Developmental Origins of Adult Health and Disease: The Role of Periconceptional and Foetal Nutrition

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Abstract: The ‘developmental origins of adult health and disease’ hypothesis stated that environmental factors, particularly maternal undernutrition, act in early life to programme the risks for adverse health outcomes, such as cardiovascular disease, obesity and the metabolic syndrome in adult life. Early physiological tradeoffs, including activation of the foetal hypothalamo–pituitary–adrenal (HPA) axis, confer an early fitness advantage such as foetal survival, while incurring delayed health costs. We review the evidence that such tradeoffs are anticipated from conception and that the periconceptional nutritional environment can programme the developmental trajectory of the stress axis and the systems that maintain and regulate arterial blood pressure. There is also evidence that restriction of placental growth and function, results in an increased dependence of the maintenance of arterial blood pressure on the sequential recruitment of the sympathetic nervous system and HPA axis. While the ‘early origins of adult disease’ hypothesis has focussed on the impact of maternal under-nutrition, an increase in maternal nutritional intake and in maternal body mass intake has become more prevalent in developed countries. Exposure to overnutrition in foetal life results in a series of central and peripheral neuroendocrine responses that in turn programme development of the fat cell and of the central appetite regulatory system. While the physiological responses to foetal undernutrition result in the physiological trade off between foetal survival and poor health outcomes that emerge after reproductive senescence, exposure to early overnutrition results in poor health outcomes that emerge in childhood and adolescence. Thus, the effects of early overnutrition can directly impact on reproductive fitness and on the health of the next generation. In this context, the physiological responses to relative overnutrition in early life may directly contribute to an intergenerational cycle of obesity.

The early origins of a hypothesis

The ‘early’ or ‘foetal’ origins of adult disease hypothesis describes a hypothesis that was originally put forward by Barker et al. in Southampton in the UK that stated that environmental factors, particularly nutrition, act in early life to programme the risks for the early onset of cardiovascular and metabolic disease in adult life and premature death [1–4]. This hypothesis has been further developed through a worldwide series of epidemiological studies that has extended the original observations of associations between specific patterns of prenatal and postnatal growth and cardiovascular disease to include associations between early growth patterns and an increased risk for hypertension, impaired glucose tolerance, non-insulin-dependent or type 2 diabetes, insulin resistance, central obesity and the metabolic syndrome in adult life (as summarized in [5]). There have been a number of mechanistic frameworks proposed to explain the biological basis of the associations observed between birth weight and health outcomes in the epidemiological and subsequent clinical and experimental animal studies [5]. In 1992, Hales and Barker coined the term the ‘thrifty phenotype’ hypothesis, which suggested that when the foetal environment is poor, there is an adaptive response, which optimizes the growth of key body organs to the detriment of others and leads to an altered postnatal metabolism, which is designed to enhance postnatal survival under conditions of intermittent or poor nutrition. It was proposed that these adaptations only became detrimental when nutrition was more abundant in the postnatal environment, than it had been in the prenatal environment [6,7]. The concept that there are embryonic and foetal adaptive responses to a suboptimal intrauterine environment that result in permanent adverse consequences is consistent with the definition of ‘programming’ by Lucas in 1991 [8] as either the induction, deletion, or impaired development of a permanent somatic structure or the ‘setting’ of a physiological system by an early stimulus or insult operating at a ‘sensitive’ period, resulting in long-term consequences for function.
It has also been recently stated that whereas developmental physiologists and physicians may use programming to describe the process whereby a stimulus or insult at a sensitive period of development, has lasting effects on the structure or function of the body, that this term has different meanings in other areas of biology, and that therefore programming should not be used as a term in the context of the developmental origins of adult disease [9]. It has been proposed that the term developmental plasticity rather than programming would be more appropriate [9]. The formal definition of developmental plasticity is the ability of a single genotype to produce more than one alternative form of structure, physiological state or behaviour in response to environmental conditions [9]. There has also been a proposal to separate those homeostatic responses that represent early adaptations to changes in the intrauterine environment and that may have long-term consequences, from those which need not confer immediate advantage but are induced in the expectation of future adaptive changes; this latter group of responses has been defined as ‘predictive adaptive’ [10]. In this model, selection across generations operates to favour protection of those predictive adaptive responses that aid survival to reproductive age [10]. The programmed or plastic responses made during development that have immediate adaptive advantage might also act to limit the range of postnatal adaptive responses to a new environment and would be considered to be ‘inappropriate’ predictive adaptive responses.

Although the evolutionary view provides a clear biological framework to understand the importance of the prenatal environment for the continued reproductive success and health of subsequent adult populations, not all responses to the current prenatal environment may be potentially predictive of the postnatal environment. It has been demonstrated in a range of clinical studies and in experimental studies carried out primarily in the rodent that suboptimal intrauterine nutrition may result in the loss of structural units, such as nephrons, cardiomyocytes or pancreatic β-cells within developing organ systems [5]. Such responses may neither be adaptive nor predictive, although they will result in the programming of a reduced functional capacity in organ systems for life. For this reason, the term developmental programming continues to be used as an overarching term that encompasses the broad range of molecular, cellular, structural and functional responses that occur following exposure to a range of environmental stimuli acting during critical periods of development, which in turn result in long-term consequences for adult health and disease.

There have been recent extensive reviews that have summarized the important series of studies that have investigated the impact of exposure of the pregnant dam to either global nutrient restriction or to restriction of specific nutrients on subsequent cardiovascular or metabolic health in the offspring [5, 11, 12]. These reviews have highlighted the important role that exposure of the rat pup to excess glucocorticoids plays in the developmental programming of pathological outcomes including hypertension and insulin resistance [5, 11, 12]. While the rodent offers significant advantages in terms of a short gestation and the availability of useful transgenic and null mutant models, there are clear advantages to using an animal model more akin to human beings, in studies of developmental programming. For this reason, in this review, we will focus on studies that have demonstrated the physiological impact of early exposure to either a suboptimal or excess nutritional environment in the pregnant sheep and her foetus. As in human beings, after the period of organogenesis in early gestation, the sheep foetus has the capacity to generate a range of appropriate metabolic, physiological and neuroendocrine responses to changes in its environment and studies in the sheep foetus have therefore provided insights into those foetal adaptations to changes in its nutrient environment that ensure foetal survival, but which may in turn result in adverse health outcomes in later life. In a series of experimental studies, we have investigated the impact of exposure of either the sheep embryo or foetus to a poor nutritional environment and separately the impact of exposure of the sheep foetus to an increased nutritional environment.

Development of the neuroendocrine and cardiovascular system

Impact of periconceptional undernutrition.

Studies investigating the historical cohort of the Dutch winter famine [13–15], which was a 5-month period of malnutrition experienced by pregnant women during the winter of 1944–1945 in Amsterdam, the Netherlands, found that individuals who were exposed to the famine as an embryo or foetus during early gestation had an increased prevalence of coronary heart disease, increased body mass index, and glucose intolerance due to a deficit in insulin secretion. These pathophysiological outcomes were independent of size at birth and social risk factors and were associated with an elevation of the low-density to high-density lipoprotein ratio, increased levels of plasma fibrinogen, decreased levels of factor VII and a poorer perception of self-health than were seen in individuals exposed to the famine during mid gestation or late gestation [13]. It is unclear, however, why exposure to poor maternal nutrition, at a stage when the nutrient demands of the embryo are minimal, result in long-term consequences for the cardiovascular system. This has prompted a series of investigations on the impact of maternal undernutrition during the periconceptional period on the foetal growth trajectory, and the development of organ systems before and after birth (fig. 1).

We have recently investigated the impact of maternal undernutrition during the periconceptional period (from at least 45 days before conception until 7 days after conception) on the placental and foetal growth trajectory in the sheep (term = 150 ± 3 days gestation) [16] and found that in control pregnancies an increase in maternal weight gain during the periconceptional period was associated with an increase in placental and foetal weights at about day 55 of gestation. This relationship was altered, however, by exposure to maternal undernutrition during the periconceptional period.
In twin control pregnancies at ~day 55 of gestation [16], placental weights were significantly higher than in singleton control pregnancies, and there was no relationship between placental and foetal weights. In ewes carrying twin foetuses exposed to periconceptional undernutrition, however, an inverse relationship emerged between maternal weight gain and placental and foetal weights such that ewes that lost more weight during the periconceptional and early gestation periods had heavier placentae and larger foetuses at ~day 55 of pregnancy.

These observations suggest that there is a ‘predictive’ compensatory response by the placenta to nutrient restriction during the periconceptional period. While an altered foetoplacental growth trajectory in early pregnancy is consistent with the observation that the level of periconceptional nutrition alters the allocation of cells within the developing blastocyst, we have also reported that maternal undernutrition in the periconceptional period programmes the development of the foetal neuroendocrine and cardiorenal systems [17–19].

In these experiments, periconceptional undernutrition resulted in an increase in arterial blood pressure and rate pressure product, which was not dependent on the activation of the renin–angiotensin system and resulted in an increased activation of the foetal hypothalamic–pituitary–adrenal (HPA) axis in twin, but not singleton, foetuses during late gestation [17–19]. When maternal undernutrition is more severe (reduced to 28% of maintenance levels) and imposed beyond the periconceptional period and into early pregnancy (i.e. from 60 days prior to conception and up to 30 days of pregnancy), there was a reduced foetal growth rate, hyperactivation of the foetal HPA axis and premature delivery occurred in 50% of singleton pregnancies [20,21].

One possibility is that the impact of periconceptional undernutrition on the foetal HPA axis operates in early development to programme cardiovascular and metabolic responses to ensure that the foetus adapts successfully to the predicted ‘poor’ postnatal environment. We have recently demonstrated that the relative weight of the foetal adrenal and adrenal IGF-I, IGF-IR, IGF-II, IGF-IIR and CYP17 mRNA expression were each lower in twin compared to singleton foetuses as early as 55 days gestation [22]. In twin foetuses, periconceptional undernutrition resulted in the loss of the relationships between adrenal weight and IGF-I expression and between adrenal CYP17 and IGF-II expression, which were present in controls [22]. These findings suggest that differences in the timing of the prepartum activation of the foetal adrenal in twins and singletons have their origins in early gestation and highlight the importance of the interaction between the periconceptional environment and embryo number in setting the growth trajectory of the foetal adrenal [22].

It has been argued that the neuroendocrine stress axis represents a phylogenetically ancient signalling system that...
allows a foetus to match its rate of development to the prevailing environmental conditions [23]. While an earlier activation of the foetal HPA axis may be important to enable survival of the foetus in an adverse environment, stress-induced acceleration of development of the HPA axis may come at a cost, expressed as reduced ‘fitness’ in early childhood or later adult life [24]. That the early environment may have a life-long impact on the development of the HPA axis is highlighted by the observations that when maternal undernutrition is imposed from days 0–30 of pregnancy, there is an increase in the circulating plasma cortisol levels in female lambs and an alteration in cardiovascular function in lambs at 1 year of age, with an increase in pulse pressure product, a decrease in rate pressure product, and a leftwards shift of the baroreflex curve [25,26].

One mechanistic pathway through which maternal undernutrition may alter embryo, foetoplacental and postnatal development is through altering the epigenetic regulation of imprinted gene expression within the developing embryo [27,28]. The application of epigenomic approaches and the determination of those imprinted or non-imprinted genes and transposon insertion sites that are targets for early determination of those imprinted or non-imprinted genes [27,28]. The application of epigenomic approaches and the determination of those imprinted or non-imprinted genes and transposon insertion sites that are targets for early nutritional effects on epigenetic gene regulation is an important new area of investigation. An understanding of the generation and maintenance of epigenetic changes in gene regulation in the developing germine will provide insights into the mechanisms underlying trans- or intergenerational programming.

Impact of placental restriction of foetal substrate supply;

While exposure to maternal undernutrition during critical windows of exposure may impact on foetoplacental growth trajectory and development of the foetal HPA and cardiovascular system, a major cause of poor foetal nutrition is placental insufficiency resulting in a restriction of foetal substrate supply. Several different experimental approaches have been used to produce placental insufficiency with resultant foetal growth restriction in small and large animal models, including surgical removal of the majority of endometrial caruncles from the uterus of the non-pregnant ewe prior to mating [29–31]. This latter procedure restricts the number of placentomes that are formed from the beginning of pregnancy, thereby limiting placental growth and function and thus restricting foetal growth. In this model, there is a restriction of placental delivery of oxygen and glucose to the foetus, resulting in chronic foetal hypoxaemia and hypoglycaemia, particularly in late gestation.

In a series of studies, we have demonstrated that the foetus makes a number of neuroendocrine, metabolic and cardiovascular adaptations to chronic placental insufficiency to ensure foetal substrate utilisation decreases in parallel with placental substrate supply and thus ensures foetal survival [29,30,32,33]. We have shown that plasma noradrenaline concentrations were significantly higher in chronically hypoxic, growth restricted foetal sheep than in control foetuses between 110 and 140 days of gestation and that plasma cortisol concentrations were also higher in these foetuses when compared to controls from around 130 days gestation [29,32–34].

These neuroendocrine responses to chronic foetal stress in turn play key roles in maintaining peripheral vascular resistance and foetal arterial blood pressure. While there is no difference in the mean arterial blood pressure between normally grown and placentaly restricted (PR) foetal sheep, there is a direct relationship between blood pressure and the mean gestational PO$_2$ in control animals, which is not present in the PR group [30]. Importantly, in a recent series of studies in which we infused phenolamine, an $\alpha$-adrenergic antagonist, in PR and control foetuses, we demonstrated that the maintenance of mean arterial pressure in the PR foetal sheep depended to a significantly greater extent on $\alpha$-adrenergic activation than in control foetuses. Furthermore, the hypotensive response to $\alpha$-adrenergic blockade was present in foetuses before the onset of the prepartum cortisol increase and there was a direct relationship between the magnitude of the foetal hypotensive response and the foetal arterial PO$_2$ [29].

We have also found that intrafoetal infusion of an angiotensin converting enzyme (ACE) inhibitor, captopril, had a greater suppressive effect on basal blood pressure in hypoxic PR or in normoxic foetal sheep after 135 days gestation when compared to before 125-day gestation [30]. We speculated that the greater hypotensive response to ACE inhibition in the older PR foetuses was related to the greater increase in circulating cortisol that occurs in these animals from 135-day gestation [35].

Thus, there appears to be a sequential activation of the sympathetic nervous system, foetal HPA axis and renin-angiotensin system in the chronically hypoxaemic, growth-restricted foetus that act to maintain arterial blood pressure throughout late gestation. Such neuroendocrine and cardiovascular adaptations may underpin the sparing of brain growth that occurs in the chronically hypoxic sheep and human foetus during late gestation [31]. While increased sympathetic tone may contribute to the sparing of brain growth and, potentially, foetal survival in response to an adverse intrauterine environment, it may have longer-term negative outcomes including an enhanced risk of poor regional blood flow in early life and an increased risk of hypertension in adult life. In a recent study, we have also investigated the impact of placental restriction on the growth and development of the heart.

Heart growth occurs via hyperplastic growth (increasing cell number) of mononucleated cardiomyocytes early in development followed by a transition from hyperplastic to hypertrophic growth (increasing cell size) after binucleation of the cardiomyocytes occurs through karyokinesis without cytokinesis [36]. In the human heart, cardiomyocytes undergo binucleation in foetal life, with less than 10% of cardiomyocytes being capable of mitosis by 4 weeks of age [37]. Thus, at birth, the human heart contains the majority of the cardiomyocytes that it will have for life and this results in a limited capacity for cellular regeneration within the adult heart after injury. Because the heart is fairly
mature at birth, any environmental stimulus that alters the timing of the transition from hyperplastic to hypertrophic growth of the cardiomyocytes may have long lasting consequences for heart growth and function [38].

We have demonstrated that there is an increase in the proportion of mononucleated cardiomyocytes in the hearts of PR foetuses [34]. While mononucleated and binucleated cardiomyocytes were smaller in absolute terms in the heart of the growth restricted foetus, the relative size of the cardiomyocytes, when expressed relative to heart weight was larger in the PR foetus compared to controls (fig. 2). The increase in the relative proportion of mononucleated cardiomyocytes and the relative sparing of the growth of individual cardiomyocytes in the growth restricted foetus may be adaptations to the suboptimal intrauterine environment that may have long-term consequences for heart development in postnatal life [38].

Thus, restriction of maternal, embryonic and foetal nutrition or the restriction of placental growth and function, can each result in different outcomes for the subsequent development of the HPA axis, the sympathetic nervous system and the cardiovascular system before birth and while these adaptations may enhance the probability of foetal survival, they may each contribute to the association between an adverse intrauterine environment and an increased risk of hypertension and cardiovascular disease in adult life.

Impact of maternal overnutrition on development of systems regulating body fat composition

Although the main focus of the field of "developmental origins of adult health and disease" has been on the effects of poor foetal nutrition, the issue of maternal and hence foetal overnutrition is of growing importance in the context of the current global obesity epidemic. The period of history during which human populations have been exposed to a relative excess of nutrition has been relatively brief, and there are few studies that have investigated the immediate foetal adaptations to periods of relatively high nutrition and the subsequent sequelae of these adaptations.

An extensive series of studies has reported that there is a J-shaped or U-shaped relationship between birth weight and adult fat mass, with a higher prevalence of adult obesity occurring in individuals with birth weights at either the low or high end of the birth weight distribution. LaCoursiere et al. [39] recently found that the incidence of women being overweight or obese at the start of pregnancy increased from 25% to 35% between 1991 and 2001. It has been proposed that high nutritional consumption or body fat mass during pregnancy is associated with induction of a degree of maternal insulin resistance, an increased foetal nutrient supply, foetal overgrowth and infant fatness. A recent Danish study of more than 300,000 children born between 1936 and 1983 [40] reported a stable association between having a birth weight greater than 4000 g and being overweight at 6–13 years of age. It has been argued that an increase in foetal nutrient supply, as a consequence of an increase in maternal

Fig. 2. Heart development in growth restricted foetuses. (A) There is a higher percentage of mononucleated cardiomyocytes in hearts from placentally restricted (PR) foetuses (dark bars) compared to control foetuses (open bars) both before and after 135 days gestation when there is a prepartum surge in foetal plasma cortisol concentrations. (B) There is no difference in the length of binucleated cardiomyocytes from hearts of control and PR foetuses. (C) When normalised to foetal heart weight, PR foetuses have longer cardiomyocytes compared to control foetuses. Reproduced with permission from Morrison et al. [34]. *PR group significantly greater than control foetuses (P < 0.05).
energy intake or resulting from maternal glucose intolerance, may result in an increased risk of childhood and later obesity. In a recent longitudinal cohort study of children [41], it was demonstrated that exposure to either maternal obesity or maternal gestational diabetes significantly increased the odds ratio for the development of obesity and the metabolic syndrome. Furthermore, rapid weight gain during the first weeks or months of life has been shown to be associated with an increased risk of overweight and obesity in childhood and in early adulthood [41]. In a large, prospective contemporary cohort study [42], dietary energy intake in formula-fed or mixed-fed infants at as early as 4 months of age was positively related to early childhood weight gain and subsequent body weight and body mass index up to 5 years of age. In a separate study [43], it was also reported that in a cohort of infants who received only soy-based or cow milk-based formula, that each 100 g increase in absolute weight gain during the first week of infancy was associated with a 28% increase in the risk of becoming an overweight adult. While there are clear associations between exposure to an increased energy supply during the perinatal period and being overweight or obese in childhood and later life, the mechanisms underlying these associations are unknown.

In the adult, appetite and energy balance homeostasis are primarily regulated by a complex neuronal circuitry located within the hypothalamus that receives nutrient, hormonal and neural signals from a range of sources, including fat cells, the pancreas, the gastrointestinal tract and other brain regions. A range of neuropeptides including the orexigenic neuropeptides, neuropeptide Y (NPY) and agouti-related protein (AgRP), and the anorexigenic neuropeptides, pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), are expressed within the hypothalamus and together act in synchrony to regulate energy balance [44]. NPY is a 36-amino acid neuropeptide that markedly stimulates appetite and is predominantly localised in the arcuate nucleus of the hypothalamus with low levels of expression within the dorsomedial nucleus (DMN). NPY neurones project to hypothalamic regions that play important roles in energy balance including the paraventricular nucleus (PVN), DMN, perifornical region and the lateral hypothalamic area. The blood–brain barrier is effectively reduced within the area of the arcuate nucleus and NPY neurones are therefore able to sense and respond to a range of peripheral metabolic signals, including insulin, glucose, ghrelin, and the adipocyte-derived hormone, leptin. A series of experimental studies in the rodent has demonstrated that glucose, insulin or leptin derived from the maternal circulation or present in her breast milk exert a dominant influence on the development of the appetite regulatory neural network and that the immediate postnatal period is of particular importance for the long-term programming of food intake in the rodent [44]. However, the role of maternal metabolic and hormonal signals and the critical windows during which programming of appetite may occur in the litter-bearing, altricial rodent are likely to be different from those in non-litter-bearing, precocial species, such as human beings and sheep.

Maternal nutrition and the development of the neural network regulating appetite.

We have previously reported that genes for the appetite regulating neuropeptides, NPY, AgRP, POMC and CART are each highly expressed in the ventromedial portion of the ARC of the foetal sheep hypothalamus by 110-day gestation, which is consistent with their pattern of expression in the adult sheep hypothalamus [45]. Furthermore, and in contrast to the rodent, NPY projections are also present in the foetal PVN during late gestation [46]. Messenger RNA for the long isoform of the leptin receptor (OB-Rb) is also expressed in both the ARC and ventromedial nucleus of the foetal sheep hypothalamus [45]. We have recently demonstrated [44] that maternal overnutrition in the sheep in late pregnancy significantly increased lamb milk intake in early postnatal life and resulted in the development of an increased mass of subcutaneous fat in lambs by as early as 1 month of age. Importantly, the suppression of the expression of a key appetite inhibitor, CART in the hypothalamus in response to an increase in fat mass, did not occur in lambs born to ewes that had been overnourished in late pregnancy. Furthermore, in these lambs, the central expression of the leptin receptor, OB-Rb, decreased as fat mass increased, consistent with a potential reduction in the sensitivity to the central appetite-inhibitory actions of leptin in lambs of well-fed ewes [44]. These novel findings suggest that an increase in foetal nutrition during late gestation may alter the development of the central energy-regulating neural networks to result in a relative resistance to signals of increased fat mass in later life (fig. 3) [44]. Bouret et al. [47] have reported that the leptin is required for the normal development of neuronal projections within the appetite-regulating neural network during the perinatal period. This raises the intriguing possibility that metabolic or hormonal signals could act during the perinatal period to alter the structural and functional properties of the central neural network that regulates energy balance during adult life.

Conclusions

The ‘foetal or early origins of adult disease’ hypothesis originally put forward by Barker et al. stated that environmental factors, particularly maternal undernutrition, act in early life to programme the risks for adverse health outcomes, such as cardiovascular disease, obesity and the metabolic syndrome in adult life. Subsequent commentators have reflected that early physiological tradeoffs, such as activation of the foetal HPA axis, which confer an early fitness advantage such as foetal survival, while incurring delayed health costs, would be selectively favoured in evolutionary terms [24]. In this review, we have provided evidence that such tradeoffs are being anticipated from conception and that the periconceptional nutritional environment can programme the developmental trajectory of the HPA stress axis and the systems that maintain and regulate arterial blood pressure.
We have presented evidence that restriction of placental growth and function, associated with chronic foetal hypoxaemia and foetal growth restriction also results in an increased dependence of the maintenance of arterial blood pressure on the sequential recruitment of the sympathetic nervous system and HPA axis.

We have also argued that while the ‘early origins of adult disease’ hypothesis has focussed primarily on the impact of undernutrition, an increased fat and energy intake has become a dominant characteristic of the human diet in many parts of the developed world for the first time in history. In contrast to foetal undernutrition, exposure to foetal overnutrition does not result in foetal neuroendocrine responses required for foetal survival. Nevertheless, exposure to overnutrition in foetal life results in a series of central and peripheral neuroendocrine responses that programme subsequent metabolic health. Thus, while exposure to foetal undernutrition results in the physiological trade off between foetal survival and poor health outcomes that only emerge after reproductive senescence, exposure to early overnutrition results in poor health outcomes that emerge in childhood and adolescence and can potentially impact on the health of the subsequent generation. In this context, the physiological responses to relative overnutrition in early life may directly contribute to an intergenerational cycle of obesity.

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