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

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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; Mühner & 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 carbonoxolone (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, 1997a). Placental 11-HSD2 is inhibited by carbonoxolone 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 carbonoxolone injections requires a product of the maternal adrenal gland, since carbonoxolone 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

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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, 1997a). In addition, MLP-induced hypertension is associated with a reduction in both the activity (Langley-Evans et al. 1996c; DS Gardner, unpublished results) and expression (CB Whorwood and SC Langley-Evans, unpublished 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, 1997b). 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, 1997b).

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. 1996a). 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. 1996b). 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. 1996a). 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. 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, 1997a) or surgical adrenalectomy (Fig. 2), then MLP-induced hypertension is prevented. Furthermore, replacement of corticosterone to either pharmacologically (Langley-Evans, 1997a)- 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
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 with unlike superscript letters were significantly different (post hoc analyses by Student's t test; P < 0.01).

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)

<table>
<thead>
<tr>
<th>Dietary group</th>
<th>Control</th>
<th>MLP</th>
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<tr>
<td></td>
<td>Initial</td>
<td>7 d</td>
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<tr>
<td>SV</td>
<td>Mean SE</td>
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<tr>
<td>AV</td>
<td>147 4</td>
<td>149 5</td>
</tr>
<tr>
<td>SC</td>
<td>146 8</td>
<td>166± 6</td>
</tr>
<tr>
<td>AC</td>
<td>143 7</td>
<td>174± 3</td>
</tr>
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</table>

1 The effect of diet was significant (ANOVA; F = 29.85, P < 0.0001).
2 The effect of corticosterone replacement was significant (ANOVA; F = 50.67, P < 0.0001).
3 The interaction between diet and corticosterone replacement was significant (ANOVA; F = 3.47, P < 0.06).
4 Mean value was significantly different from the initial value for MLP-AV rats (Bonferroni/Dunn test; P < 0.05).
5 A total of twenty-four male offspring from control (180 g casein/kg) 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 = 11.99, P = 0.002) and sex (F = 16.21, P = 0.0001) 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 < 0.01).

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 hypertensive 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 suggest programming at the central level (Langley-Evans et al. 1996b). Altered central metabolism of glutamate, indicated by increased glutamine synthetase (EC 6.3.1.2) activity in MLP (Langley-Evans et al. 1996b), may influence blood pressure control, since glutamate is excitatory in the nucleus tractus solitarius (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-oriented programming in early life.
The peripheral pressor response was established to be significantly lower in MLP rats than controls (MLP 37 °C, controls, 44 °C ng angiotensin II; P = 0.01). Mean values for MLP rats were significantly different from those for control rats: P < 0.05.

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References


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