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MiniReview

Developmental Origins of Health and Disease: New Insights

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Abstract: Epidemiological and animal studies show that small changes in the developmental environment can induce phenotypic changes affecting an individual's responses to their later environment. These may alter the risk of chronic disease such as metabolic syndrome or cardiovascular disease. Recent research shows that animals exposed to such a mismatch between prenatal and postnatal environment develop obesity, reduced activity, leptin and insulin resistance, elevated blood pressure and vascular endothelial dysfunction. Epigenetic processes are involved in such effects, targeted to promoter regions of specific genes in specific tissues. Such fine control of gene expression suggests that the mechanisms have been retained through evolution through their adaptive advantage, rather than representing extreme effects of developmental disruption akin to teratogenesis. There may be adaptive advantage in a developmental cue inducing a phenotypic change in generations beyond the immediate pregnancy, and a range of data that support this concept. In animals, epigenetic effects such as DNA methylation can be passed to successive generations. Environmental toxins, including endocrine disruptors, may induce greater risk of chronic disease, even at low exposure levels, if they affect such normal developmental epigenetic processes. Appropriate interventions may have long-term multigenerational effects to reduce the risk of chronic disease.

The concept that health in adulthood could be influenced by the processes of development in early life is ancient – it was known at least by the time of Hippocrates. In experimental science, the work of Dörner et al. supported it [1] and in human populations that of Forsdahl [2] showed how poor conditions in early life remain with individuals in terms of later risks. The applications and implications of this to medicine were demonstrated extensively by the work of Barker et al. [3,4]. This led to the concept of foetal origins of adult disease. Many of the seminal observations in the field revolved around the association between low birth weight and later risk of disease, observations that have been extensively replicated but which are still actively discussed [5]. Mechanistically, the concept was encapsulated in the 'thrifty phenotype' hypothesis [6] that posited that, under conditions of poor or unbalanced nutrition the foetus made adaptations, including reducing somatic growth, in order to survive. These immediate adaptations may have altered phenotype in a way that was detrimental in later life and was associated with increased risk of chronic diseases such as type 2 diabetes, hypertension and coronary heart disease. These ideas have now been revised in the light of new data and by drawing on concepts derived from other disciplines including toxicology.

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Beyond low birth weight

The first important revision is the perception that the prenatal challenges that induce a phenotype that may have potentially detrimental characteristics in adult life. They need not necessarily be accompanied by a reduction in foetal growth leading to low birth weight [7]. This concept is in fact evident from the earlier epidemiological studies, which clearly show a graded inverse association between low birth weight and risk of later disease across the normal birth weight range. Despite the fact that the retrospective historical cohorts examined births occurring in the mid-20th century, a time at which survival of intrauterine growth restricted babies would have been limited, nonetheless many investigators have focused their attention on the long-term consequences of foetal growth restriction. It is now clear that, while under some circumstances a reduction in foetal growth may be part of the strategy adopted to adapt to a prenatal challenge, this is not invariably so and an overall reduction in foetal growth does not lie on the causal pathway to induction of the other phenotypic characteristics. A related issue concerns the importance of timing because, for example, challenges in the periconceptional period can induce effects on the offspring without altering late gestation growth or size at birth.

Related to this is the perception that prenatal challenges may fall into several categories [8]. At one extreme, a severe challenge may induce a frank disruption of development. This might be induced by severe undernutrition, exposure to toxic levels of chemical agents or to maternal illness. Even the balance in the micronutrient levels in the maternal diet

might be important (e.g. in the case of folic acid) [9,10]. These disruptive processes on foetal development are akin to teratogenesis and their relatively low incidence suggests that they play a minor role in the aetiology of common chronic diseases in later life. If the intrauterine challenge is less severe, it may induce foetal adaptations and also reduce foetal growth, and this would lead to the thrifty phenotype proposed by Hales and Barker [6]. Lastly, and reflecting the majority of environmental conditions lying within the normal range, are a set of adaptive responses. The embryo or foetus makes these to environmental cues that are not usually associated with reduced birth weight or indeed other adverse phenotypic consequences at birth. These processes, which have been termed forecasting [11] or predictive adaptive responses [12], are made in expectation of the future postnatal environment predicted on the basis of the prenatal cues, and aim to tune the phenotype of the offspring to meet optimally the challenges of that environment. This would then confer a Darwinian advantage in promoting survival and likelihood of reproductive success.

Predictions and matches

The processes of prediction referred to above involve those of developmental plasticity, and there are many examples in non-mammalian species of the importance of such predictive adaptive processes [13]. There are also many mammalian examples in the wild (e.g. coat thickness and seasonal breeding behaviour in voles) [14]. The predictive adaptive response hypothesis is also open to direct experimental testing in animals. For example, one implication is that pathophysiological effects should be less in animals exposed to poor nutrition postnatally if they had been challenged with similarly poor nutrition prenatally. This appears to be the case with feeding of a high-fat diet in both the pig [15] and the rat [16]. Some evidence of detrimental effects of a mismatch between prenatal and postnatal diet on insulin resistance has also been shown in the rat [17]. In the sheep, a species that is similar to human beings with respect to cardiac and renal maturation at birth, a range of cardiovascular effects have been shown in offspring of ewes undernourished for the first month of gestation but not given a postnatal nutritional challenge (i.e. mismatched) compared to those who were exposed to both prenatal and postnatal nutritional challenges (i.e. matched nutrition) [18]. As pointed out by Rickard and Lummaa [19], there have been few tests of the predictive adaptive response hypothesis in human beings in relation to the metabolic syndrome. There is confirmation of the hypothesis in relation to reproductive function in human beings [20].

Mechanisms underlying mismatch

The detrimental effects are seen in developed societies with increasing affluence but can also explain why human populations undergoing socio-economic change, or economic migrant groups, show increased risk of these chronic diseases.

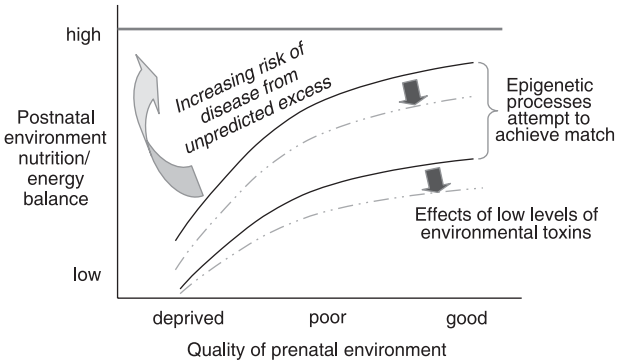

Fig. 1. Diagram showing how mismatch between prenatal and postnatal environment increases risk of chronic disease later in life. Blue lines show range of postnatal environments for which the phenotypes induced by the prenatal environment are matched, and hence able to remain healthy. Epigenetic processes are particularly important during development in attempting to produce an optimal match, based on developmental environmental cues. As the quality of the prenatal environment decreases, this range becomes narrower and depressed, increasing the likelihood of disease from unpredicted excess in the postnatal environment. Thus, developing societies are at risk when even a small improvement in socio-economic conditions occurs from a low baseline. In many parts of the world, the level of postnatal nutrition/energy balance exceeds that to which human can develop appropriate phenotype, as shown by the red line. Even levels of environmental toxins that alone would not be pathogenic can induce substantial effects on risk of later chronic disease by altering the epigenetic matching, depressing the level and range of the healthy range as shown by the brown lines.

Recent research shows that animals exposed to such a mismatch between prenatal and postnatal environment develop obesity, reduced activity, leptin and insulin resistance, elevated blood pressure [21,22] and vascular endothelial dysfunction. The mismatch concept [23] can explain why effects such as obesity are now seen in developed societies even in children, and why in developing societies they can become manifest even within a relatively small increase in economic circumstances. It is important to realize that the plastic phase of human development does not stop at birth, so that environmental influences in infancy and early childhood can have long-term health implications [24,25]. Design of effective preventative measures necessitates an understanding of underlying mechanisms. In rodents, we have found an important role for molecular epigenetic processes in producing such effects, processes that are targeted to promoter regions of specific genes in specific tissues. They include changes in DNA methylation at specific CpG dinucleotides and also in histone structure associated with suppression of gene transcription [26,27]. Such fine control of gene expression endorses the view that the mechanisms have been retained through evolution as a result of the adaptive advantage that they confer (fig. 1), rather than representing extreme effects of developmental disruption. Moreover, there may be adaptive advantage in a developmental cue inducing a phenotypic change in generations beyond the immediately affected pregnancy. Such effects, which might

be termed non-genomic inheritance [28], may be mediated by a range of effects including alterations in maternal adaptations to pregnancy in successive generations [29] or behavioural influences. There is now increasing evidence in animal models for transmission of phenotypic attributes that parallel those linked to risks in human beings [30–33]. The adaptive advantage of such effects has been discussed [34]. Recent data, however, also show that epigenetic effects such as DNA methylation can be passed to successive generations [35,36]. This suggests that they might persist through meiosis. There is now evidence for transmission via the male lineage that may also involve miRNA-mediated effects [37].

Environmental toxicants, including endocrine disruptors, can play a role in inducing greater risk of chronic disease even at low exposure levels, especially if they act via the normal epigenetic processes involved in developmental plasticity that alters the phenotype of the offspring induced in expectation of its future environment. In this context, it is interesting that a recent study shows that the effects of maternal exposure to bisphenol A on the offspring are mediated in part by DNA hypomethylation, but are prevented by maternal dietary supplementation [38]. Thus, the results of current research are beginning to emphasise the long-term multigenerational effects that appropriate interventions, perhaps including those that reduce environmental toxicant exposure, may confer to reduce the risk of chronic disease in subsequent generations.

Conclusion

Animal research has shown the importance of environmentally induced changes in gene expression, which operate via epigenetic mechanisms during development to influence the phenotype of the offspring in an attempt to match this to the predicted future environment. In the face of an energy-rich postnatal environment (e.g. the feeding of a high-fat diet), animals develop equivalent components of the human metabolic syndrome, and these effects are more pronounced when the mismatch between the developmental and later environment is greater. The developmental 'environmental' cues investigated so far predominantly involve maternal diet and endocrine status; however, there is growing concern that environmental toxicants, which are known to produce epigenetic effects, might also interact with these maternal factors to increase risk of chronic diseases such as metabolic syndrome in the offspring. If so, the consequences for human populations going through socio-economically driven nutritional and lifestyle transitions, and also exposed to environmental toxicants, must be considered. Further basic research to examine these interactions is required, and translation to human populations will be needed. We have recently shown that early postnatal manipulation of offspring exposed to a poor developmental environment can prevent the induction of adverse aspects of their metabolic phenotype later, even if they are fed an obesogenic diet [39]. The phenotypic prevention was accompanied by reversal of the accompanying epigenetic changes. Although the postnatal manipulation in animals involved leptin administration, such work offers in principle the prospect of devising targeted interventions in human beings to prevent the longer-term adverse effects of exposure to a poor developmental environment. However, considerably more fundamental work is required before such considerations can be taken further.

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References

1 Dörner G. Perinatal hormone levels and brain organization. Anat Neuroendocrinol 1975;**1**:245–52.
2 Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? Br J Prev Soc Med 1977;**31**:91–5.
3 Barker DJP. Fetal origins of coronary heart disease. BMJ 1995;**311**:171–4.
4 Barker DJP. Mothers, Babies and Health in Later Life, 2nd edn. Churchill Livingstone, Edinburgh, UK, 1998.
5 Huxley R, Owen CG, Whincup PH et al. Is birth weight a risk factor for ischemic heart disease in later life? Am J Clin Nutr 2007;**85**:1244–50.
6 Hales CN, Barker DJ. The thrifty phenotype hypothesis. Br Med Bull 2001;**60**:5–20.
7 Gluckman PD, Hanson MA. The conceptual basis for the developmental origins of health and disease. In: Gluckman P, Hanson M (eds). Developmental Origins of Health and Disease. Cambridge University Press, Cambridge, UK, 2006;33–50.
8 Gluckman PD, Hanson MA, Spencer HG, Bateson PPG. Environmental influences during development and their later consequences for health and disease: implications for the interpretation of empirical studies. Proc Biol Sci 2005;**272**:671–7.
9 Rao S, Yajnik CS, Kanade A et al. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. J Nutr 2001;**131**:1217–24.
10 Torrens C, Brawley L, Anthony FW et al. Folate supplementation during pregnancy improves offspring cardiovascular dysfunction induced by protein restriction. Hypertension 2006;**47**:982–7.
11 Bateson P. Fetal experience and good adult design. Int J Epidemiol 2001;**30**:928–34.
12 Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004;**305**:1733–6.
13 Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol 2005;**20**:527–33.
14 Lee TM, Zucker I. Vole infant development is influenced perinatally by maternal photoperiodic history. Am J Physiol 1988;**255**:R831–8.
15 Norman JF, LeVeen RF. Maternal atherogenic diet in swine is protective against early atherosclerosis development in offspring consuming an atherogenic diet postnatally. Atherosclerosis 2001;**157**:41–7.
16 Khan I, Dekou V, Hanson M, Poston L, Taylor P. Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. Circulation 2004;**110**:1097–102.
17 Benyshek DC, Johnston CS, Martin JF. Postnatal diet determines insulin resistance in fetally malnourished, low birth

weight rats (F1) but diet does not modify the insulin resistance of their offspring (F2). Life Sci 2004;**74**:3033–41.
18 Cleal JK, Poore KR, Boullin JP et al. Mismatched pre-and postnatal nutrition leads to cardiovascular dysfunction and altered renal function in adulthood. Proc Natl Acad Sci USA 2007;**104**:9529–33.
19 Rickard IJ, Lummaa V. The predictive adaptive response and metabolic syndrome: challenges for the hypothesis. Trends Endocrinol Metab 2007;**18**:94–9.
20 Jasienska G, Thune I, Ellison PT. Fatness at birth predicts adult susceptibility to ovarian suppression: an empirical test of the Predictive Adaptive Response hypothesis. Proc Natl Acad Sci USA 2006;**103**:12759–62.
21 Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. Am J Physiol Endocrinol Metab 2000;**279**:E83–7.
22 Vickers MH, Breier BH, McCarthy D, Gluckman PD. Sedentary behavior during postnatal life is determined by the prenatal environment and exacerbated by postnatal hypercaloric nutrition. Am J Physiol Regul Integr Comp Physiol 2003;**285**:R271–3.
23 Gluckman PD, Hanson MA. Mismatch – Why Our World no Longer Fits Our Bodies. Oxford University Press, Oxford, UK, 2006.
24 Singhal A, Lanigan J. Breastfeeding, early growth and later obesity. Obes Rev 2007;**8**:51–4.
25 Stettler N, Stallings VA, Troxel AB et al. Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula. Circulation 2005;**111**:1897–903.
26 Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr 2005;**135**:1382–6.
27 Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. Br J Nutr 2007;**12**:1–10
28 Beedle AS, Gluckman PD, Hanson MA. Non-genomic but transgenerational inheritance of disease risk. BioEssays 2007;**29**:145–54.
29 Torrens C, Brawley L, Barker AC, Itoh S, Poston L, Hanson MA. Maternal protein restriction in the rat impairs resistance artery but not conduit artery function in pregnant offspring. J Physiol 2003;**547**:77–84.
30 Torrens C, Brawley L, Dance CS, Itoh S, Poston L, Hanson MA. First evidence for transgenerational vascular programming in the rat protein restriction model. J Physiol 2002;**543**:41–2.
31 Benyshek DC, Johnston CS, Martin JF. Glucose metabolism is altered in the adequately-nourished grand-offspring (F3 generation) of rats malnourished during gestation and perinatal life. Diabetologia 2006;**49**:1117–9.
32 Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2005;**288**:R34–8.
33 Zambrano E, Martinez-Samayoa PM, Bautista CJ et al. Sex differences in transgenerational alterations of growth and metabolism in progeny (F2) of female offspring (F1) of rats fed a low protein diet during pregnancy and lactation. J Physiol 2005;**566**:225–36.
34 Jablonka E, Oborny B, Molnar I, Kisdi E, Hofbauer J, Czaran T. The adaptive advantage of phenotype memory in changing environments. Phil Trans R Soc Lond B Biol Sci 1995;**350**:133–41.
35 Burdge GC, Slater-Jefferies J, Torrens C, Phillips ES, Hanson MA, Lillycrop KA. Dietary protein restriction of pregnant rats in the F0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F1 and F2 generations. Br J Nutr 2007;**97**:435–9.
36 Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 2005;**308**:1466–9.
37 Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F. RNA-mediated non-Mendelian inheritance of an epigenetic change in the mouse. Nature 2006;**441**:469–74.
38 Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Nat Acad Sci 2007;**104**:13056–61.
39 Gluckman PD, Lillycrop KA., Vickers MH et al. Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. Proc Natl Acad Sci USA 2007;**104**:12796–800.

