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The positive and negative consequences of stressors during early life

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ABSTRACT

We discuss the long-term effects of stress exposure in pre- and early postnal life. We present an evolutionary framework within which such effects can be viewed, and describe how the outcomes might vary with species life histories. We focus on stressors that induce increases in glucocorticoid hormones and discuss the advantages of an experimental approach. We describe a number of studies demonstrating how exposure to these hormones in early life can influence stress responsiveness and have substantial long-term, negative consequences for adult longevity. We also describe how early life exposure to mild levels of stressors can have beneficial effects on resilience to stress in later life, and discuss how the balance of costs and benefits is likely dependent on the nature of the adult environment.

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1. Introduction

Very few animals live in an environment that does not change in time and space. For most, day turns to night, seasons come and go, and habitats differ from one place to the next. Such changes are largely predictable. Animals are generally well adapted to deal with this kind of environmental variation, having evolved biological rhythms and movement patterns that maximise their success in passing on their genes to the next generation. Other kinds of environmental change are less predictable—the weather and food supplies fluctuate, predator and competitor numbers vary, and social pressures change. Facing unpredictable, and potentially dangerous, episodic change is more challenging. To deal with these threats, animals have evolved a suite of stress responses that can be turned on when the challenge appears, inducing changes in physiology and behaviour that maximise survival, and turned off again when the challenge has passed. In vertebrates, the main endocrine system that allows animals to cope with unpredictable change is the hypothalamic–pituitary–adrenal (HPA) axis. Perceived stressors activate the HPA axis, resulting in hormonal changes, largely involving the glucocorticoid hormones, which turn off currently non-essential activities and stimulate others. The animal enters a so-called 'emergency state' [1], in which activities such as growth, body maintenance, and reproduction are suspended, and energy is directed towards counteracting and surviving the imminent danger. This prioritisation is obviously adaptive, but if growth and body maintenance are suspended for long periods, this can be damaging over the long term, potentially increasing disease risk and the pace of degeneration in later life [2].

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Stress responses are therefore both a friend and foe, and the costs and benefits are balanced to give the best fitness outcome. The extent to which long-term costs matter in an evolutionary sense varies among species. Evolution through natural selection has shaped the life history traits of animals (age and size at maturity, patterns of growth, number of offspring, relative investment in self maintenance) to maximise their lifetime reproductive success. For some species, growing fast and then having a single major reproductive event followed by death gives the best fitness outcome, while for other species, the best strategy is growing slowly, living a long time and repeatedly producing small numbers of offspring. For the former life history strategy, costs that are incurred over the long term are less important to fitness than is the case for the latter strategy. We should therefore expect animals with different life histories to have evolved different coping strategies. Furthermore, the probability of encountering environmental stressors is likely to vary in both time and space since some periods and places are safer than others. Therefore, any information that the developing animals can obtain on the prevailing environmental circumstances they may live in will enable the phenotype to be adjusted to better prepare them to cope with what they are most likely to encounter. This information on their future environment may calibrate their stress responses in a manner that maximises Darwinian fitness benefits (i.e. lifetime reproductive output). Hence we expect some environmental shaping of the stress responses.

It is only relatively recently that developmental biologists have come to appreciate that the environment is not simply permissive of development but can also instruct it. As a result, a new discipline has emerged, termed ecological developmental biology, or Eco-Devo [3]. While genes set the potential range of phenotypes possible, we now know that the pattern of gene expression is influenced by environmental inputs and that these can span generations. A distinction is drawn in the Eco-Devo literature between direct and indirect environmental effects both of which can affect the developing animal. In the former case, the environment directly affects the developing individuals, and in the latter case, it is through environmental effects on the physiology or actions of the parent(s), most usually the mother. In species with high levels of pre- and postnatal parental care, developing offspring are buffered against some direct environmental effects; birds and mammals, for example, regulate the developmental temperature of their offspring within narrow limits. Other factors, however, do affect the developing offspring. The level of exposure to stressors in early life, in particular, when the architecture of the body is being determined, may be crucial in calibrating the developing animal's stress response system. These types of beneficial adjustments of phenotypic traits based on signals transmitted directly or indirectly to the developing animals have been termed 'predictive adaptive responses' (PARS) [4]. This relies on some environmental stability—that is the conditions experienced during development need to be predictive of subsequent conditions over an appropriate time frame. It is not clear whether the apparent pathologies associated with early stress exposure [5] are in fact a consequence of phenotypic adjustments that make the best of bad situation or represent stress levels outside of the evolved coping capabilities. An additional complexity is added in that, at least for some stressors, exposure to mild levels in early life gives rise to an enhanced resilience to stress that can be advantageous in later life. This positive effect of stress exposure is termed hormesis and is discussed further below in Section 4.

In this mini-review, we discuss stress exposure in both prenatal and early postnatal life within the evolutionary framework outlined above. We describe a number of relevant experiments that we have carried out on the consequences of early life stress exposure over differing time scales. The experiments that we describe have been carried out mainly in birds, for a number of reasons. Birds are endothermic vertebrates which, like mammals, maintain their developing embryos at an optimal temperature during development; *in ovo* in the bird, *in utero* in the mammal. Birds and mammals have a high level of parental care, and nutrients are supplied prenatally by the mother to the embryo via the egg yolk or the placenta. Like primates, birds are long-lived, iteroparous breeders, having relatively slow reproductive rates (e.g. compared with salmon or mice), slow senescence rates, and long lives. Importantly, however, that the avian embryo develops within a sealed system makes it possible to experimentally separate effects due to the pre- and postnatal environment and to separate direct and indirect environmental effects.

We do not provide a fully comprehensive review of the literature in this extensive, multidisciplinary field. Rather, we discuss a number of key issues that can be profitably viewed in an evolutionary framework. We focus on stressors that induce increases in glucocorticoid hormones, such as increased predation risk or social stress. In an experimental context, the increase in glucocorticoids can be stimulated by presenting the stressor itself or via direct hormonal manipulations. While early life stress exposure can have a large number of consequences, we emphasise here the effects on telomere dynamics during growth and development, which thereby have the potential to produce long-term effects on health and longevity. Telomeres are specialised areas of non-coding DNA and associated proteins that occur at the ends of the chromosomes. In vertebrates, the telomeres comprise tandem repeats of the nucleic acid sequence TTAGGG, and the very end of the telomere is folded back on itself to form a loop. Telomeres enable the cell machinery to recognise these looped chromosome ends and also protect the coding sequences from the loss during cell division. This loss occurs because, during DNA replication, the very end of the lagging DNA strand is not completely replicated. Additional telomeric sequence can be lost because of oxidative damage to the nucleotides, which interrupts replication; the high guanine content of telomeres appears to make them particularly vulnerable to oxidative damage. Once telomeres become critically short, their function is impaired and, under normal circumstances, cells cease dividing and either die or remain in an altered non-dividing state. Telomeres can be restored. In most animals, including vertebrates, this involves the enzyme telomerase, which is variably active in different tissue types. In many long-lived vertebrates, including humans and many long-lived birds, telomerase is downregulated in most somatic cells, thus limiting the cells' replicative potential. The resulting cell loss, and the accumulation of senescent cells, are thought to contribute to a decline in tissue and organ function with age. Following this, telomere length and loss have been shown to relate to survival [6,7], and several studies have found that early life telomere length is the best predictor of longevity. What determines early life telomere length, which has a significant heritable component and involves direct and indirect environmental effects, is difficult to disentangle. An increasing body of literature from both animal and human work is demonstrating that stress exposure in early life can increase telomere loss, and suggests that this is linked to glucocorticoid exposure [7,8]. Stress experienced by parents not only affects their own health but can also have long-lasting repercussions for their offspring. This can come about because the offspring experience the same adverse environment that is affecting their parents, or indirectly because of the environmental conditions that the parents provide, either pre- or postnatally. To better understand these connections, an experimental approach is critical, in which, for example, effects due to the individual's early and adult environment, or the parent and offspring environment, can be teased apart. Longitudinal studies that follow individuals across their life course are also important so that identifying long-term outcomes for individuals, and age-related changes, is not confounded by certain phenotypes being more or less likely to survive to old age. Such studies are very difficult to do in humans.

2. Prenatal effects

Several human and animal studies have established links between stressful conditions during embryonic and foetal development and disease risk later in life. The well-documented effects that appeared in children born during the Dutch 'Hunger winter' famine at the end of World