

Topical Review

Developmental processes and the induction of cardiovascular function: conceptual aspects

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The epidemiological basis of the developmental origins of disease concept is now widely accepted. The current impetus in research concerns establishing the underlying mechanisms. We discuss the wider biological nature of the phenomenon, with particular reference to ‘maternal effects’, the processes observed in many species by which the mother can induce phenotypic effects in her offspring. Animal models permit investigation of the induction of cardiovascular phenotypic attributes which resemble pathological effects in humans. We discuss the importance of transitions in aspects of the pre- versus the postnatal environment, with emphasis on nutrition and energy expenditure, and the critical role which the timing of environmental cues plays in inducing effects on the offspring. Coupled with the effects of specific maternal dietary components, the effects on the offspring are argued to involve epigenetic mechanisms. In this review we provide a conceptual framework for synthesising experimental and clinical data, important for considering the impact of the developmental origins concept in a life-course approach to the prevention of cardiovascular disease.

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Introduction

The effects of unbalanced diet and body composition in pregnancy on the subsequent risk of health and disease in the offspring have been well established from epidemiological studies (Barker, 2001) and are strongly supported by numerous experimental observations. The significance of these early life events to the global patterns of disease and their implications for public health policy have been discussed (Gluckman & Hanson, 2005). In this review we consider the biological nature of this phenomenon, with particular reference to the induction of cardiovascular phenotypes in animals. First, the phenomenon will be considered in the context of ‘maternal effects’, a widespread biological phenomenon in many species. Then, we will discuss the importance of the pre- to postnatal environmental transition in mammals, and the role of specific maternal dietary components and timing of effects on underlying mechanisms will be considered. We conclude with a general synthesis and framework for considering experimental and clinical data. Whilst there is a relative dearth of data specifically relating

to cardiovascular function in this context, the broader examples we cite and the theoretical basis discussed are directly applicable to this area of physiology.

Maternal effects

The transmission of cues about the nature of the environment from the parental generation to their offspring is a well-established process in developmental biology (see West-Eberhard, 2003). In *Daphnia* the induction of the ‘helmet phenotype’ as a defence against high predator densities is one example (Laforsch & Tollrian, 2004). A further dramatic example is provided by the desert locust (*Schistocerca gregaria*) in which the population density detected by the female alters the chemical composition of the fluid secreted around her eggs, determining the percentage of larvae which will develop into the gregarious versus solitary forms. These are different not only in body colouration but also in wing shape, behaviour, metabolism and food preference (Wilson *et al.* 2002). In mammals, the meadow vole (*Microtus pennsylvanicus*) provides an example in

which the day length to which the pregnant dam is exposed in early pregnancy determines the coat thickness of the offspring (Lee & Zucker, 1988). This has a later survival advantage but has no value at the time of the 'choice' of coat thickness. These examples are important because they demonstrate that phenotypic changes may be made during development which do not convey any immediate advantage during the developmental period, only a later advantage in the environment experienced by the independent mature organism. Because the changes induced, whilst transgenerationally transmitted, are not genomically transmitted but rather involve epigenetic marks such as methylation to DNA, they have been termed epigenetic inheritance. This concept is very well established in both animal and plant kingdoms and its biological importance is increasingly recognized (see Jablonka & Lamb, 1995).

Such responses, whether induced by nutrition, endocrine milieu, thermal or fluid and electrolyte levels, day length, maternal stress, etc. have been termed by us 'predictive adaptive responses' (PARs; see Gluckman & Hanson, 2004a,b, 2005) building on the concepts of Bateson (2001). We distinguish PARs from the 'coping' responses that follow intra-uterine adaptations to a prenatal threatening environment, which are usually considered in the context of the 'thrifty phenotype' hypothesis (Hales & Barker, 2001). In the latter the developing organism makes immediate adaptive responses to an immediate environmental challenge by reducing either body growth or growth of individual organs to promote its chances of immediate survival. It then has to cope throughout its life with the consequences of the irreversible components of this prenatal adaptive strategy. Hales & Barker (2001) suggested that such thrifty phenotypes would have an advantage in a postnatally deprived environment but would be disadvantageous in an enriched one. Whether the outcome is advantageous or disadvantageous is purely chance. In some respects this concept is akin to that of *exaptation* (Gould & Vrba, 1982) by which traits that are part of an adaptive response of an organism to one environment then serve to be beneficial in another: here the two environments would be pre- and postnatal (provided the latter is deficient). In contrast, PARs confer no immediate advantage (it is in fact conceptually possible that they could have a small disadvantageous immediate effect) but are induced to confer long-term advantage later in life.

The thrifty phenotype model provided the original basis for the widely recognized association between low birthweight and later risk of disease. However, the experimental and clinical data strongly point to a broader phenomenon which has led to further development of the conceptual basis of the impact of early life events on long-term health. Bateson (2001) postulated that the fetus might gain a long-term fitness advantage if it could

predict or 'forecast' its future environment and Jablonka had indicated the fitness advantage of such 'phenotypic memory' (Jablonka *et al.* 1995). The changes in fetal structure and function during development induced by the fetal environment could occur in the absence of any change in fetal growth. The processes of developmental plasticity involve far more than just effects on body size. Indeed, a plethora of human and animal studies show that the environment during development can affect phenotype in either adverse or beneficial ways in the absence of changes in fetal growth. Sometimes, however, these effects are related to prenatal growth in a graded manner across the entire range of size at birth. We do not believe that this necessarily implies causality between reduced growth and phenotypic change. It may be rather that reducing growth is part of a prenatal strategy to cope with adversity, and occurs in parallel with other phenotypic changes which have a predictive component, or that a reduction in growth is a response invoked only when the prenatal environmental challenge is particularly strong and other adaptive responses are inadequate. If this is true then the association between birth size and later risk of cardiovascular disease need not be viewed as due to a direct causal relationship but could be an epiphenomenon due to independent effects on the fetus in terms of its growth and its long-term development. The consequences of these two types of adaptive response need not be the same.

Further distinctions should also be made from the effects of a very severe environmental challenge *in utero*: starvation, infectious agents and the administration of glucocorticoids at critical developmental windows can produce a *disruption* of development which is unrelated to any adaptive advantage either at the time or later. Here, then, a change in phenotypic characteristics, including a possible effect on growth, should be viewed as a direct adverse effect and not an adaptation. This type of effect is not confined to an extremely poor developmental environment: at the other end of the spectrum it should be noted that environmental excess (e.g. during diabetic pregnancy) may also induce detrimental effects including teratogenic change on the developing offspring (see Bateson *et al.* 2005, for review).

Distinguishing long-term consequences of adaptive responses from those that reflect a disruption of development may be difficult (Bateson *et al.* 2005). For example, is the reduction in nephron number *in utero* in response to maternal nutritional manipulation (Langley-Evans *et al.* 2003) or dexamethasone administration (Wintour *et al.* 2003) an adaptive response with long-term sequelae or is it a disruptive effect produced by an extreme exposure to steroids or undernutrition during a critical window of renal development? Because fetal renal blood flow is only 3% of combined ventricular output in late gestation, compared to 20% of cardiac output in the adult (Moritz *et al.*

2005), it is difficult to envisage that any reduction in fetal renal growth constitutes an energy-saving adaptive response. Nonetheless, the relationship between nephron number and maternal vitamin A intake in the rat (Merlet-Benichou *et al.* 1999) suggests that alteration of this development can have long-term consequences.

The range of long-term effects that can be induced by subtle early (e.g. embryonic) life events is striking. It is difficult to envisage how such latent effects can be considered in terms of immediately adaptive responses, especially as they can persist transgenerationally (see below). It is clear that the phenomenon of predictive adaptive responses is widespread. Theoretical modelling indicates that phenotypic memory, whereby environmental impact on one generation has advantageous effects on the next generation(s), is a powerful tool in a repertoire of processes aimed at promoting species survival through changing environments (Jablonka *et al.* 1995). We have suggested (Gluckman & Hanson, 2005) that predictive adaptive responses are the basis of this phenotypic memory and that they are likely to be underpinned by epigenetic mechanisms. They are regulated processes and provide the basis for explaining many long-term consequences of early life events, particularly those not associated with a disturbance in fetal growth. We should note, however, that some environmental cues will induce mixed adaptive responses.

It seems probable that all three types of response – developmental disruption, immediate, and predictive adaptation – have been included under the rubric of ‘programming’. We do not find this term helpful as it still echoes its use for the genetic programme of development (Jacob & Monod, 1961) and has deterministic connotations which are not compatible with the more plastic nature of developmental gene–environment interactions in the induction of phenotype. Moreover, it implies that the nature of the programme to be executed is encoded in the command to execute it (Bateson, 2001).

Importance of the pre- to postnatal transition

These concepts emphasize the importance of environmental transitions in development. Most focus has been on the transition between the prenatal and postnatal environment but this may be better considered as a transition between the environment during the plastic phase of development and the mature, post-plastic phase. Birth itself may be incidental to this transition because different organ systems have different windows of plasticity, some of which are postnatal. Further transitions are not dichotomous – each stage of development can affect the next and responses in one phase may thus affect the capacity to respond to the environment in later stages. Thus we have an increasing awareness that

potential transitions between the embryonic or early fetal and late gestation environments, and indeed between the pre- and post-weaning postnatal environments, maybe of great importance (Harding, 1997; Bloomfield *et al.* 2003, 2004; Singhal *et al.* 2003; Wlodek *et al.* 2003; Cleal *et al.* 2004; Hambidge *et al.* 2005; Edwards *et al.* 2005). The recent studies of Ozanne & Hales (2004) demonstrate the importance of the transition elegantly, because mice whose dams were fed a low protein diet during pregnancy and then a cafeteria diet post weaning lived significantly less long than those whose dams were fed a normal diet during pregnancy. Conversely, feeding a low protein diet to the dams during suckling extended the longevity of their offspring. How the precise nature, magnitude and speed of such transitions affects the offspring has not yet been established – this is an important, if inevitably expensive, study to perform. A clue that there must be an upper limit to the deleterious effects of the poor–rich transition also comes from the study of Ozanne & Hales (2004) because longevity in their mouse offspring was similarly reduced in those weaned onto normal chow and a cafeteria diet. A more detailed consideration of the characteristics of such transitions has been proposed (Gluckman & Hanson, 2004b). Their relevance to humans is shown in Fig. 1.

Maternal diet

Whilst a range of experimental manipulations before and during pregnancy have been utilized, including exposure to nicotine, xenoestrogens, pesticides, bacterial endotoxins, glucocorticoids and manipulation of maternal stress responses (Barbazanges *et al.* 1996; Thiruchelvan *et al.* 2003; Ling *et al.* 2004; Newbold *et al.* 2004; Akingbemi *et al.* 2004; Levin, 2005) the majority of studies have involved alterations to the maternal diet during pregnancy. Particular emphasis has been placed on reduction of global nutrient intake (e.g. Ozaki *et al.* 2000, 2001), feeding a high fat diet (Norman & LeVeen, 2001; Khan *et al.* 2004a) or a low protein diet (Langley & Jackson, 1994; Brawley *et al.* 2003). The effects of a high fat diet are reviewed in this issue (Armitage *et al.* 2005). The focus here will be on the interpretation of the effects of a low protein diet. The widespread consumption of foods of high calorific content, especially those of high glycaemic index, is proposed to exacerbate the effects of early life environments in the aetiology of obesity. Because humans, like rodents and even invertebrates, defend their protein intake within narrow limits, the consumption of a diet with a reduced protein to carbohydrate and fat ratio necessitates ingestion of an increased non-protein calorific load (see Simpson *et al.* 2003). In our evolutionary past, the hunter-gatherer diet was high in protein, even if its availability was uncertain. The precise size of the contemporary effect varies across the globe, but FAO statistics indicate that the fat and carbohydrate content of the Western diet has increased

from 86 to 87.5% between 1961 and 2000, with the corresponding fall in protein content from 14% to 12.5%. This necessitates a 14% increase in energy intake from carbohydrate and fat to maintain dietary protein intake (reviewed in Simpson *et al.* 2003). In animals, feeding a diet with 50% reduction in protein in early gestation, the first half of gestation or throughout pregnancy induces cardiovascular abnormalities in the offspring (Langley & Jackson, 1994; Kwong *et al.* 2000; Brawley *et al.* 2003; Nishina *et al.* 2003) including elevated blood pressure, endothelial dysfunction, glucose intolerance, disturbances in metabolism and specific tissue gene expression. The precise component of the low protein diet which mediates the effect is not known, although attention has focused recently on glycine because, although a non-essential

amino acid, it is required in large quantities in the human fetus in late gestation and thus becomes 'conditionally essential'. Supplementation of the low protein diet with glycine in the rat prevents hypertension in the offspring (Jackson *et al.* 2002) and also the disordered placental lipid levels (Burdge *et al.* 2002). In addition it rectifies the abnormalities in responses of the uterine arteries of the pregnant dam in late gestation (Brawley *et al.* 2004).

Timing of effects

The original concept of the fetal origins of adult disease (Barker, 2001) focused attention on reductions in fetal growth in late gestation as a direct response to an adverse intra-uterine environment, which then produced

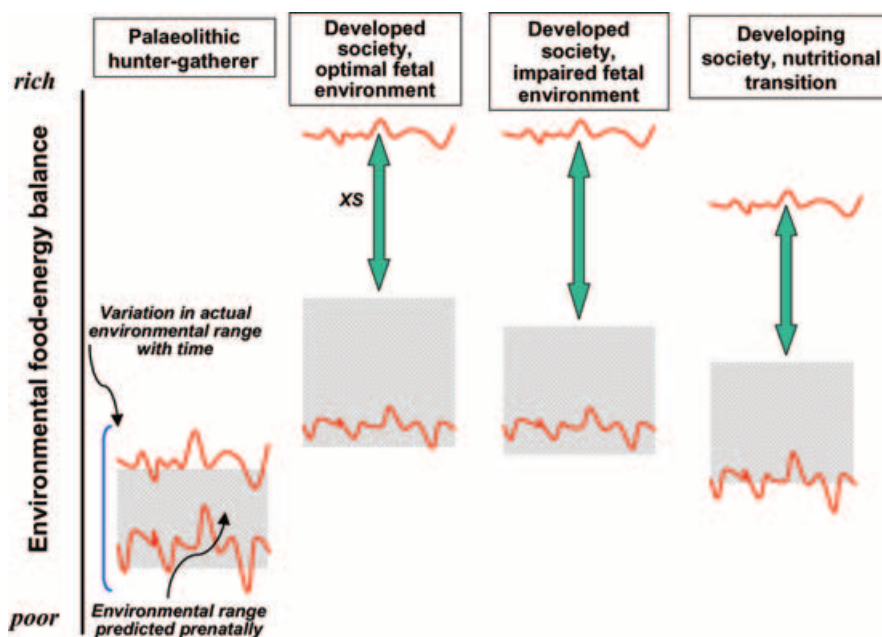


Figure 1. Diagram to show a conceptual framework for the influence of predictive adaptive responses (PARs) under various food availability–energy expenditure conditions in the postnatal environment

Red lines show the range of environmental conditions occurring over time. Stippled regions show the range for which mature individuals have maximal fitness as determined during early development by PARs. Those living in a food–energy environment outside their PARs range are at increased risk of 'lifestyle' disease such as metabolic syndrome. For a Palaeolithic hunter-gatherer society the level of food–energy balance is low and the range narrow, and this period of evolutionary adaptiveness ensured an approximate match between the physiology of the adult and the range of environments experienced. PARs allowed the individual to cope with the extremes of this range. The risk of disease such as metabolic syndrome was irrelevant given that low life expectancy resulted from other causes. In contemporary developed societies, the range of food–energy balance has moved upwards, especially at the upper limit. However, the intra-uterine environment remains relatively constrained due to the limits on maternal size. Therefore the persistent presence of PARs leaves the individual with a set of predictive adaptations mismatched with the actual environment faced and this leads to a gap between the upper limit of the range of optimal fitness and the environment actually faced. Such individuals are not well-adapted to live in this range and this confers increased risk of metabolic disorder with accompanying morbidity and mortality. The XS range is even larger following pregnancies with excessive constraint, due, for example, to unbalanced maternal diet or body composition, disease or placental insufficiency; under these conditions the PARs range shifts downwards and is narrower. The XS range is nearly as wide in developing societies undergoing economic transition, even if the food–energy balance has not yet reached the level of developed societies, because for many generations small maternal size and relatively poor nutrition have constrained the fetus and the processes of PARs have set the postnatal fitness range lower. Such societies are particularly at risk as the size of the food–energy transition increases further.

detrimental long-term consequences. Recent research has, however, drawn attention to the ways in which the environment of the early embryo or the fetus in the first trimester of pregnancy can induce phenotypic changes. Kwong *et al.* (2000) demonstrated that the low protein diet fed during only the first 4.25 days of pregnancy (pre-implantation) in the rat produced hypertension in the offspring. Nutritional manipulation in the pre-implantation period in the sheep produces effects on the length of gestation and maturation of the hypothalamic–pituitary–adrenal (HPA) axis (Bloomfield *et al.* 2003, 2004), blood pressure in late gestation and the endocrine and cardiovascular responses of lambs at 2¹/₂ years of age (Cleal *et al.* 2004; Poore *et al.* 2004). In addition, a follow-up study of offspring of mothers who suffered the Dutch ‘hunger winter’ in 1944/5 reveals that famine exposure during the first trimester produced effects on the offspring which were not accompanied by a reduction in birth weight (Roseboom *et al.* 2001). Recently we showed in the guinea pig (Khan *et al.* 2004b) that global undernutrition during the first half of pregnancy produced elevated blood pressure and left ventricular hypertrophy in the absence of a reduction in birth weight; undernutrition in late pregnancy reduced birthweight, as expected, but did not lead to hypertension or significant left ventricular hypertrophy in the adult offspring.

That such effects can be produced in early gestation emphasizes their later predictive, rather than immediate, adaptive value. Indeed, in the sheep, thickening of the cardiac interventricular septum in adults was seen in offspring whose ewes received an early undernutrition challenge, as in the guinea pig, but the effect was absent in offspring who also received undernutrition in the postweaning period (Boullin *et al.* 2005). Hence the predictive value of the first insult appears to protect against the detrimental effects of the second. These effects are most striking in male offspring, with changes in body composition and fat deposition being more evident in female offspring. It would appear that males preserve growth, but trade off cardiovascular and renal function, thus maintaining body size, whereas females trade off growth for metabolic responses and fat deposition. Each of these processes can be interpreted as giving a reproductive advantage.

Mechanisms

The importance of methyl group provision, derived especially from dietary glycine, is referred to above. Glycine supplementation of the low protein diet prevents hypertension in the adult offspring in the rat, although supplementation with casein, alanine or urea does not (Jackson *et al.* 2002). Apart from its effects on the maternal cardiovascular adaptations to pregnancy, glycine

supplementation also reduces the elevation of maternal plasma homocysteine levels in animals fed the low protein diet during pregnancy, and this may give an additional cardiovascular protective effect on both the pregnant dam and her fetuses. The effects on the uterine artery appear to be mediated primarily via promotion of vasodilator function, and glycine supplementation restores uterine artery NO production (Brawley *et al.* 2004). These effects may partially explain the effect of the low protein diet on the offspring, as presumably it would promote nutrient supply to them *in utero*. However, considerable interest is also focused on the ways in which altered methyl group provision may affect epigenetic processes in the developing offspring. Such processes may affect both histone acetylation, and thus the accessibility of regions of the genome for transcription, and DNA methylation at CpG islands, which is known to act at gene promoter regions to regulate their expression. Such processes are well known for imprinted genes (Constancia *et al.* 2004). The provision of methyl groups for the process depends on the availability of cofactors including folate, vitamin B6 and B12. Dietary folate supplementation affects the expression of the agouti mutation in the mouse (Waterland & Jirtle, 2003) preventing obesity and cancer as well as the yellow coat colour in the offspring. We have now shown that folate supplementation prevents elevated blood pressure, endothelial dysfunction and the reduction in eNOS expression in the vasculature of the offspring in the rat (Torrens C, Brawley L, Anthony FW, Dance CS, Dunn R, Jackson AA, Poston L and Hanson MA, unpublished observation). The precise timing of the window when changes in DNA methylation may produce permanent effects on the offspring is not known, but in the rat it would appear to extend beyond the embryonic phase: Pham *et al.* (2003) showed that uterine artery ligation in late gestation produced alterations in the methylation of the p53 gene in the kidney of the adult offspring. This is interesting because p53 is involved in tumour suppression, monitoring DNA damage and apoptosis and could therefore mediate some of the effects on nephron number of the low protein diet.

Epigenetic changes inducible during the suckling period are demonstrated by the findings of Weaver *et al.* (2004) who showed changes in histone acetylation and transcription factor (NGFI-A) binding to the promoter of the glucocorticoid receptor gene in the hippocampus in offspring of mothers who showed different degrees of licking and grooming of their pups. Administration of a histone deacetylase inhibitor restored histone acetylation, DNA methylation, NGFI-A binding, glucocorticoid receptor expression and HPA responses to stress. These results are interesting because changes in the HPA stress responses in humans may lead to aspects of the metabolic syndrome (Flanagan *et al.* 1999). Changes in the expression of imprinted genes during suckling may also be important

for offspring growth and metabolism (see Constancia *et al.* 2004, for review). Finally, Lillycrop *et al.* (2004) have shown changes in the expression of peroxisome proliferator-activated receptor alpha (PPAR α) in the liver of offspring of dams fed the low protein diet which are accompanied by a reduction in DNA methylation of the gene and are reversible by dietary folate supplementation of the dam. Such effects would be expected to alter fatty acid metabolism in the liver and are targeted to specific parts of the genome as changes in PPAR γ were not observed in those experiments.

There is clearly considerably more work to be done on the area of epigenetic regulation of early development, and one of the most intriguing aspects of the phenomenon is that recent work demonstrates that the methylation patterns may be in part transmitted to more than one subsequent generation. Thus the effects of the low protein diet or of glucocorticoid administration during pregnancy can be seen on cardiovascular function and on glucose homeostasis in the F2 offspring, even in the absence of an additional nutritional challenge during the pregnancy of the F1 offspring (Torrens *et al.* 2002; Drake *et al.* 2005). Possible underlying mechanisms include effects on the oocytes developing in the fetus *in utero*, effects on maternal adaptations to pregnancy in the F1 generation or direct transmission of methylation patterns to subsequent generations (see Drake & Walker, 2004, for review). The association of such processes with cardiovascular and metabolic dysfunction makes it clear that non-genomic inheritance of factors for risk of disease needs considerably more attention.

Conclusion

The genotype of the early embryo contains a record of the evolutionary past of the species, including changes which have been manifest by mutation, natural and sexual selection, genetic drift, etc. It also contains echoes of the environmental exposures of recent antecedent generations, in the form of persistent epigenetic marks on the genome. Transition from the genotype of the early embryo to the phenotype of the offspring by the time of weaning involves a range of epigenetic processes, including predictive adaptive responses, developmental plasticity and, under some circumstances, developmental disruption. Further transitions in phenotype occur in childhood and into adult life. The level of matching between developmental and later environments, or more specifically between the predicted and actual later environments, influences these transitions in phenotype and, in turn, the risk of disease. Understanding these processes will help us to devise interventions to limit the progression to disease in susceptible individuals and sections of the population.

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