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REVIEW

Organismal stress, telomeres and life histories

Pat Monaghan*

ABSTRACT

Most organisms, including ourselves, are exposed to environmental stressors at various points during life, and responses to such stressors have been optimised by evolution to give the best fitness outcomes. It is expected that environmental change will substantially increase long-term stress exposure in many animal groups in the coming decades. A major challenge for biologists is to understand and predict how this will influence individuals, populations and ecosystems, and over what time scale such effects will occur. This requires a multi-disciplinary approach, combining studies of mechanisms with studies of fitness consequences for individuals and their descendants. In this review, I discuss the positive and negative fitness consequences of responses to stressful environments, particularly during early life, and with an emphasis on studies in birds. As many of the mechanisms underlying stress responses are highly conserved across the vertebrate groups, the findings from these studies have general applicability when interpreted in a life history context. One important route that has recently been identified whereby chronic stress exposure can affect health and longevity over long time frames is via effects on telomere dynamics. Much of this work has so far been done on humans, and is correlational in nature, but studies on other taxa, and experimental work, are increasing. I summarise the relevant aspects of vertebrate telomere biology and critically appraise our current knowledge with a view to pointing out important future research directions for our understanding of how stress exposure influences life histories.

KEY WORDS: Birds, Glucocorticoids, Longevity

Introduction

Most organisms are well adjusted for coping with predictable environmental change, such as changes in day length, seasonal changes in habitats or changes they encounter when traversing stable migration routes (Wingfield, 2013). Unpredictable change, which perturbs the homeostatic state of the individual, is generally more difficult to deal with. It is likely to be very costly for organisms to remain in a state of continual readiness to deal with events that might never, or only infrequently, occur. To cope with this, they have evolved 'on–off' systems of stress responses that enable them to respond rapidly and appropriately on encountering environmental stressors, returning to homeostasis within the shortest time possible.

In vertebrates, this response to stressful events, such as the sudden appearance of predators, rapid pursuit of prey, sudden inclement weather or food shortage, involves activating a suite of molecular, physiological and behavioural responses; these are highly conserved across the vertebrate groups (Wingfield, 2003; Boonstra, 2004). A key component of this system is the hypothalamic–pituitary–adrenal (HPA) axis, which controls the levels of stress hormones produced. Baseline levels of these hormones maintain homeostatic energy balance and regulate other aspects of normal physiological state (McEwen and Wingfield, 2003; Schultner et al., 2013). When confronted by a stressor, the activation of the HPA axis results in a sharp increase in the glucocorticoid stress hormones from baseline levels, occurring within minutes to hours (particularly corticosterone and/or cortisol, depending to some extent on life history stage and species). This mobilises energy reserves and switches the organism to an 'emergency state' in which its physiology and behaviour become geared to maximising its chances of surviving at the expense of other activities; glucocorticoid levels then return to baseline (Romero, 2004). While there will be costs associated with high energy expenditure and temporary suspension of growth, reproduction or body maintenance, the exposure to elevated glucocorticoids that characterises this acute stress response is usually short term. It provides an overall fitness benefit relative to what would have pertained without the stress response (Wingfield, 2008).

Exposure to repeated or protracted stressful circumstances, from which the organism is unable to escape, can induce a state of chronic stress. The assumption that animals do not suffer chronic stress or 'anxiety' was encapsulated in 1785 by Robert Burns in the closing lines of his poem 'To a mouse' (rendered here in an anglicised version – his italics), in which he envies the mouse its presumed lack of memory of past, or fear of future, events:

'Still thou are blessed compared with *me*!
The *present* only toucheth thee
But I *backward* cast my eye on prospects drear
And *forward* though I cannot see, I *guess* and fear.'

and supported more recently by Robert Sapolsky in his book *Why Zebras Don't Get Ulcers* (Sapolsky, 2004). However, while there is some debate over the occurrence of chronic stress in the wild (Boonstra, 2013b), there is evidence that it can occur as a consequence of predator or conspecific intimidation, high population density or prolonged food shortage (Clinchy et al., 2013; Schultner et al., 2013; Creel et al., 2013). This is an important issue, because it influences our understanding of the range of circumstances for which animals have evolved coping mechanisms that optimise fitness costs and benefits. Under chronic stress, the overall exposure to glucocorticoids, and other aspects of the stress response, is increased via protracted elevation of baseline levels, heightened acute responses and/or slower clearing of acute elevations (Sorensen et al., 2003; Boonstra, 2004; Romero, 2004). This gives rise to a number of changes, including cessation of growth and reproductive activities, and suppression of immune function (Wingfield, 2003; McEwen and Wingfield, 2003). Turning off these vital functions for a long period becomes very costly indeed, and results in muscle wasting, suppression of cell growth and tissue repair, increased cell death, greater susceptibility to infection and accelerated ageing (Sapolsky, 2000). There is evidence that some dampening of the HPA axis during chronic stress can occur, reducing these pathological effects (Cyr et al., 2007).

Institute of Biodiversity, Animal Health and Comparative Medicine, College of Medical, Veterinary and Life Sciences, Graham Kerr Building, University of Glasgow, Glasgow G12 8QQ, UK.

*Author for correspondence (pat.monaghan@glasgow.ac.uk)

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Exposure to protracted stressful circumstances might affect more than one generation (Nestler, 2012). Early exposure, *in ovo* or *in utero*, to elevated glucocorticoids of maternal origin is known to have long-term effects on the HPA axis in birds and mammals, most often heightening sensitivity to stressful events in later life and thereby increasing overall glucocorticoid exposure; such heightened sensitivity can also occur as a result of stress exposure in early post-natal life (Boonstra, 2004; Wingfield, 2003; Seckl, 2004; Spencer et al., 2009; Harris and Seckl, 2011). To understand why chronic or exaggerated stress responses occur, the long-term negative consequences induced by the responses need to be compared with the fitness consequences of facing stressful environments without elevating stress hormones, and not, as is often done, with animals in the absence of both the stressor and the hormone exposure. It is the balance of costs and benefits that matters, though we still understand relatively little about benefits. Furthermore, selection will favour early life benefits at the expense of late life costs. In evolutionary terms, being chronically stressed is still likely to be better than being dead. Furthermore, exposure to some degree of stress in early life could have some positive consequences, and might tailor or even improve the way organisms cope with later exposure to stressful events.

In this review, I first discuss positive and negative fitness consequences of environmental stress exposure, particularly during early life, with an emphasis on studies in birds. The aim of many of these studies is not to provide information for potential application to humans, but rather to understand how animals cope with stressful environments. Nonetheless, as many of the mechanisms are highly conserved across the vertebrate groups, the findings do have general applicability when interpreted in a life history context. However, it is important to emphasise that understanding the biology of stress matters not just in a biomedical context. It is expected that global climate change, anthropogenic disturbance, environmental degradation and pollution will substantially increase long-term stress exposure in many animal groups in the coming decades (Wingfield, 2008). A major challenge for biologists is in understanding and predicting how this will influence individuals, populations and ecosystems, and over what time scale such effects will occur. This requires a multi-disciplinary approach, combining studies of mechanisms with studies of fitness consequences for individuals and their descendants (Wingfield, 2008; Denver et al., 2009). One important route that has recently been identified whereby chronic stress exposure can affect health and longevity over long time frames is via effects on telomere dynamics (Beery et al., 2012). Much of this work has so far been carried out on humans, and is correlational in nature, but an important link that is ‘too toxic to ignore’ (Blackburn and Epel, 2012) is emerging. I therefore summarise the relevant aspects of vertebrate telomere biology and critically appraise our current knowledge with a view to pointing out important future research directions for our understanding of how stress exposure influences life histories.

Stress exposure and fitness

There is a large body of literature on what has been termed the ‘ecology’ of stress (Boonstra, 2013a). The HPA axis is recognised as a major route through which the physiological and behavioural responses of vertebrates to environmental challenges are orchestrated in an effective and adaptive manner. The concept of animals entering an ‘emergency life history stage’ when faced with stressful circumstances has been particularly useful and influential (Wingfield, 2013), as have the concepts of allostasis and allostatic load, though there has been some criticism of how these concepts have been interpreted (McEwen and Wingfield, 2003; Romero et al., 2009). In simple terms, allostasis can be viewed as the processes that support a return to homeostasis, such as secretion of appropriate levels of hormones of the HPA system, catecholamines and cytokines, and their resulting consequences. Allostatic load is the extent to which these processes have to be activated, and so in very stressful circumstances, the allostatic load will be high. The basic pattern is that a sudden temporary stressor turns on the coping mechanisms, which are turned off again when the stressful event is over and homeostasis restored. The longer the stress lasts, however, or the higher the allostatic load, the more long-term damage is likely to occur.

It is clear from studies across many taxa that stress exposure early in life has fundamental effects on the phenotype (Cottrell and Seckl, 2009; Harris and Seckl, 2011), and, depending on the magnitude of the stressor, these phenotypic changes can have positive and negative consequences over varying time scales. Glucocorticoid stress hormones, which can alter gene expression, play a vital role in development, being particularly important for normal brain and lung function; excess levels do, however, have a suite of adverse effects (Harris and Seckl, 2011). As mentioned in the Introduction, one important consequence of exposure to relatively high levels of stress hormones both pre-natally and post-natally is that this can permanently modify the sensitivity of the HPA axis itself. For example, experimental exposure of chicken embryos to experimentally increased corticosterone, the primary stress hormone in birds, is associated with a slower decline in circulating levels during the recovery phase (Fig. 1). Such *in ovo* exposure represents a maternal (i.e. inter-generational) effect. The extent to which the deposition of these hormones in eggs is adaptive is unclear; females may simply be unable to avoid passing their own elevated stress hormones to their offspring. Alternatively, they may strategically deposit hormones in eggs in order to shape offspring phenotypes in an adaptive manner, preparing their offspring to be better able to cope with the adverse environmental circumstance that they are also likely to encounter. This only works of course if there is a good correlation between maternal and offspring environments. Maintaining the acute stress response for longer could be adaptive

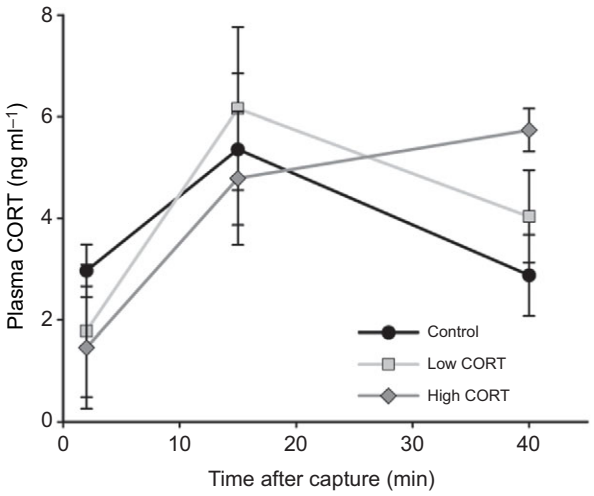

Fig. 1. The effect of experimental manipulation of corticosterone levels (within the natural range) in chicken eggs on the acute stress response of the resulting chicks. Data are shown for the control group, a group given a relatively small *in ovo* elevation of corticosterone (Low) and a group given a relatively high *in ovo* elevation of corticosterone (High). The figure shows the time course of plasma corticosterone (CORT) levels in response to an acute handling stress. Adapted from Haussmann et al. (Haussmann et al., 2012).

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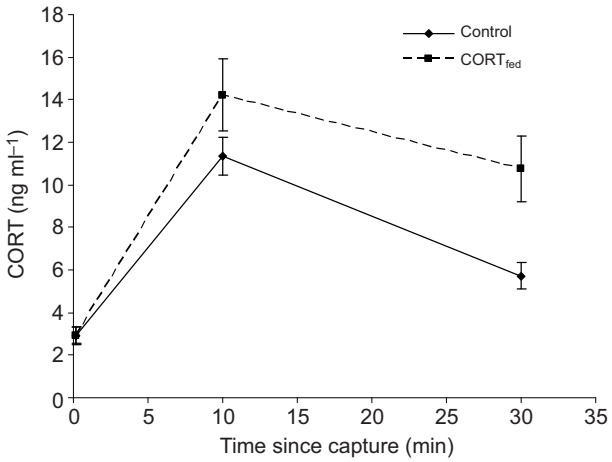

Fig. 2. Changes in plasma concentrations of corticosterone during handling stress in 3 month old zebra finches whose early life corticosterone levels had been manipulated for a short period during post-natal growth. The group that had been exposed to higher levels of corticosterone in early life (dashed line) showed a significantly heightened response to the same stressor. Adapted from Spencer et al. (Spencer et al., 2009).

in environments where stressful events are more frequent, but we do not know whether this is so. Similar long-term increases in HPA sensitivity have been found with early post-natal exposure to increased levels of glucocorticoids in zebra finches *Taeniopygia guttata* (Fig. 2). In this study, the glucocorticoid levels of young chicks were increased by direct manipulation of hormone levels over a 16 day period between days 12 and 28 post-hatching. When tested again at 3 months of age, corticosterone levels in an acute stress response increased at a faster rate and to a higher peak in the manipulated group, and took longer to recover. In this case, the long-term effect on the phenotype came about through a direct effect of stressful environments on the chicks, rather than via effects of stressful environments on their mothers. Such effects could come about through routes such as early life 'programming' of the glucocorticoid and endocannabinoid systems in the brain [see Senst and Bains in this issue for details of this system (Senst and Bains, 2014)]. However, in other studies, for example in chickens, early life stress resulted in a dampening of the stress response (Goerlich et al., 2012), which has also been found in some other bird species and in rodents (Marasco et al., 2012). In rodents and primates, pre-natal stress exposure can elevate baseline glucocorticoid levels, though in humans the opposite may occur (Harris and Seckl, 2011). A number of different factors might be at play here such as the extent to which domestication has selected for reduced stress sensitivity, the time scale over which the effects are measured, the stage at which the manipulation is carried out, the degree of precociality at birth or hatching and aspects of the experimental protocol [see Marasco (Marasco et al., 2012) for a discussion of these factors]. More studies are needed in order to identify whether there are any ecological or life history factors that are predictive of the effect of early stress exposure on later stress responsiveness, and whether the pre- and post-natal effects differ or interact (Marasco et al., 2012). We also need more studies that investigate the potential benefits in different environmental circumstances.

The negative consequences of early life stress exposure have been investigated in most detail. It is clear that the long-term consequences of increased early stress exposure can be severe, and include impaired learning ability and poor health in later life (Harris

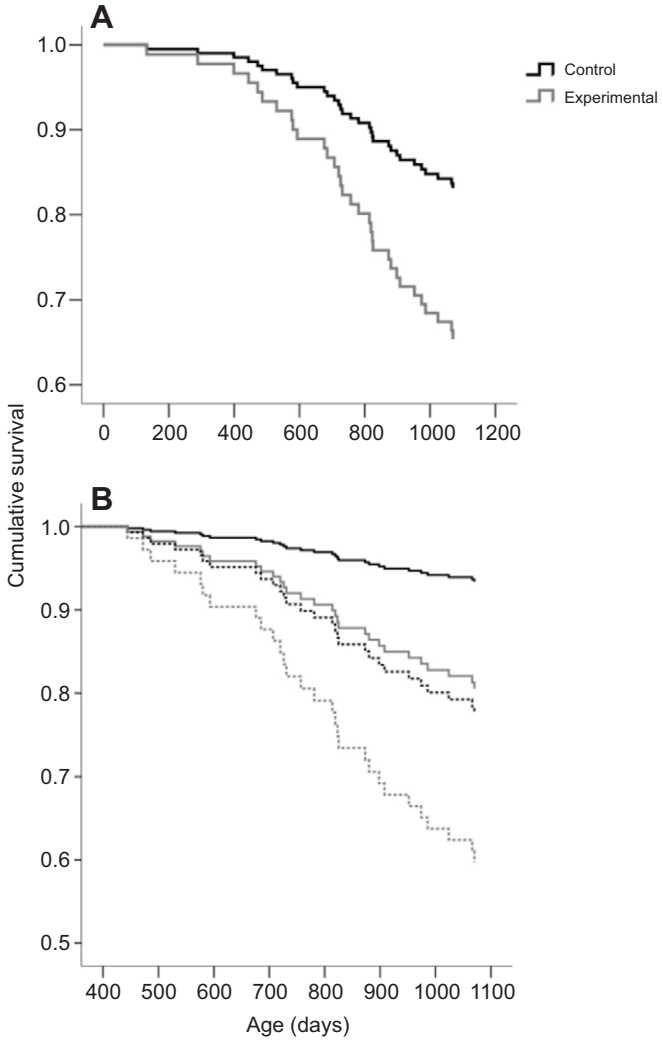

Fig. 3. The effect of early life exposure of individuals and their breeding partners on longevity. (A) Survival up to 3 years of age for zebra finches that were experimentally exposed to elevated corticosterone levels for a 16 day period during early life (grey line) in comparison with the control group (black line). There was no difference in survival of the birds as juveniles or young adults, but the decrease in survival with age was significantly different between the groups. (B) The survival of these birds in relation to their own early life treatment and that of their breeding partner. The survival of control birds is shown in black, with the solid line being that of control birds mated with control birds, and the dotted line (third line down) being control birds mated with birds that had received the elevated corticosterone in early life. The survival of the treated birds is shown in grey, with the solid line representing those whose mate was a control bird, and the dotted line (bottom line) representing early stress birds mated with early stress birds. Being mated with an early stress bird significantly accelerated age-related mortality. There was again no significant difference between the sexes. Adapted from Monaghan et al. (Monaghan et al., 2012).

and Seckl, 2011). In the case of the zebra finches in the above experiment, those birds experimentally exposed to higher corticosterone levels as chicks had increased rates of senescence and much-reduced lifespans (Fig. 3A). Surprisingly, this reduced longevity was also transmitted to their breeding partners (Monaghan et al., 2012). Control birds that were paired with a stress-exposed partner also had reduced longevity, and where both members of the pair had experienced elevated stress hormones early in life, the mortality rate of both was substantially higher; only 5% of control birds that were mated to a control bird had died after 3 years,

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whereas over 40% of early stress treatment birds mated to an early stress bird had died over the same period (Fig. 3B). Furthermore, the negative effect of the partner's treatment persisted even after the pair members were no longer together. A notable feature of this experiment is that the birds did not choose their own mates; mates were allocated by the experimenter. It would be interesting to know whether the outcome would have been different had the birds been allowed to choose their own mates. Research on the effect of stress in early life suggests that mate choice can influence mating success; the song of male zebra finches that have been exposed to elevated corticosterone in early life is less attractive to females (Spencer et al., 2005). It is therefore possible that their low attractiveness is not simply due to the potential poor performance of these males in rearing young but also because of direct effects they can have on partner health. The study on the effect of early stress exposure on longevity in zebra finches (Monaghan et al., 2012) also shows that it is not only early life stress exposure that matters; conditions during adulthood, in this case the state of close conspecific associates, can also take their toll.

How do such long-term effects come about? Vertebrate stress responses and ageing are closely inter-linked. Chronic stress is associated with increased exposure to oxidative and other damage and appears to accelerate the ageing process (Pardon and Rattray, 2008). In the case of the zebra finches in Fig. 3, there were no survival differences evident amongst the groups until after the first year of life; both survival prospects and the rate of ageing were then affected. In investigating the effect of stressful environments on longevity, it is important to take more account of the fact that higher mortality rates do not necessarily mean accelerated senescence (Monaghan et al., 2008). Variation in average age at death amongst populations, species or experimental treatment groups can arise as a consequence of differences in susceptibility to non-age-related mortality factors such as predation or disease, or intrinsic changes that alter overall vulnerability (sometimes called 'frailty'). It is possible that changes in cognitive abilities and decision-making capabilities could reduce survival prospects. Exposure to chronic stress might therefore elevate the risk of death at all ages. In other words, the trend line of mortality rate against age might be shifted in its elevation rather than its slope. This kind of effect has been found in *Drosophila*: flies subjected to dietary restriction exhibit an immediate drop in the risk of death, but the age-related increase in mortality rate still proceeds at the same pace (Hulbert et al., 2004). In contrast to the intense research effort devoted to studies of senescence, such non-age-related effects have received relatively little investigation outside of a medical context (Monaghan et al., 2008; Inness and Metcalfe, 2008).

The above studies raise many questions. Why are some animals particularly susceptible to long-term adverse consequences of early stress exposure, and does the stage at which the exposure occurs affect the outcome? A key question from an evolutionary perspective is, if increased sensitivity arising from early stress exposure is associated with long-term costs, why does it occur? As mentioned above, appropriate studies of the potential benefits are very limited, and the effect of different adult environments has been little studied. The degree of stress exposure is also likely to be important. Exposure to mild stressors can have beneficial effects through what is termed hormesis (Costantini et al., 2010). This is a situation where low levels of exposure to a particular stressor produce a beneficial effect, even though at higher levels the effects are detrimental. This is well known in the toxicological literature, and is illustrated in Fig. 4A. A particularly interesting hormetic effect is where early life exposure to a stressor appears to 'prime' the system such that individuals exposed to higher levels of the same stressor later in life are better able to cope (Fig. 4B). This 'priming' effect has been demonstrated experimentally in the zebra finch (Costantini et al., 2012). Juvenile zebra finches exposed to a mild heat stress were, in comparison with control birds that had no pre-exposure, better able to cope with a higher heat stress in adult life, as indicated by the level of oxidative stress that they experienced (Fig. 5). This potentially beneficial effect of early stress exposure, which is similar conceptually to what has been widely reported in the immune system, has been little studied. Why should such priming be necessary? It is possible that this is associated with the costs of being able to mount an effective response, which are not worth incurring unless the environment is one where the stressor is likely to be experienced. In principle, hormetic effects could also apply inter-generationally, where exposure to maternal stress hormones results in a more effective response in offspring.

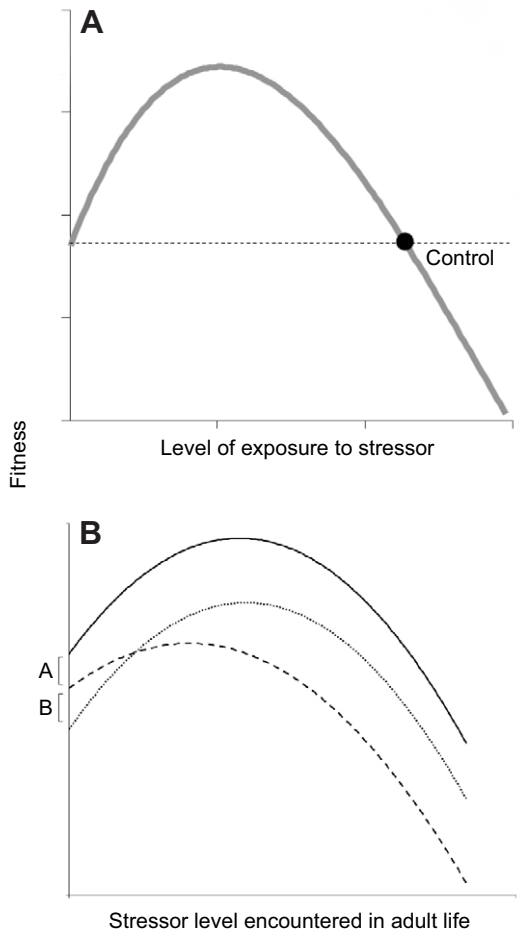

Fig. 4. The operation of hormetic effects. (A) The dose-dependent response to a stressor that is characteristic of hormesis; exposure to low levels of a stressor increases fitness, but higher levels have detrimental effects. (B) This illustrates how exposure to low levels of a stressor can improve the ability to cope with higher levels of exposure to the same stressor in later life. This early life 'priming' of the response could increase fitness at all levels of subsequent exposure by fitness amount A (solid, thick line) or the early exposure may carry a cost (fitness amount B) that is evident only if there is no further exposure to the stressor (dotted line; note that the difference in the fitness levels of the two lines is only to avoid them being superimposed. Also shown (dashed line) is the hormetic relationship between exposure to different doses of the stressor in individuals that have not experienced any exposure to low levels in early life. Adapted from Costantini et al. (Costantini et al. 2010).

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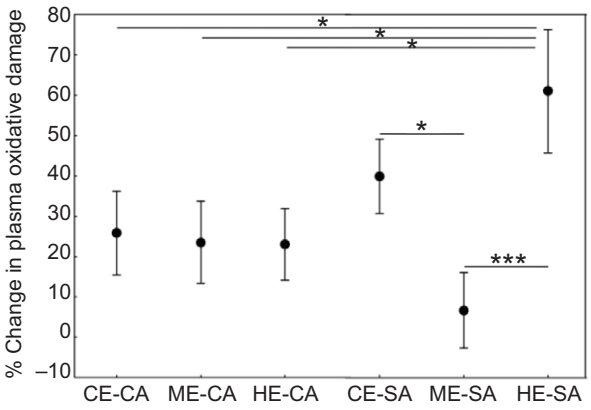

Fig. 5. Level of oxidative stress experienced by zebra finches when exposed to brief periods of heat stress in adulthood. Those birds that had experienced mild heat stress in early life (ME-SA group) showed the smallest change in average oxidative damage levels (mean ± s.e.m.), which were significantly higher in the birds that had no early life exposure (CE-SA group) or experienced a higher level of heat stress in early life (HE-SA group). There were no differences in oxidative damage levels amongst the groups in the absence of heat stress in adulthood (CE-CA, ME-CA and HE-CA groups). *P≤0.05 and ***P≤0.001. Adapted from Costantini et al. (Costantini et al., 2012).

There are obvious links and similarities between hormesis and early life programming, and also with the well-recognised type of beneficial phenotypic adjustment, acclimation (Woods and Harrison, 2002). Early life programming could be considered as a type of hormesis, with the phenotype being adjusted as a consequence of mild exposure to stress in early life. The benefits are presumed to be most evident where there is matching between early life and adult environments, and more experimental testing of this is needed (Monaghan, 2008). Acclimation is a direct effect of current conditions; it tends to be studied in adult animals, is relatively rapid and more reversible. Early life phenotypic adjustments might be more permanent as a consequence of critical windows in development. To what extent the underlying mechanisms involved in these processes are similar is currently unclear, but there is considerable potential for important experimental work manipulating the timing and degree of the stressor, and the adult environment.

Telomeres and longevity

An important route whereby stress exposure could have negative effects on health much later in life, and affect longevity, is through acceleration of telomere loss. Telomeres are repetitive, non-coding sequences of DNA that occur at the ends of the linear chromosomes of eukaryotes. In 2009, Elizabeth Blackburn, Carol Greider and Jack Szostak were awarded the Nobel Prize in ‘Physiology or Medicine’ for discovering the fundamental processes whereby telomeres and the enzyme telomerase maintain genome integrity. Telomeres allow the DNA repair machinery to distinguish true chromosome ends from double-stranded breaks, so that intact chromosomes do not get joined together by mistake. Also, the DNA replication process is such that the very end part of one of the strands is not completely replicated, and, as a consequence of this ‘end replication problem’, loss of important coding sequences during cell division needs to be prevented. In a very wide range of taxa, both these negative effects on the genome are prevented by telomeres, which mark chromosome ends and protect them from degradation. The telomeric DNA sequence is generally rich in guanine, and is a repeat of usually six bases. The sequence is TTAGGG in all vertebrates (Bodnar, 2009) and is similar in other eukaryotes (Gomes et al., 2011). The consistency in their structure across eukaryotes suggests that telomeres are an ancient, highly conserved and effective system of genome protection (Epel et al., 2006; Gomes et al., 2011). Telomeric DNA usually ends in a single-stranded ‘overhang’ of the TTAGGG sequence that folds back on itself to form a structure referred to as the ‘T-loop’. A minimum number of repeats is necessary for proper folding to occur. In addition to protecting the chromosome ends, telomeres also appear to be involved in regulating chromosome segregation during both mitosis and meiosis (Aubert and Lansdorp, 2008; Keefe, 2007).

Most of what we know about telomeres is from the biomedical literature and based on *in vitro* studies of human or model organism cells from the perspective of improving our understanding of how telomere dysfunction causes disease. Telomeres generally get shorter each time a cell divides. In the absence of restoration, a critical length is eventually reached at which telomeres become dysfunctional. At this point most cells cease to divide, and either die or remain but with an altered secretory profile (Baird, 2008a). The magnitude of telomere loss with each round of cell division is greater than would be expected to occur simply as a consequence of the end replication problem (Takai et al., 2003; Lansdorp, 2005). Because telomeric DNA is much more susceptible to oxidative damage than non-telomeric DNA, at least partly due to the high guanine content and reduced repair capacity in the telomeric regions (Gomes et al., 2010), redox balance in the cell is thought to be an important factor influencing telomere loss rate (Passos et al., 2007; Houben et al., 2008). A relatively high proportion of oxidative damage occurs in the telomeric DNA, demonstrated *in vivo* and *in vitro*, which will increase shortening rates (Shalev, 2012). While most studies of the effects of oxidative damage on telomere loss are *in vitro* (Richter and von Zglinicki, 2007), correlative and experimental studies are beginning to demonstrate these effects *in vivo* (Houben et al., 2008; Cattan et al., 2008).

A number of telomere restoration mechanisms are known to occur (Capkova Frydrychova et al., 2008; Cenci, 2009), the most studied and widespread being the action of the enzyme telomerase, which can replace telomeric DNA. Telomerase levels are typically higher in cells where more proliferative potential is needed, for example in vertebrate embryonic and adult stem cells, the male germ line, activated lymphocytes, basal cells of the epidermis, proliferative endometrium and intestinal crypt cells (Gomes et al., 2011). Telomerase activity is relatively low in mammalian mature oocytes and early cleavage embryos; it increases from the blastoderm stage but is then down-regulated in most somatic cells when embryonic development is complete (Liu et al., 2007). While much less is known about other vertebrate taxa, the pattern of telomerase activity in the embryos of birds and mammals seems to be similar (Taylor and Delany, 2000), with a down-regulation in most somatic cells. There is evidence that inter-specific variation in somatic telomerase activity might vary with lifespan in birds (Haussmann et al., 2007) and body mass in mammals (Seluanov et al., 2007); however, there are currently insufficient data for comprehensive comparative analyses.

An important and interesting question, for which a comparative approach is important, is why are telomeres not always restored if the consequences of their attrition are so severe? The main cost associated with telomere restoration is increased risk of tumour formation. This is particularly important in long-lived species where the number of cell divisions needed to accumulate the mutations required for a cell to become malignant is sufficient (Rodriguez-

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Brenes et al., 2013). Amongst the higher vertebrates, short-lived species often have long telomeres and somatic telomere restoration, while long-lived species have shorter telomeres and little somatic restoration. This supports the hypothesis that tumour protection is important. However, this is clearly not the whole story as many long-lived ectotherms have high telomerase activity in somatic tissues (Gomes et al., 2010).

Studies of the inheritance of telomere length are also very limited, based largely on parent–child correlations in humans from measurement of white blood cell telomeres. Findings from the human studies are inconsistent and estimates of heritability vary widely, partly as a consequence of variable sample sizes, differences in the ages at which parent and child telomere length are measured, and the difficulty in accounting for maternal effects and shared environments in the analyses (Gilley et al., 2008). The most reliable data produce heritability estimates in the region of 45%, which clearly indicates a considerable non-genetic component to the inheritance pattern (Baird et al., 2006; Huda et al., 2007; Baird, 2008b; Fraga, 2009). While significant maternal– and paternal–child telomere length correlations have been reported in humans, some (but not all) studies also found an effect of parent age on offspring telomere length; there is also some evidence in humans of a stronger correlation between father and child than between mother and child (Nordfjäll et al., 2010). However, a highly significant mother–offspring correlation was found when telomere lengths in mother and child were measured at the time of parturition (Akkad et al., 2006). Much may depend on what happens during early embryonic life when telomere length is reset. In birds, studies are very limited, but the correlation seems to be stronger between mothers and offspring (Horn et al., 2011). We clearly need much more investigation of the inheritance of telomere length based on a pedigree that enables partitioning of the different sources of variation, and the similarity between parents and offspring at different life stages to be evaluated.

There are a large number of studies, mainly in humans, suggesting that the consequences of relatively short telomere length are severe (Aubert and Lansdorp, 2008; Kappei and Londoño-Vallejo, 2008). Short telomeres have been linked to a wide variety of inherited diseases, often, in the case of premature ageing syndromes, relating to genetic defects in telomerase function. More common age-related diseases, such as cancer and cardiovascular disease, have also been linked to shortened telomere length (Aubert and Lansdorp, 2008). Telomere length itself may be directly involved in organismal ageing by effecting a decline in the number of functional cells with age; telomere loss rate may also be indicative of more widespread levels of oxidative damage. Even within stem cells, of great importance in tissue maintenance and repair in adult multicellular organisms, telomere loss occurs and seems to coincide with the loss of stem cell function (Lansdorp, 2008; Rossi et al., 2008; Fraga, 2009). A declining capacity to produce enough differentiated cells to maintain tissue function is likely to be an important contributor to ageing (Rossi et al., 2008; Flores et al., 2008). Several studies have found that women have longer telomere lengths in white blood cells than men of the same age, which concurs with their longer lifespan (Kimura et al., 2008). Studies of the relationships between telomere length and survival in humans have produced mixed results, with some studies finding the expected relationship between short telomere length and reduced life expectancy and others not. One problem with these human studies is that they usually involve people who are already old at the time of sampling [usually over 70 years and in some cases over 90 years (Cawthon et al., 2003; Njajou et al., 2009; Cawthon, 2009)] and are therefore likely to be a biased subset of the population. However, in a within-pair analysis of Swedish twins, with a greater than normal age range in such studies (63–95 years), the twin with the shorter telomere length was found to have three times the risk of death (Bakaysa et al., 2007). There have been very few studies examining the relationship between survival prospects and telomere dynamics in non-human populations. Red blood cell telomere lengths have been linked to subsequent survival in wild birds, with those individuals having the shortest telomere length and/or highest loss rate having the lowest survival prospects (Haussmann et al., 2005; Pauliny et al., 2006; Bize et al., 2009; Salomons et al., 2009; Barrett et al., 2013). Recent research on zebra finches has shown that early life telomere length is the best predictor of longevity (Heidinger et al., 2012), with long-lived individuals having relatively long telomeres at all measurement points (Fig. 6). An important question therefore is: what environmental factors influence early life telomere length, and,

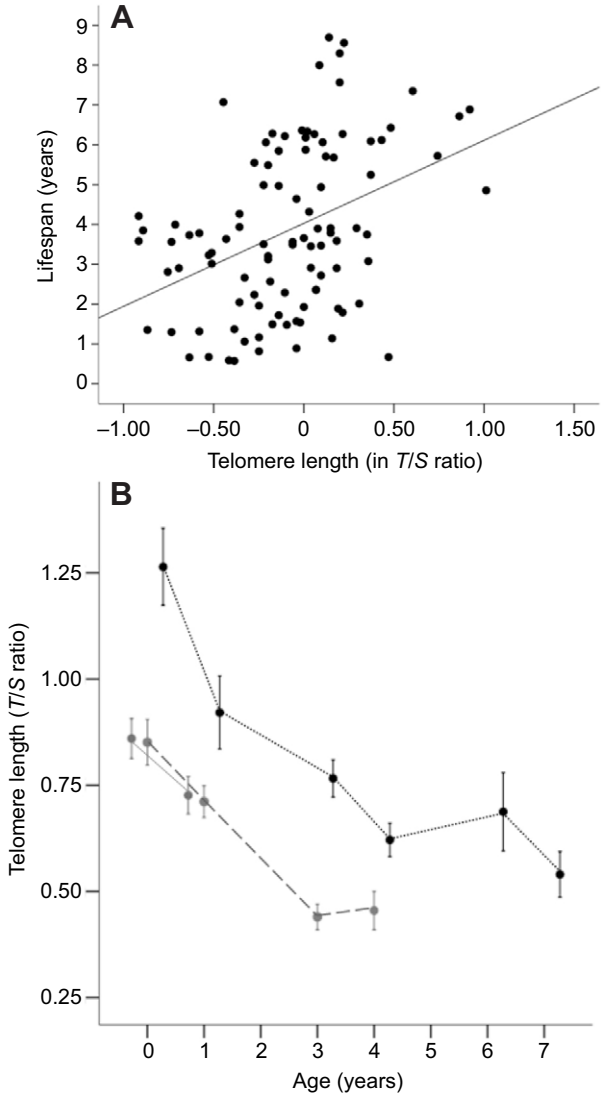

Fig. 6. Telomere length and lifespan relationships in a longitudinal study of zebra finches. (A) The relationship between telomere length at 25 days (log-transformed relative telomere length: *T*/*S* ratio from q-PCR) and subsequent lifespan in zebra finches. (B) The average telomere length of the birds with the shortest (solid grey line), middle (dashed grey line) and longest (dotted black line) lifespans at all the measurement points; the data show that the long-lifespan birds had longer telomeres at all ages at which they were measured. Adapted from Heidinger et al. (Heidinger et al., 2012).

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in the context of this review, does early life stress exposure affect telomere dynamics?

Stressful environments and telomere loss

A number of environmental factors that are likely to produce chronic stress have been linked to shorter telomere lengths in adults (Epel et al., 2010; Haussmann and Marchetto, 2010), including experimentally induced changes in growth rate, infection status and social crowding in rodents (Jennings et al., 1999; Kotrschal et al., 2007; Tarry-Adkins et al., 2008; Tarry-Adkins et al., 2009; Ilmonen et al., 2008), which are associated with shorter telomere lengths in leucocytes; social crowding has also been found to be associated with shorter leucocyte telomere length in chickens (Sohn et al., 2012). How these effects occur remains unclear. They could be mediated by several aspects of the stress response, such as glucocorticoids, inflammatory responses and oxidative stress. Most investigated so far are the links to glucocorticoids and oxidative stress. A meta-analysis of studies where physiological stress has been induced experimentally through glucocorticoid elevation shows that this consistently produced an increase in oxidative stress (Costantini et al., 2011). *In vitro* cellular studies suggest that cortisol can accelerate telomere loss, so exposure to elevated glucocorticoids could be an important candidate mechanism influencing telomere loss *in vivo* (Choi et al., 2008). Research in women suggests that higher secretion of cortisol in response to environmental stress is associated with shorter leucocyte telomere length, but it is difficult to separate cause and effect here as the study was correlational rather than experimental (Tomiyama et al., 2012). There are a number of potentially confounding factors that are difficult to avoid in human studies as the investigators are not able to randomly allocate individuals to different degrees of stress exposure. The most likely route whereby stress affects telomere loss is via oxidative stress. Studies on penguins *Aptenodytes patagonicus* suggest that high oxidative stress in chicks that underwent catch-up growth was associated with reduced red blood cell telomere length (Geiger et al., 2012), while in dragon lizards *Ctenophorus pictus* high levels of anti-oxidant defences appear to play a role in preventing or slowing telomere loss (Ballen et al., 2012). In order to fully understand these relationships, and to tease apart causal and confounding factors, we need more carefully controlled experiments in which telomere loss is studied within individuals exposed to different levels of oxidative stress.

Much of the human work on the effects of chronic stress on telomere dynamics has been done with adults. Recent studies do, however, suggest that exposure to environmental stress *in utero* is also associated with shorter telomere length. New-born babies produced by women who suffered from environmentally induced stress in pregnancy had shorter telomere lengths (Entringer et al., 2013). While the authors of this study controlled statistically for other potentially confounding factors, it is possible that it is not the stress during pregnancy that causes the shorter telomere length, but rather that a particular maternal phenotype is more likely to produce babies with shorter telomeres, and to suffer stress in pregnancy; indeed, such mothers may also be more likely to have partners with short telomere length, which could be important if telomere length has a strong paternal inheritance. However, the importance of stress exposure during early development is further supported by experimental studies on chickens, in which *in ovo* corticosterone levels were manipulated in randomly allocated groups (Haussmann et al., 2012). This was associated with a higher proportion of short telomere lengths in red blood cells 25 days after hatching. In addition, the chicks from the corticosterone-treated eggs showed evidence of higher levels of oxidative stress (Haussmann et al., 2012). Experimental studies that we have underway in the European shag *Phalacrocorax aristotelis* suggest that exposure to stress during early post-natal growth also gives rise to shorter telomere lengths. Importantly, these bird studies also demonstrate that the effects of stress exposure are not confined to cells of the immune system.

Recent work, involving correlative studies in humans and experimental work in rats, suggests that exposure to stressful circumstances elevates telomerase in white blood cells, and that this increase can take place very rapidly. In human subjects, an 18% increase in telomerase was reported in leucocytes within 1 h of the end of the stress exposure, and was linked to the measured increase in cortisol (Epel et al., 2010). While this could help to mitigate the effects of stress on immune function, or indeed be part of an immune response to stress, it does not appear to be sufficient to prevent the stress-exposed groups from having shorter telomeres. Again, in these correlational studies, it is difficult to separate cause and effect. However, in a recent experimental study on rats (Beery et al., 2012), telomerase activity was found to be 54% higher in stressed rats (exposed to a range for randomised acute stressors; Fig. 7). The consequences of such telomerase elevation for longevity remain to be investigated. The extent to which changes in telomerase activity are involved in increased telomere loss outside of the immune system is unclear, and this effect might be less important in animals with low telomerase activity in most somatic cells.

Conclusions and future directions

Organisms have evolved a suite of stress responses that enable them to cope with adverse environmental conditions. These responses are not without costs, and their repeated or long-term activation can have negative effects on health and longevity. This does not mean, however, that even the effects of chronic stress are devoid of any fitness benefits; in fitness terms, organisms living in protracted stressful circumstances might be even worse off in the absence of the physiological state induced. Of course, non-adaptive effects may occur where the organism finds itself placed in situations that are outside of its evolved capacity to cope. As selection works on overall lifetime reproductive stress, and thus reduced lifespan may be compensated for by early onset of reproduction, this may be a price worth paying if breeding success is higher than it would have been without the phenotypic adjustments.

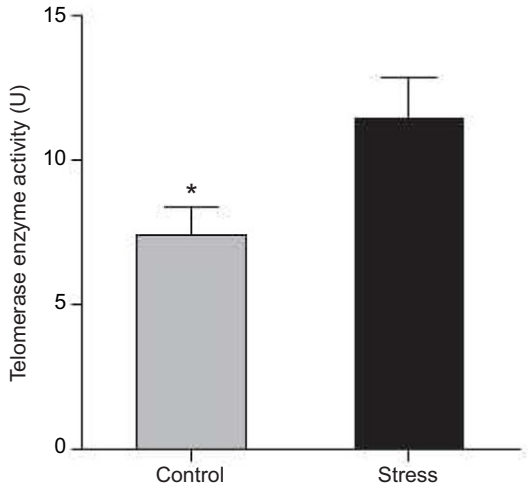

Fig. 7. Telomerase activity in leucocytes measured in rats in control and stressed treatment groups. Adapted from Beery et al. (Beery et al., 2012).

We need to understand much more about these costs and benefits associated with stress responses, and the time scales over which they operate. Early life exposure to stress appears to produce particularly long-term phenotypic changes, adjusting aspects of morphology, physiology and behaviour to suit the conditions that appear to prevail; important environmental factors involve changes in nutrition levels, predator exposure, temperature, social conditions and suchlike. We also need to know much more about the reversibility or not of such physiological changes, their adaptive significance, the level and duration of exposure required to induce them and how context specific their effects on fitness are. We also need to know the effect of varying levels of environmental stability on whether such early life effects occur and what their consequences are; it does not make sense to adjust the phenotype early in life to conditions that are unlikely to be experienced thereafter. Understanding the timing, nature and duration of critical periods in development or life history stages at which the consequences are more profound, and/or more permanent, and how these differ across taxa, is very important. Because there is considerable inter-individual variation in responses and in optimal outcomes, it is important that we have carefully designed experiments to address these questions; confounding variables need to be controlled if we are to effectively tease apart the factors involved and identify adaptive effects. It is important too that studies in the natural environment complement those in the laboratory, and that experiments take account of the relevance of particular stressors, and levels of exposure, to the species under study. Inter-generational effects, and the routes whereby these might be generated [see Saab and Mansuy in this issue (Saab and Mansuy, 2014)] are of great interest; here again, careful experimental design that separates direct and indirect environmental and genetic effects is extremely important. This is not a simple task, as when an organism is exposed to stress during embryonic development, its own germ line, and thereby its offspring, could be directly affected.

The consequences of stress exposure in adulthood, the reversibility of its effects and whether the nature of the consequences, and the fitness outcomes, differ from exposure in pre- or early post-natal life also need further study. How adult stress exposure levels interact with early life exposure and affect adult resilience is a topic that has recently come to the fore and, again, needs more experimental work. The study on the effect of the early life stress exposure on telomere loss in breeding partners described in this review emphasises that social as well as physical factors can be very important, though the routes through which these operate are likely to be complex.

Much work in the natural environment, and in captivity, has involved birds and the glucocorticoid stress responses. This needs to be broadened to encompass other stress responses. The links between telomeres, stress, oxidative balance and ageing are currently of considerable interest, but because much of the work to date has been done in humans, experimental studies are limited, reducing our capacity to distinguish cause from effect. Studies in mammals often involve telomere changes in cells of the immune system, as the red blood cells do not contain DNA; mammalian white blood cells often express telomerase, which appears to be up-regulated to some degree during stress. Studies of effects on cells other than immune cells are therefore also needed. In contrast, bird studies of telomere dynamics generally use red blood cells, and where effects in this branch of the haematopoietic system occur, they suggest that the effects of stress on telomere loss are more widespread and may involve progenitor cells.

Work of the type outlined in this review is very important if we are to understand the consequences of environmental change for individual life histories and for populations. More extreme perturbations and fluctuation in conditions are occurring, which are likely to decrease environmental similarity between life stages and generations, and thereby render non-adaptive the coping strategies that organisms have evolved to meet the challenge of environmental variation.

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