

Langley-Evans SC, Phillips GJ, Gardner DS & Jackson AA (1996*c*) The role of glucocorticoids in programming of maternal diet induced hypertension in the rat. *Journal of Nutritional Biochemistry* **7**, 173–178.

Langley-Evans SC, Welham SJM, Sherman RC & Jackson AA (1996*d*) Weanling rats exposed to maternal low-protein diets during discrete periods of gestation exhibit differing severity of hypertension. *Clinical Science* **91**, 607–615.

Law CM, deSwiet M, Osmond C, Fayers PM, Barker DJP, Cruddas AM & Fall CHD (1993) Initiation of hypertension and its amplification throughout life. *British Medical Journal* **306**, 24–27.

Law SC, Barker DJP, Bull AR & Osmond C (1991) Maternal and fetal influences on blood pressure. *Archives of Disease in Childhood* **66**, 1291–1295.

Lever AF & Harrap SB (1992) Essential hypertension: A disorder of growth with origins in childhood. *Journal of Hypertension* **10**, 101–120.

Levitt NS, Lindsay RS, Holmes MC & Seckl JR (1996) Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. *Neuroendocrinology* **64**, 412–418.

Lindsay RS, Lindsay M, Edwards CRW & Seckl JS (1996) Inhibition of 11β-hydroxysteroid dehydrogenase in pregnant rats and the programming of blood pressure in the offspring. *Hypertension* **27**, 1200–1204.

Mackenzie HS & Brenner BM (1995) Fewer nephrons at birth: A missing link in the etiology of essential hypertension. *American Journal of Kidney Disease* **26**, 91–98.

McEwen BS, deKloet ER & Rostene W (1986) Adrenal steroid receptors and actions in the nervous system. *Physiological Reviews* **66**, 1121–1188.

Meaney MJ, Aitken DH, van Berkel C, Bhathagar S & Sapolsky RM (1988) Effect of neonatal handling on age related impairments associated with the hippocampus. *Science* **329**, 766–768.

Milner RDG & Gluckman PD (1996) Regulation of intrauterine growth. In *Pediatrics and Perinatology*, pp. 285–289 [PD Gluckman and MA Heymann, editors]. London: Arnold.

Mulay S, Varma DR & Solomon S (1982) Influence of protein deficiency in rats on hormonal status and cytoplasmic glucocorticoid receptors in maternal and fetal tissues. *Journal of Endocrinology* **95**, 49–58.

Petry CJ, Ozanne SE, Wang CL & Hales CN (1997) Early protein restriction and obesity independently induce hypertension in 1-year old rats. *Clinical Science* **93**, 147–152.

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press

Provencher PH, Saltis J & Funder JW (1995) Glucocorticoids but not mineralocorticoids modulate endothelin-1 and angiotensin II binding in SHR vascular smooth muscle cells. *Journal of Steroid Biochemistry and Molecular Biology* **52**, 219–225.

Rudolph AM (1984) The fetal circulation and its response to stress. *Journal of Developmental Physiology* **6**, 11–19.

Seckl JR (1997*a*) 11β-Hydroxysteroid dehydrogenase in the brain: A novel regulator of glucocorticoid action. *Frontiers in Neuroendocrinology* **18**, 49–99.

Seckl JR (1997*b*) Glucocorticoids, feto-placental 11β-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. *Steroids* **62**, 89–94.

Sherman RC, Jackson AA & Langley-Evans SC (1997) Early administration of angiotensin converting enzyme inhibitor captopril prevents the development of hypertension programmed by intrauterine exposure to maternal low protein diet in the rat. *Clinical Science* (In the Press).

Sleight P, Robinson JL, Brooks DE & Rees PM (1975) Carotid baroreceptor resetting in the hypertensive dog. *Clinical Science* **48**, 261–263.

Stewart PM, Whorwood CB & Mason JI (1995) Type 2 11β-hydroxysteroid dehydrogenase in fetal and adult life. *Journal of Steroid Biochemistry and Molecular Biology* **55**, 465–471.

Talman WT, Granata AR & Ries DJ (1984) Glutaminergic mechanisms in the nucleus tractus solitarius in blood pressure control. *Federation Proceedings* **43**, 39–44.

Tangalakis K, Lumbers ER, Moritz KM, Towstoless MK & Wintour EM (1992) Effect of cortisol on blood pressure and vascular reactivity in the ovine fetus. *Experimental Physiology* **77**, 709–717.

Thom TJ, Epstein FH, Feldman JJ, Leaverton PE & Wolz M (1992) *Total Mortality and Mortality from Heart Disease, Cancer and Stroke from 1950 to 1987 in 27 Countries: Highlights of Trends and Their Interrelationships Among Causes of Death. National Institutes of Health Publication.* Bethesda, MD: National Institutes of Health.

Walker BR & Williams BC (1992) Corticosteroids and vascular tone: mapping the messenger maze. *Clinical Science* **82**, 597–605.

Walton A & Hammond J (1938) The maternal effects on growth and conformation in Shire horse–Shetland pony crosses. *Proceedings of the Royal Society of London* **125**, 311–335.

Ward R (1990) *Hypertension: Pathophysiology, Diagnosis and Management.* New York: Raven Press.

Whitworth JA, Brown MA, Kelly JJ & Williamson PM (1995) Mechanisms of cortisol-induced hypertension in humans. *Steroids* **60**, 76–80.

Wilkinson R (1994) Renal and renovascular hypertension. In *A Textbook of Hypertension*, pp. 831–857 [JD Swales, editor]. Oxford: Blackwell.

Woodall SM, Johnston BM, Brier BH & Gluckman PD (1996) Chronic maternal undernutrition in the rat leads to delayed postnatal growth and elevated blood pressure of offspring. *Pediatric Research* **40**, 438–443.

© Nutrition Society 1998

https://doi.org/10.1079/PNS19980037 Published online by Cambridge University Press