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What are the effects of maternal and pre-adult environments on ageing in humans, and are there lessons from animal models?

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Abstract

An open issue in research on ageing is the extent to which responses to the environment during development can influence variability in life span in animals, and the health profile of the elderly in human populations. Both affluence and adversity in human societies have profound impacts on survivorship curves, and some of this effect may be traceable to effects in utero or in infancy. The Barker Hypothesis that links caloric restriction in very early life to disruptions of glucose-insulin metabolism in later life has attracted much attention, as well as some controversy, in medical circles. It is only rarely considered by evolutionary biologists working on phenotypic plasticity, or by biogerontologists studying model organisms such as *C. elegans* or *Drosophila*. One crucial mechanism by which animals can respond in an adaptive manner to adverse conditions, for example in nutrition or infection, during development is phenotypic plasticity. Here we begin with a discussion of adaptive plasticity in animals before asking what such phenomena may reveal of relevance to rates of ageing in animals, and in humans. We survey the evidence for effects on adult ageing of environmental conditions during development across mammalian and invertebrate model organisms, and ask whether evolutionary conserved mechanisms might be involved. We conclude that the Barker Hypothesis is poorly supported and argue that more work in human populations should be integrated with multi-disciplinary studies of ageing-related phenomena in experimental populations of different model species that are subjected to nutritional challenges or infections during pre-adult development.

Keywords: Ageing; Phenotypic plasticity; Adaptation; Evolution; Model organisms; Barker hypothesis

1. Adaptive phenotypic plasticity in animals

Phenotypic plasticity refers to variation in the phenotype – for example, morphology, life history, behaviour, or metabolism – of a given genotype when individuals

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complete their development in different environments (Schlichting and Pigliucci, 1998). Some amount of plasticity across environments is an almost ubiquitous feature of phenotypic variation. In some such cases, variation in the phenotype may reflect a form of developmental constraint, an inability across environments to map phenotypes in a highly repeatable manner onto underlying genetic variation. Variability in the environment during growth may influence development in minor, largely unpredictable, ways to result in quantitative variation in the phenotype. Environmental challenges of a particular nature may lead to more predictable but still rather subtle effects on development. Much effort in animal studies has been directed at understanding the evolution of more discrete or alternative phenotypes, usually involving sets of traits or a syndrome, that are produced in response to alternative environments during pre-adult development. When such extreme examples of plasticity are adaptive, a physiological mechanism in response to an environmental cue perceived during ontogeny regulates alternative paths of development to the adult phenotype (Fig. 1A). The cue acts as a predictor for the environment in which a specific regime of natural selection is expected for the adults of a particular phenotypic class. In many cases, phenotypic plasticity has indeed evolved as such an adaptive response to recurrent patterns of environmental heterogeneity, either in time or space.

Phenotypic plasticity is of interest to evolutionary biologists as a potential means of adaptation to divergent environments whilst minimising any genetic load resulting from individuals that are mismatched to their environment. To developmental biologists, phenotypic plasticity provides attractive material to understand more about the control of development via physiological mechanisms that regulate gene expression during ontogeny (Brakefield et al., 2003). From a genetic perspective, whilst sensitivity to the environment during development at alleles of many genes may be involved, whether there are specific regulatory genes that determine plasticity and how they function is especially interesting. More complete descriptions of such 'genes for plasticity' may take us closer to understanding developmental switches via 'gatekeeping' systems such as that involved in regulating human puberty (e.g. Seminara et al., 2003). Genomics approaches will reveal not only how cascades of gene expression change following the initial response to the environmental cue and downstream of such controls of development, but also how they differ among the alternative adult phenotypes following development. The roles of epigenetic processes and of gene imprinting in the control of developmental plasticity remain unknown. Another issue of interest is the contrast between the diverse responses which characterise plasticity, and genetic canalisation, in which a single genotype yields similar phenotypes in different environments and where developmental properties tend to limit variation in the final phenotype. Integrating genetical studies of canalisation and plasticity should enable novel insights about the concept of developmental stability.

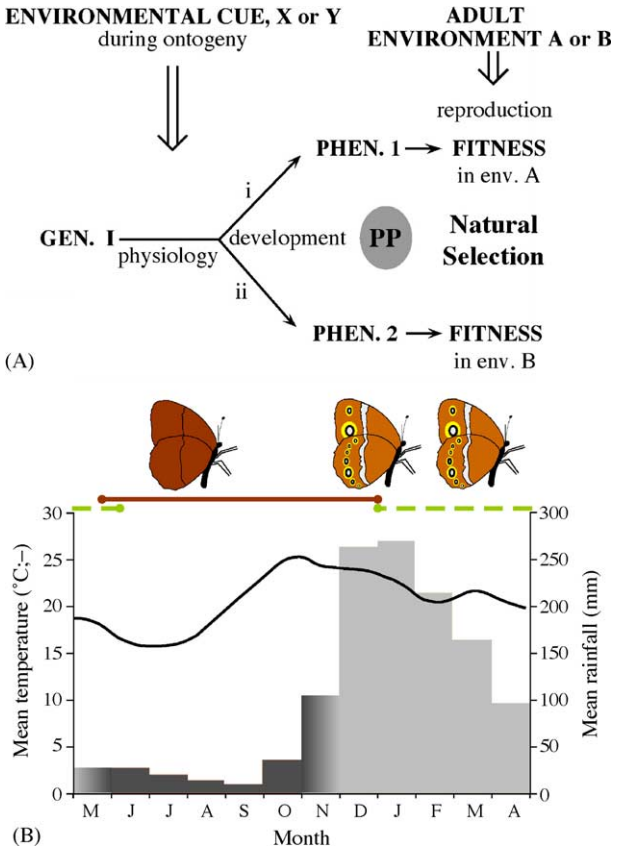

Fig. 1. (A) Scheme showing the basic components of phenotypic plasticity (PP) in which two alternative forms (adult phenotypes 1 and 2) can be produced by development from a single genotype (I). An environmental cue for the adult environment acts via physiological mechanisms to modulate the pathway of development (i or ii). If the phenotypic plasticity is adaptive then natural selection yields a higher relative fitness for each form in the environment (A or B) in which it spends most of its adult life. (B) An example of this mode of plasticity involving responses to wet-dry seasonal cycles in *Bicyclus* butterflies in East Africa. A dry season is followed by a wet season (dark and light grey, respectively). Two generations of the wet season form (WSF) with conspicuous eyespots occur in each rainy season. Larvae of both of these cohorts develop at high average temperatures. The second WSF generation reproduces before food plants die out, and the larvae develop at progressively declining temperatures. This cohort produces the generation of the dry season form (DSF) without eyespots that persists through the period of low rainfall (redrawn from Brakefield and Reitsma (1991)).

Adaptive developmental plasticity is exemplified in the seasonal forms of *Bicyclus* butterflies in parts of Africa where active adults of different generations fly in each of the alternating dry and wet seasons (Fig. 1B). The alternative seasonal forms are adapted to the particular seasonal environment in which they spend most of their adult life (Beldade and Brakefield, 2002; Lyytinen et al., 2004), and are produced in response to low or high temperature during larval growth. The differences in temperature lead to changes in timing of release of ecdysteroid hormones in early pupae, which in turn modulates known developmental pathways of wing pattern formation (Brakefield et al., 1996, 1998).