

The developmental origins of the metabolic syndrome

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Both epidemiological and clinical evidence suggest relationships between the antenatal environment and the risk of developing insulin resistance and associated cardiovascular disease (part of the metabolic syndrome) in middle age. However, interpretation of these findings has been controversial. Recent experimental observations provide considerable evidence for a causal model linking adaptive responses to early environmental cues and the later risk of disease. Evolutionary and life history theory provide possible explanations of why these phenomena have persisted and how they might cause disease. In this article, we review the clinical and experimental perspectives on the ‘developmental origins of disease’ model in the context of these new concepts.

Both epidemiological and clinical evidence suggest that prenatal factors play a role in the origin of the metabolic syndrome and its components: hypertension, insulin resistance, central obesity and dyslipidemia. Experimental studies demonstrate that an adverse embryonic or fetal environment can induce structural and functional abnormalities in the pancreatic islet cells and lead to permanent changes in insulin sensitivity. There has been controversy about the relative contribution of non-genetic factors acting in early life to the rising incidence of type 2 diabetes and the metabolic syndrome. We review the growing clinical and experimental evidence and the current knowledge of possible underlying mechanisms. An evolutionary perspective can assist our understanding of how gene–environment interactions in early development, adaptive for our ancestors, can now contribute to the rising incidence of disease. We suggest that part of the strategy for addressing metabolic disease is an increasing focus on maternal and child health.

Responses to environmental change – a developmental perspective

Homeostatic responses provide an immediate survival advantage. If they act during windows of developmental plasticity they might have permanent echoes as a result of biological ‘tradeoffs’. A second set of responses to environmental stimuli, termed predictive adaptive responses (PARs), need not confer immediate advantage but is induced in the expectation of future adaptive advantages.

They also induce irreversible changes in structure and function. For example, in the meadow vole (*Microtus pennsylvanicus*), the coat at birth is thicker in animals born in the autumn than in those born in the spring [1]. Using the processes of developmental plasticity, the fetal vole has determined postnatal coat thickness while *in utero*, based on maternally derived signals of day length [2]. This offers no immediate advantage (all pups are exposed to similar temperatures *in utero* and in the nest), but reflects anticipation of the later environment and, as such, promotes survival to reproduce. These concepts are relevant to understanding the recent observations relating the early environment to the risks of the metabolic syndrome in later life.

Evidence for developmental origins of the metabolic syndrome

Several epidemiological studies have related birth weight or size at birth to subsequent risk of developing insulin resistance and/or type 2 diabetes mellitus in middle age. The relationships with disease risk extend continuously across the normal range of birth weights, and are not just a function of the very low or high weights. In younger cohorts, the relationship between birth size and insulin resistance is U-shaped, reflecting effects associated with gestational diabetes in larger babies (see [3] for review). Similar relationships have been found for other components of the metabolic syndrome, including cardiovascular disease [4] and dyslipidemia [5]. There is also an interaction between lesser prenatal growth and postnatal weight gain. Thus, the risk of developing insulin resistance is greatest in those who are small or thin at birth and who then develop relative obesity postnatally. Individuals at greatest risk have an earlier pre-pubertal adiposity rebound and gain weight faster in the late pre-pubertal period [6,7].

The weight of epidemiological evidence is substantial [3]. Nevertheless, it has created controversy. The studies were criticized as retrospective, confounded by other variables (e.g. socioeconomic status) and as biologically implausible. Critics questioned the size of the relationship between birth weight and surrogate measures of cardiovascular disease risk (e.g. blood pressure) [8]. However, stronger and robust relationships exist between birth size and the incidence of clinical disease (e.g. heart disease or

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clinical hypertension). Furthermore, prospective clinical and experimental observations demonstrate clear relationships between measures of the fetal environment and risk of developing insulin resistance. Children and young adults born small have lower insulin sensitivity, even in the pre-pubertal period [9].

It is misleading to consider size at birth as causal in the pathway to disease. In epidemiological studies, birth size can only be considered as an integral of interactions between environmental and genomic influences during fetal life. A poor intrauterine environment constrains fetal growth, and it is these environmental factors that induce change in metabolic and cardiovascular development, independent of effects on fetal growth.

Experiments in several species show that it is easy to induce insulin resistance and other manifestations of the metabolic syndrome, including hypertension and endothelial dysfunction, by manipulating maternal nutrition or exposing the mother to synthetic glucocorticoids [10–12]. Following maternal under-nutrition in rats, pups develop fasting hyperinsulinemia, hyperleptinemia, hyperphagia and have increased lethargy [13,14]; they also develop central obesity [13] and have reduced muscle mass [15]. In similar experiments, changes in hypothalamic appetite regulatory peptides and a preference for fatty food consumption are reported [16].

Biological basis of the phenomenon

Developmental plasticity and PARs can only act through a limited number of mechanisms. The first is epigenetic change in gene expression. In the agouti mouse, the degree of imprinting of the agouti gene can be influenced by periconceptual maternal nutrition, and this involves a folate-dependent change in DNA methylation [17]. Similarly, folate or glycine administration during pregnancy can reverse the vascular effects on the offspring of the low-protein diet [18–20]. Specific changes in renal DNA methylation have been reported recently in the rat [21].

The second mechanism involves altered tissue differentiation. For example, adult nephron numbers are reduced both in humans who are born small and in animals manipulated experimentally *in utero*, which later develop hypertension [22,23]. This might be the result of a biological trade-off to conserve energy in response to deprivation during a crucial developmental window, having immediate but no long-term adaptive value. Alternatively, it might simply be a result of developmental disruption with no adaptive value, analogous to teratogenesis. Similarly, in the rat, the developing pancreatic islet undergoes a wave of developmental apoptosis during the perinatal period, presumed to reflect a transition from a fetal to a postnatal form of islet cell with a different regulatory profile [24]. The rate of β -cell apoptosis is increased in infant rats whose mothers are fed a low-protein diet [25], perhaps because of an increased sensitivity to cytokines [26]. Inhibition of this apoptosis in the neonatal period prevents the development of subsequent diabetes [27]. Again, whether this is simply a developmental disruption or an adaptive response conveying potential future advantage is unclear.

The third mechanism involves altered homeostatic processes. Offspring of rats fed a low-protein diet have an altered ratio of periportal to perivenous hepatocytes, leading to an altered ratio of phosphoenolpyruvate carboxykinase to glucokinase-enriched cells and greater hepatic glucose production [28,29]. The expression of enzymes involved in lipid homeostasis, including carnitine palmitoyl transferase, is suppressed [30]. Skeletal muscle from growth-retarded infant rats is relatively resistant to both insulin and insulin-like growth factor I [31]. There is also mitochondrial dysfunction and reduced expression of protein kinase C- ζ , which might lead to altered glucose transporter 4 (GLUT-4) mobilization in muscle [32,33]. Cardiac muscle also shows reduced synthesis of GLUT-1, GLUT-4 and hexokinase II [34].

A general model

Several models have been developed to explain these effects. The ‘thrifty genotype’ hypothesis suggested that modern humans evolved by selecting genes that promoted insulin resistance [35]. Such ‘thrifty genes’ would confer a survival advantage to hunter-gatherers, but would lead to a greater disease risk in a modern nutritionally rich environment. Because insulin is an important fetal growth hormone, this could explain the link between birth size and disease risk. Studies of mutations in the glucokinase gene support this [36]. An alternative, the ‘thrifty phenotype’ model focused on environmental factors [37], proposing that the fetus makes adaptive changes to intrauterine nutrient limitation by slowing its growth and inducing insulin resistance/deficiency. This confers the additional advantage of allowing the organism to survive long enough to reproduce in a nutritionally deprived environment. These two hypotheses are not mutually exclusive, as illustrated by the finding that the relationship between birth size and risk of insulin resistance is dependent on a particular peroxisome proliferator-activated receptor γ 2 polymorphism [38].

We have developed a more general model combining features of both these concepts. In our model, the fetus constantly interprets the environment created by the maternal milieu and placental function. Some fetal responses are homeostatic or immediately adaptive; others simply reflect developmental disruption but might have echoes throughout life (e.g. reduced nephron numbers). Still others have little immediate adaptive value, but confer advantage by establishing metabolic physiology appropriate for the postnatal environment predicted to exist (Figure 1). If the fetus predicts a nutritionally poor postnatal environment, it chooses a developmental path appropriate for a lower postnatal nutritional range; the fetus predicting an enriched postnatal environment adopts a different path. Such responses are appropriate if the predicted and actual postnatal environments match, but inappropriate if they do not. Thus, the upper limit of the postnatal nutritional environment tolerated without risk of disease depends on the fetal prediction, which depends on maternal and placental physiology. There is considerable potential for discrepancy between the predicted and actual postnatal environment as a result of maternal and/or placental disease, and because of

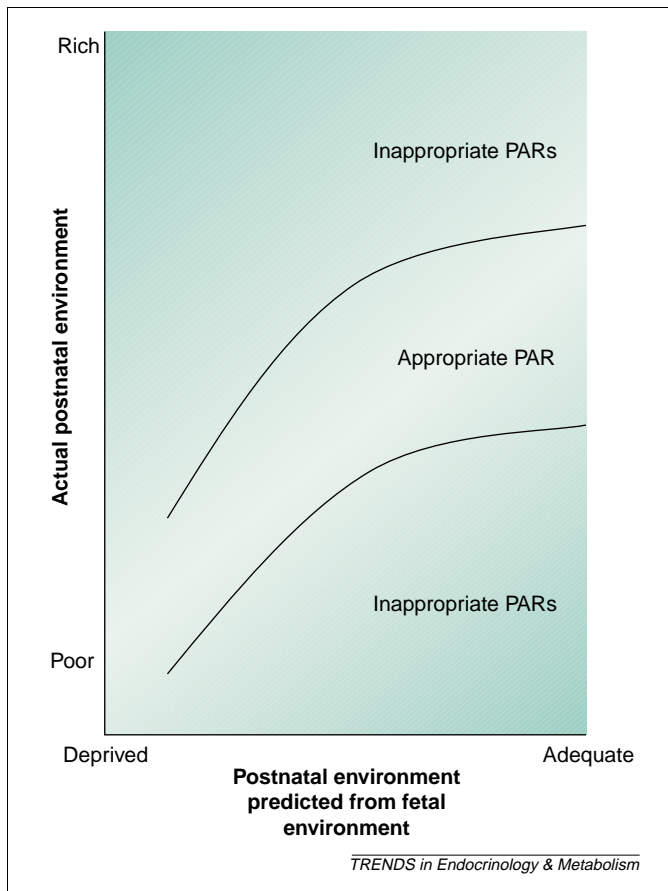


Figure 1. The nature of the predictive adaptive response (PAR) is determined by the predicted and actual postnatal environment. The fetus sets a range of homeostatic settings appropriate for postnatal life according to the information it receives *in utero*. If the actual postnatal environment matches the prenatal prediction, then the PARs are appropriate and disease risk is low; if they do not match, then the disease risk is increased. Note that the postnatal range associated with health might be narrowed if the fetal environment has been poor. This is because the plastic responses made during development for immediate adaptive advantage might later act to limit the range of postnatal adaptive responses possible.

maternal constraint. A change in actual environment (e.g. as a result of migration to a different ecological niche) constitutes a further path to inappropriate prediction.

Maternal constraint

Fetuses do not grow to their maximum genetic potential because growth is constrained to match the size of the mother [39]. This is necessary in monotocous species to allow vaginal delivery; otherwise, there would be a substantial risk of obstructed labor if a large male mated with a small female. Although maternal constraint operates in all human pregnancies, it is greater in adolescent mothers, in the nulliparous pregnancy, in short mothers and in multiple pregnancies [40].

An evolutionary perspective

Although Darwinian selection generally operates on a multigenerational time scale and on the assumption of a unidirectional or permanent change in the environment, there are many situations where a shorter, transient environmental change occurs. Without PARs, modeling suggests that transient environmental change would carry

a high risk of extinction of the gene pool. PARs allow for the widest possible gene pool to be maintained [41]. Selection favored protection of those PARs aiding survival to reproduce. This would have assisted ancestral hominids to develop a phenotype suitable for a hunter-gatherer lifestyle, migration and survival in a wide range of habitats. Maternal constraint biased this phenotype towards insulin resistance, a preference for a high-fat diet and omental fat deposition. Because life expectancy was short and the postnatal environment was more likely to be restricted than plentiful, there would have been no selection against this phenotype. Thus, although covert, Neolithic humans would probably have had traits that favored insulin resistance and omental obesity in an enriched postnatal environment.

The predictive strategies that promoted survival in prehistory now have a cost in a modern postnatal environment. The model emphasizes that it is the relative difference in nutrition between the pre- and postnatal environment, rather than an absolute level of nutrition, that determines disease risk.

PARs and patterns of disease

There are implications for possible interventions because improved maternal and fetal health might allow a broader range of postnatal environments to be tolerated. This has been proposed as one explanation of the French paradox, given that in France maternal nutrition was improved by legislation before other nations [42]. The speed of nutritional transition in a society is crucial because the prenatal environment changes much more slowly than the postnatal environment; the former is determined by maternal size, body composition and metabolism, features that were partly determined when the mother herself was a fetus. Because it is the relative shift in fetal to postnatal environment that influences disease risk, these mechanisms can operate across the full range of developmental environments. The PARs model can explain the rapid increase in insulin resistance/metabolic syndrome seen in deprived populations migrating to more enriched circumstances. The epidemic of type 2 diabetes in the Indian subcontinent might be a consequence of improved postnatal nutrition against a background of impaired fetal growth as a result of severe maternal constraint and small maternal size.

Prenatal factors might be important in childhood and adolescent obesity, as suggested by the experimental data [13–16]. A human experiment of history supports this hypothesis. In a previously well-fed population subject to wartime famine, pregnant women exposed to famine in the first trimester gave birth to offspring who subsequently had greater risk of developing truncal obesity and insulin resistance [43,44]. Infants in India, who are generally exposed to greater maternal constraint, not only have low birth size, but also have relatively less skeletal muscle and more central fat [45]. Measures of maternal nutrition and birth size are inversely correlated with central obesity in adolescence [46]. Offspring of smokers are relatively smaller at birth and are more likely to develop obesity in adolescence [47], as are offspring of first pregnancies where maternal constraint is greater [48,49].

Maternal and transgenerational effects

Non-genetic, intergenerational effects are well described in plants and animals [50,51]. As a result of the Dutch winter famine, women who were undernourished as fetuses in the first trimester subsequently gave birth to smaller fetuses when they themselves became pregnant [52]. In the rat where the F1 generation is exposed *in utero* to a low-protein diet, the F2 generation demonstrates insulin resistance, especially if the F1 generation was fed a high-fat diet [53]. There are several possible mechanisms. First, growth-retarded fetuses have smaller uteri as adults, constraining the growth of their fetuses further [54]. Second, some epigenetic changes can be transmitted intergenerationally [18]. One implication is that the 'heritable' components of type 2 diabetes might not simply be the result of genetic factors, but might involve transgenerational epigenetic PARs.

Conclusions

Prenatal gene–environment interactions play a role in determining the postnatal phenotype that is predisposed to development of the metabolic syndrome. The speed with which a mismatch between fetal and postnatal environments can develop magnifies the risk of inappropriate PARs and might contribute to the current epidemic of type 2 diabetes and obesity. Modification of the prenatal environment might significantly ameliorate the risk of 'lifestyle-related disease' postnatally. In one population-based estimate made on a Finnish dataset, optimal fetal growth accompanied by normal infant growth would have reduced the incidence of type 2 diabetes by 57% [55]. Notwithstanding the errors and assumptions inherent in such a calculation, these observations suggest that early determinants of the metabolic syndrome might have greater importance than previously thought.

A recurrent theme in developmental physiology is that although the initial impact of a triggering event might be relatively subtle, the effects are magnified through time. In retrospective analyses, the postnatal influence always appears to dominate, but this does not mean that the initial prenatal triggering event was unimportant. Given the length of time necessary for clinical study, experimental approaches will be central to improving our understanding of the developmental component to later disease.

Acknowledgements

M.A.H. is supported by the British Heart Foundation.

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