Integrative and Comparative Biology

Integrative and Comparative Biology, volume 58, number 4, pp. 814–825
doi:10.1093/icb/icy048

Society for Integrative and Comparative Biology

SYMPOSIUM

The Evolutionary Endocrinology of Circulating Glucocorticoids in Free-Living Vertebrates: Recent Advances and Future Directions across Scales of Study

Sarah Guindre-Parker[1]

Department of Integrative Biology, University of Guelph, Summerlee Science Complex, Guelph, Ontario, Canada N1G 2W1

From the symposium "Understanding the Evolution of Endocrine System Variation through Large-scale Comparative Analyses" presented at the annual meeting of the Society for Integrative and Comparative Biology, January 3–7, 2018 at San Francisco, California.

[1]E-mail: sguindre@uoguelph.ca; slg2154@columbia.edu

Synopsis Circulating glucocorticoid hormone concentrations are dynamic, flexible, and promote adaptive responses following perturbations in an animal's environment. As a result, circulating glucocorticoid levels are thought to shape fitness and have been suggested to be a key trait for predicting how species will cope with novel environmental change. Nevertheless, the factors that shape variation in glucocorticoid-mediated coping mechanisms remain unclear because the evolutionary underpinnings of the function and regulation of these hormones are poorly understood. Here, I summarize recent advances in our understanding of the evolution of circulating glucocorticoids, which have included (i) longitudinal studies exploring microevolutionary processes that shape within- and between-individual variation in glucocorticoids, (ii) interspecific comparative studies highlighting macro-evolutionary patterns of among-species variation in glucocorticoids, and (iii) intraspecific comparative studies which help to disentangle the relative roles of environment, life-history, and behavior in shaping among-population variation in glucocorticoids. Important avenues for future research will include exploring how natural selection may act on different components of the hypothalamus–pituitary–adrenal axis, characterizing patterns of phenotypic plasticity in circulating glucocorticoids across populations and species, as well as exploring how microevolutionary processes differ across taxa or gradients of environmental conditions.

Introduction

Glucocorticoid hormones circulate at dynamic and flexible concentrations (Taff and Vitousek 2016), promoting adaptive physiological, behavioral, or morphological responses following perturbations in an animal's environment (Wingfield and Kitaysky 2002). These hormones are thought to facilitate responses to both predictable and unpredictable changes in the environment (Romero et al. 2009), because glucocorticoids serve two distinct yet crucial functions as a result of having different affinities for two receptor types (Landys et al. 2006). Baseline glucocorticoid levels circulating at relatively lower concentrations regulate daily metabolic demand and homeostasis by binding to high-affinity mineralocorticoid receptors (Landys et al. 2006), while stress-induced glucocorticoid levels circulate at elevated concentrations and bind to low-affinity glucocorticoid receptors to coordinate responses to sudden intrinsic or extrinsic stressors by initiating an emergency life-history stage (Wingfield and Kitaysky 2002; McEwen and Wingfield 2003). Both baseline and stress-induced glucocorticoid concentrations can vary within an individual across various contexts (Romero et al. 2009): typically, an elevation within the range of baseline hormone levels represents an energetically demanding period (often resulting in increased foraging and the acquisition/deposition of fat reserves, though not always) (Dallman et al. 1993; Hennin et al. 2016), whereas an elevation to stress-induced titres results

Advance Access publication June 4, 2018

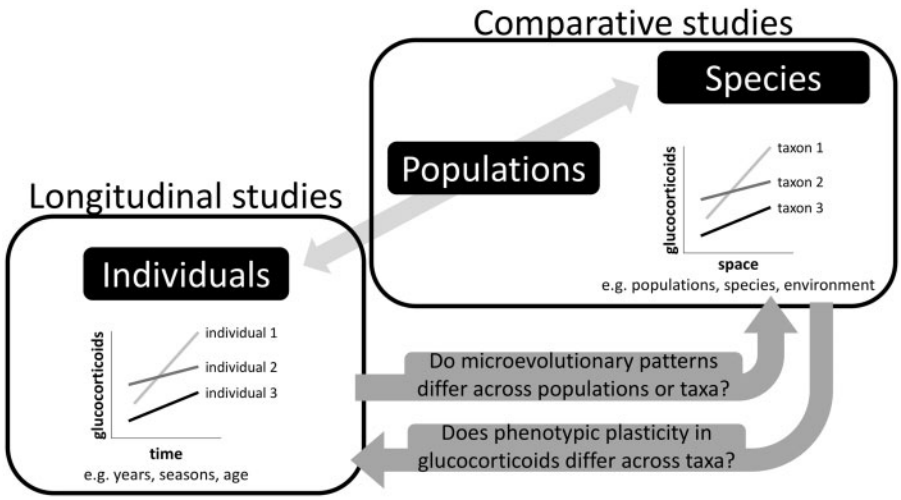

Fig. 1 Variation in circulating glucocorticoids can be studied within or across individuals, populations, or species. Longitudinal studies typically focus on the causes and consequences of individual variation in glucocorticoid concentrations through time, whereas comparative studies focus on variation in glucocorticoid concentrations across space. In order to bridge these scales of studies, researchers can examine (i) how microevolutionary patterns identified in longitudinal studies differ across space (i.e., populations, species, or environments) as well as (ii) how populations or species differ in phenotypic plasticity in glucocorticoid concentrations (i.e., through time).

in the rapid mobilization of lipid resources to promote survival in the face of a sudden stressor (e.g., storm, social challenge, predator encounter) (Sapolsky et al. 2000; Charmandari et al. 2005). As a result of these critical roles, glucocorticoid hormones have the potential to influence both reproduction and survival and have been suggested to be important mediators of fitness (Bonier et al. 2009a, 2009b).

In light of their ability to coordinate rapid phenotypic change across a variety of contexts (Wingfield and Kitaysky 2002; Taff and Vitousek 2016), glucocorticoids are thought to mediate phenotypic responses to both predictable and unpredictable changes in an animal's environment (Angelier and Wingfield 2013; Wingfield 2013). Despite evidence that glucocorticoid-mediated coping mechanisms have important consequences for how organisms respond in the face of novel environmental conditions (Lendvai et al. 2011; Crino et al. 2014), it remains unclear how variation in these coping mechanisms arises because we lack a clear understanding of the factors that shape within- and between-individual variation in circulating glucocorticoid concentrations across taxa (Angelier and Wingfield 2013). Key to understanding how variation in glucocorticoid-mediated coping mechanisms arise is understating the evolutionary underpinnings of these traits (i.e., whether glucocorticoid coping mechanisms are fixed or flexible; Taff and Vitousek 2016). Evolutionary endocrinology is a growing field that aims to describe how the secretion, regulation, or function of hormones like glucocorticoids have evolved (Zera et al. 2007; Cox et al. 2016a). Evolutionary endocrinology studies focused on circulating glucocorticoids and their function or regulation have relied on several approaches across a variety of temporal and spatial scales to understand variation in these hormones, ranging from longitudinal studies of individually-marked organisms to comparative studies across vertebrate taxa (Fig. 1). While recent reviews have discussed the evolution of circulating glucocorticoid concentrations (e.g., Cox et al. 2016b; Hau et al. 2016), I provide an original overview of how a diversity of research approaches across scales of study have improved our understanding of the evolutionary endocrinology of these hormones. Similarly, this review provides novel insight into how integrating across scales of study—including studying variation in glucocorticoids across temporal and spatial scales simultaneously—will be crucial to fill existing knowledge gaps.

Longitudinal studies

Longitudinal studies—monitoring individuals over their lifespan and across multiple generations (e.g., Gesquiere et al. 2011)—represent the most commonly used approach in evolutionary endocrinology studies of glucocorticoids and examine variation in circulating glucocorticoid concentrations through time (Fig. 1). These have advanced our understanding of how natural selection shapes the function of glucocorticoids in a number of ways, including through (i) measuring the heritability of circulating

levels of glucocorticoids, (ii) understanding the relationship between circulating glucocorticoids and fitness across a variety of contexts, and (iii) estimating the strength of natural selection on circulating concentrations of glucocorticoids and their downstream effects in free-living animals. Below, I summarize key advances in evolutionary endocrinology that stem from longitudinal research.

Heritability in circulating glucocorticoids

Understanding the heritability of a trait, particularly a phenotypically plastic one such as circulating concentrations of glucocorticoid hormones, represents an important advance in predicting whether hormones may respond to natural selection (Cox et al. 2016b). Narrow sense heritability represents the proportion of variance in a phenotype that is attributable to additive genetic effects and can be estimated in free-living populations in a number of ways, including (i) using correlational phenotypic data paired with a population pedigree to estimate the proportion of phenotypic variation that is explained by additive genetic variance (Bairos-Novak et al. 2018), (ii) using a cross-fostering manipulation to disentangle the effects of rearing environment from genetic effects on the offspring's phenotype (Jenkins et al. 2014), or (iii) as calculated based on the ratio of the response to selection in a phenotypic trait relative to the strength of selection in natural or experimental contexts (i.e., from the breeder's equation) (Cox et al. 2016b). Heritability estimates fall between 0 and 1, where a heritability of 0 indicates a lack of any additive genetic contribution to variance in a trait, whereas a score of 1 indicates that 100% of the variance in a trait is shaped by additive genetic effects. Although selection experiments in lab-reared populations have shown that glucocorticoids are heritable in birds, fish, and mammals (Pottinger and Carrick 1999; Bartels et al. 2003; Evans et al. 2006), few studies have estimated heritability in free-living vertebrates, likely since doing so in the field requires hormone data paired with long-term multi-generation pedigrees. Nevertheless, two recent studies in swallows showed that the heritability of baseline glucocorticoids was low though significant (0.13–0.15), and the heritability of stress-induced glucocorticoids heritability was higher than baseline (0.34–0.38). Similarly, stress-induced glucocorticoids in Richardson's ground squirrels (*Urocitellus richardsonii*) were estimated to be heritable (0.40–0.75; from mother–offspring or sibling–sibling phenotypic correlations). Additional work in barn owls (*Tyto alba*) has found indirect support for a heritable component in shaping glucocorticoids, though heritability was not estimated directly (Almasi et al. 2010). The heritability estimates of glucocorticoid stress-responses reported from these free-living populations are similar to those calculated from captive animals, including zebra finches (*Taeniopygia guttata*, $h^2 = 0.20$) (Evans et al. 2006), Japanese quails (*Coturnix japonica*, $h^2 = 0.20–0.30$) (Satterlee et al. 1988), rainbow trout (*Oncorhynchus mykiss*, $h^2 = 0.41$) (Pottinger and Carrick 1999), and commercial large white turkeys (*Meleagris gallopavo*, $h^2 = 0.13–0.24$) (Brown and Nestor 1973). Nevertheless, since heritability is specific to the population in which it was measured, it remains challenging to generalize findings from captive to free-living animals (or across different populations)—more research calculating these estimates across species and populations is necessary in order to draw conclusions on the heritability of circulating glucocorticoids in free-livings vertebrates. Estimating heritability in captive populations remains valuable for a number of reasons (e.g., genetic, maternal, and environmental effects can be better controlled and their relative importance better isolated compared with free-living animals) (Pelletier et al. 2009), though doing so may be of limited use in understanding the heritability of glucocorticoids in free-living animals.

Currently, estimating the heritability of circulating glucocorticoid concentrations in free-living populations is likely limited by the availability of longitudinal hormone datasets for pedigreed populations. As an alternative, researchers often report the repeatability of these hormones rather than heritability estimates—repeatability represents an index of consistent among-individual differences in hormones across contexts and is often presented as the upper bound of heritability (Lessells and Boag 1987; Wolak et al. 2012) though this is not always accurate (Dohm 2002). Similarly to heritability, repeatability typically produces a score ranging from 0 to 1 where larger values indicate higher within-individual consistency relative to among-individual variation in a trait. Two recent meta-analyses have found that circulating glucocorticoid levels are repeatable in vertebrates (baseline glucocorticoid repeatability = 0.23–0.29; stress-induced glucocorticoid repeatability = 0.38–0.39) (Schoenemann and Bonier 2018; Taff et al. 2018), but cautioned that there was a great deal of heterogeneity in repeatability estimates across studies, taxa, type of hormone assay used, and sampling interval (Schoenemann and Bonier 2018; Taff et al. 2018). Similarly, there may exist variability in the heritability of these hormones (or the underlying

tissues or biomolecules that generate it) across populations, taxa, or environments which to date remains unexplored—by estimating the heritability of circulating glucocorticoid titres in a wider variety of taxa and environments, we can begin to unravel some of these patterns more clearly.

Heritability estimates alone are of limited use to furthering our understanding of the factors that shape variance in glucocorticoid phenotypes. In addition to calculating the proportion of variance in glucocorticoids that is attributable to heritable additive genetic effects, it will be informative for future studies to partition remaining phenotypic variance in these hormones among a wider variety of factors, including potential cohort effects, permanent environmental effects, maternal or paternal effects, or transgenerational effects (see Taylor et al. [2012] as an example). By leveraging tools from quantitative genetics—such as the animal model—evolutionary endocrinologists will better understand how variance in glucocorticoid phenotypes arise in free-living vertebrates (Cox et al. 2016b). To date, few studies have attempted to partition phenotypic variance in circulating glucocorticoids (but see Stedman et al. 2017).

Fitness and circulating glucocorticoids

The fitness consequences of variation in circulating concentrations of glucocorticoids represent one of the most studied topics on the evolutionary endocrinology of these hormones (Zera et al. 2007; Bonier et al. 2009a)—while a number of studies have quantified such glucocorticoid–fitness relationships across intrinsic and extrinsic contexts using longitudinal datasets (Madliger and Love 2016a; Henderson et al. 2017), it remains common for researchers to measure this relationship within a single context (i.e., in a single type of environmental condition, year, age group, sex, population). Glucocorticoids have also been proposed to mediate the trade-off between reproduction and survival, though evidence supporting the role of these hormones in mediating allocation to current versus future fitness has been equivocal (Love and Williams 2008a; Crossin et al. 2013; Mark and Rubenstein 2013; Ouyang et al. 2016). Similarly, the nature of the relationship between fitness and either baseline or stress-induced glucocorticoids remains unclear (Bonier et al. 2009a; Love et al. 2014; Madliger and Love 2016a). This topic has been discussed thoroughly elsewhere (see references below), so I only provide a brief overview on the relationship between circulating glucocorticoid concentrations and fitness and instead focus on the implications of these findings for understanding how glucocorticoid-mediated coping mechanisms may evolve.

Three non-mutually exclusive hypotheses describe potential relationships between baseline glucocorticoid levels and fitness: (i) the CORT-fitness hypothesis states that elevated baseline glucocorticoids are symptomatic of lower condition and are thus associated with lowered fitness (Bonier et al. 2009b), (ii) the CORT-adaptation hypothesis states that elevated baseline glucocorticoids may prepare individuals for the energetic demands of breeding and will be positively correlated to fitness (Bonier et al. 2009a), and (iii) the CORT-trade-off hypothesis states that elevated baseline glucocorticoids may improve reproductive success but decrease survival (Almasi et al. 2013). While these hypotheses were formulated with baseline glucocorticoids in mind, stress-induced glucocorticoid levels may also covary with fitness. Fewer studies have examined the fitness consequences of variation in stress-induced glucocorticoid concentrations, though elevated stress-induced hormone levels have been shown to decrease fitness (Blas et al. 2007; Breuner et al. 2008). Future work is needed to understand how stress-induced glucocorticoids are related to fitness across a diversity of taxa and contexts (Breuner et al. 2008).

The relationship between glucocorticoid hormone concentrations and fitness changes across a variety of contexts: for example, the direction/magnitude of the correlation between baseline glucocorticoids and fitness can vary with sex (Angelier et al. 2010), year (Henderson et al. 2017; Vitousek et al. 2018b), season (Ouyang et al. 2013), across populations (Jaatinen et al. 2013), first and second breeding attempts (Love et al. 2014), or habitat quality (Madliger and Love 2016a). Since environmental conditions also fluctuate through time and may confound the relationship between glucocorticoids and fitness, field-based experiments can help researchers disentangle these correlated effects (Dantzer et al. 2016).

Natural selection on circulating glucocorticoids

Circulating concentrations of glucocorticoids should respond to natural selection, as they vary among individuals, a component of this phenotypic variation is heritable, and glucocorticoids contribute to shaping variation in fitness. However, few studies have estimated the strength or direction of natural selection on circulating concentrations of these hormones in free-living vertebrates. Patterson et al. (2014) showed that survival selection favored elevated baseline and stress-induced glucocorticoid

titres, whereas fecundity selection favored elevated baseline but lowered stress-induced glucocorticoids in white-crowned sparrows (*Zonotrichia leucophrys oriantha*). Similarly, eastern fence lizards (*Sceloporus undulatus*) experienced positive selection on baseline glucocorticoids (John-Alder et al. 2009). It is important to study selection across a variety of contexts, however, since the direction of selection on baseline glucocorticoids fluctuated across seasons in great tits (*Parus major*) (Ouyang et al. 2013). While it is possible to estimate selection differentials on circulating glucocorticoids using a number of other published datasets (see Supplementary Materials of Cox et al. 2016b), few studies routinely report estimates of selection, likely because (i) the high degree of plasticity in glucocorticoids makes it challenging to estimate these hormones at the time when selection may act most strongly on the trait, and (ii) the phenotypic correlation between glucocorticoids and fitness may actually be confounded by environmental effects that independently shape both traits (Cox et al. 2016b). It is nevertheless possible to overcome these limitations (i.e., incorporate experiments or estimating plasticity) (Cox et al. 2016b; Dantzer et al. 2016), and studies estimating selection on circulating glucocorticoid concentrations will be necessary in order to translate what we know about the heritability and fitness consequences of these hormones into understanding evolutionary responses in free-living populations.

Glucocorticoids play an important role in coordinating changes in behavior, morphology, physiology, and life-history, and these pleiotropic effects have a number of evolutionary consequences. Firstly, glucocorticoids have the potential to influence the evolution of other traits (Dantzer and Swanson 2017) such that estimating the effects of natural selection on circulating glucocorticoid concentrations could be relevant to understanding the correlated evolution of behavior, morphology, physiology, and life-history (if a genetic correlation underlies the phenotypic association between these traits; Dantzer and Swanson 2017). The reverse is also true, and selection on behavior (or other correlated traits) can lead to evolutionary responses in circulating glucocorticoid titres (Garland et al. 2016). Secondly, glucocorticoids have a plethora of downstream effects and it is on these hormone-mediated effects rather than circulating hormone levels *per se* that natural selection will act. Indirect selection on circulating glucocorticoids may be weak overall if direct selection on hormone-mediated traits varies widely across contexts, or selection acts in opposing directions on several hormone-mediated traits at any given time. As a result of these pleiotropic effects, it has been challenging to understand how natural selection acts on glucocorticoids.

Comparative studies

Comparative studies primarily aim to explain spatial patterns of variation in circulating glucocorticoid concentrations across populations or species (Fig. 1), and have become increasingly feasible as published articles reporting glucocorticoids titres across diverse taxa and regions of the world have become readily available. While circulating glucocorticoid concentrations seem to vary widely within- and across-individuals (Madliger and Love 2016b), the chemical structure of glucocorticoids and the hypothalamic–pituitary–adrenal-axis (HPA-axis) responsible for secreting these hormones are actually highly conserved across vertebrates (Denver 2009). Nevertheless, large-scale comparative approaches are increasingly used to understand the relative roles of latitude, evolutionary history, life-history, and/or environmental factors in shaping patterns of glucocorticoid variation across populations or species. With the recent publication of HormoneBase (Vitousek et al. 2018a), phylogenetically-controlled comparative studies are increasingly possible. Below, I outline advances in our understanding of the evolution of circulating concentrations of glucocorticoids that stemmed from interspecific or intraspecific comparative analyses.

Interspecific comparative studies

Interspecific comparative studies aimed at explaining variation in circulating glucocorticoid levels across species have limited their scope by focusing on select taxa where glucocorticoid data were more readily available (i.e., amphibians, birds, or reptiles) (Eikenaar et al. 2012; Jessop et al. 2013, 2016). Nevertheless, these studies have highlighted large-scale patterns of variation in glucocorticoids across species and highlighted some of the environmental, behavioral, or life-history characteristics which co-vary with glucocorticoids on a macro-evolutionary scale. In reptiles and amphibians, baseline glucocorticoid levels were positively correlated to latitude (Eikenaar et al. 2012), suggesting short and intense breeding seasons at Northern latitudes may result in elevated energetic demand. In a similar study, stress-induced glucocorticoids were positively correlated to latitude in birds, though not in reptiles (Jessop et al. 2013). Instead, reptilian stress-induced glucocorticoid concentrations were positively correlated to net primary productivity and negatively correlated

to body mass (Jessop et al. 2013). In a comparison of temperate versus tropical avian species, circulating glucocorticoid titres covaried with a number of life-history traits; namely, baseline glucocorticoids were negatively correlated to length of breeding season, stress-induced glucocorticoids were positively correlated to annual survival, and both baseline and stress-induced titres were negatively correlated to body mass (Hau et al. 2010). Avian glucocorticoid titres also covaried with environmental characteristics, where stress-induced hormone levels were negatively correlated to net primary productivity (Jessop et al. 2013). Finally, baseline glucocorticoids in birds and reptiles were found to be negatively correlated to temperature, while stress-induced glucocorticoids were positively correlated to temperature only in birds (Jessop et al. 2016). These patterns of latitudinal variation in circulating glucocorticoid concentrations across species of at least certain taxa suggest that a global gradient of conditions that covary (i.e., environmental conditions, behavioral differences, and life-history traits) contribute to shaping glucocorticoid variation across vertebrates. The relative importance of environmental, behavioral, or life-history traits in shaping this endocrine variation is currently difficult to disentangle.

An alternative approach to understanding the evolution of glucocorticoid phenotypes at a macroevolutionary scale is to apply genetic tools to investigate potential selection or interspecific variation in genes related to the expression and function of glucocorticoids or the HPA-axis. Within the African starling clade, for example, substitutions rates within the sequence of the glucocorticoid receptor gene (*Nr3c1*) were negatively correlated to environmental variability (Hofmeister and Rubenstein 2016)—this finding provides evidence that variable environmental conditions can constrain substitutions within this genetic sequence, likely because of the importance of glucocorticoids and their receptors for coping with variable habitats. Future comparative work on glucocorticoid-related genes will improve our understanding of the level(s) at which selection may act within the HPA-axis. Incorporating transcriptomic or genomic tools and sampling key target tissues (e.g., brains, livers, and muscles) may be more feasible in a comparative context relative to a longitudinal one, where invasive sampling is not always possible (i.e., individual fitness estimates are valued).

Intraspecific comparative studies

An alternative comparative approach has been to explore variation in hormone phenotype and function across populations of the same species that differ along an environmental or behavioral gradient (e.g., differences in breeding behavior, migratory behavior, phenology, life-history, and environmental conditions). Intraspecific comparisons allow researchers to tease apart the relative contributions of different environmental characteristics in shaping variance in circulating glucocorticoid concentrations. While it can be more challenging to interpret results of these studies in an evolutionary context, they provide a greater degree of control in disentangling the relative effects of environmental, behavioral, or life-history traits on endocrine variation relative to interspecific studies (where these factors all covary with latitude).

The urban–rural gradient has been among the most studied environmental gradients in the context of understanding variation in glucocorticoid phenotypes in free-living birds (Zhang et al. 2011; Villanueva et al. 2012), reptiles (French et al. 2008), and mammals (Dowle et al. 2013). While urbanization certainly impacts animals, our understanding of the way in which urbanization shapes variation in baseline or stress-induced glucocorticoid concentrations remains equivocal. Across five species of passerines, stress-induced glucocorticoid levels were elevated in urban-dwelling individuals relative to rural ones, while baseline titres and corticosteroid-binding globulins did not differ across populations (Fokidis et al. 2009). Comprehensive reviews of avian studies across a larger number of species did not find a consistent pattern for the relationship between the degree of urbanization and circulating glucocorticoids (Bonier 2012; Sepp et al. 2018). Fokidis and Deviche (2011) examined variation in HPA-axis activity using standardized hormone injections in rural and urban curve-billed thrashers (*Toxostoma curvirostre*). While baseline glucocorticoids, stress-induced glucocorticoids, or the strength of the negative feedback of the HPA-axis did not differ for birds from urban and rural populations, urban birds had greater pituitary and adrenal sensitivity which suggests that urban-dwelling individuals have a greater capacity to secrete glucocorticoids when facing stressors (Fokidis and Deviche 2011). Alternative types of environmental gradients have also been used to understand variation in circulating glucocorticoid concentrations, including studying populations across elevation or variation in life-history traits (e.g., number of broods raised per season). Baseline glucocorticoid concentrations were elevated in high-land relative to low-land Australian great barred frogs (*Mixophyes fasciolatus*), potentially due to elevated metabolic demands associated with life at higher elevations (Graham et al. 2013). Stress-

induced glucocorticoid titres were elevated in unpredictable savanna habitats relative to predictable forests in the common bulbul (*Pycnonotus barbatus*) (Martin and Rubenstein 2008). A detailed study by Breuner et al. (2003) compared circulating glucocorticoids, corticosteroid-binding globulins, and glucocorticoid receptor densities across three populations of white-crowned sparrows (*Z. leucophrys*) that differed primarily in their investment in breeding (i.e., length of breeding season, number of broods attempted, etc.). While circulating baseline and stress-induced glucocorticoids were comparable across all three populations examined, sparrows with the longest breeding season had lowered corticosteroid-binding globulins and elevated glucocorticoid receptor densities in the liver and brain (Breuner et al. 2003). This finding suggests that individuals experiencing prolonged breeding seasons would be most physiologically responsive to perturbations in their environments whereas animals experiencing short/condensed breeding seasons would be less sensitive to potential environmental changes. Together, these studies highlight a variety of ways in which environmental conditions or life-history traits are related to circulating glucocorticoid concentrations, yet it remains challenging to interpret what these environment–phenotype correlations mean in an evolutionary context without further information about whether endocrine differences across populations are fixed or flexible.

The majority of research performed at an intraspecific scale has focused on examining differences in circulating glucocorticoid levels between two or three populations, and on study systems which differed in a few key environment, behavior, or life-history characteristics (e.g., habitat type; Martin and Rubenstein 2008). This likely represents a methodological limitation, as it can be difficult to collect data in a large number of populations simultaneously. It will be beneficial to expand the scope of future research in two primary ways: firstly, examining variation in circulating glucocorticoid concentrations across a larger gradient of environmental conditions (or behaviors, or life-histories) will be necessary. Populations and environments do not vary in binary ways in nature, so understanding the complex and potentially non-linear relationship between an animal's environment and their glucocorticoid phenotype will be important. Secondly, replicating these intraspecific studies across several taxa will be necessary in order to determine how generalizable findings from these studies may be and to place these findings within an evolutionary context. For example, the HormoneBase dataset includes population-level records of circulating glucocorticoid measurements and over 70 species include records for two or more populations (Vitousek et al. 2018a)—it would be possible to explore the ways in which these populations differed from one another environmentally or behaviorally, and examine how circulating glucocorticoid concentrations vary across populations according to these factors in a meta-analytical context.

Integrating across levels of analysis

In this review, I have outline the scales at which studies have advanced our understanding of the evolutionary endocrinology of circulating glucocorticoid titres in free-living vertebrates. Longitudinal studies can elucidate the microevolutionary processes that lead to within- and between-individual variation in circulating glucocorticoid concentrations temporally, whether this variation is heritable, how glucocorticoids shape fitness, and ultimately how natural selection acts on circulating glucocorticoid concentrations. On the other hand, intra- and interspecific comparative studies have demonstrated how differences in environmental conditions, behavior, life-history, or evolutionary history have shaped macro-evolutionary and spatial patterns of circulating glucocorticoid variation across populations and species.

Currently, our understanding of how natural selection in a population scales up to shape patterns of variation in circulating glucocorticoid levels across taxa remains limited, so a critical area of future research will be to bridge the gap between micro- and macro-evolutionary patterns of variation in these hormones (Carroll et al. 2007). Determining how microevolutionary processes vary across environments, taxa, or life-histories will provide us with an understanding of the degree to which patterns from longitudinal studies generalize to comparative contexts and vice versa (Fig. 1). From a practical perspective, this will improve our ability to predict how species facing future environmental changes (e.g., urbanization and global climate change) may come to cope with these challenges (Carroll et al. 2007). For example, understanding the degree to which glucocorticoid phenotypes are flexible and related to fitness across populations, species, or environmental contexts would allow researchers to make concrete predictions about whether specific populations would persist under altered conditions. Below, I conclude by outlining some suggestions for future research directions that would improve our understanding of how variation in circulating

glucocorticoid concentrations arises among individuals, populations, and species.

Future directions

Firstly, rather than acting directly on circulating glucocorticoids levels, selection is likely to act on the downstream effects of glucocorticoids or along multiple points of the complex HPA-axis (Hau et al. 2016) which is responsible for regulating the secretion of glucocorticoid hormones. While glucocorticoids in free-living vertebrates are predominantly studied from the perspective of circulating hormone titres sampled from the blood—or excreted in feces, urine, saliva, or hair/feathers (Sheriff et al. 2011)—these measurements only capture one component of how the HPA-axis shapes an organism's response to its environment. Circulating glucocorticoids certainly act as a crucial chemical messenger, though they only lead to physiological, morphological, or behavioral change upon binding to receptors in different tissues which subsequently initiates the expression of relevant genes (Sapolsky et al. 2000). The binding activity of glucocorticoids and its consequences on organismal physiology depends on a variety of factors on which selection may act, including the availability of proteins that bind glucocorticoids and may or may not render them biologically inactive as they circulate within the body prior to reaching target tissues (corticosteroid-binding globulin) (Malisch and Breuner 2010; Breuner et al. 2013; Schoech et al. 2013), or the densities of glucocorticoid or mineralocorticoid receptors within relevant tissues (i.e., brain, liver, and muscle) (Landys et al. 2006). The HPA-axis is also self-regulating (stress-induced concentrations of glucocorticoids exert a negative feedback on the HPA-axis to terminate the stress response) and individuals can differ in their capacity to secrete glucocorticoids; it is possible to measure the responsiveness of the HPA-axis and the efficiency of this negative feedback mechanism via hormone challenges (i.e., adrenocorticotropic hormone or dexamethasone injections; reviewed in Taff and Vitousek 2016). Performing standardized hormone injection challenges within and across individuals, populations, or species will provide a more detailed characterization of variation in glucocorticoid phenotypes beyond circulating concentrations alone. Alternatively, selection on the HPA-axis could be studied from the perspective of the genetic underpinnings of these traits: researchers are beginning to examine variation in the genetic sequence of receptor genes (Hofmeister and Rubenstein 2016) or DNA-methylation of receptor gene promoter regions (Rubenstein et al. 2016) in free-living animals. While characterizing the HPA-axis thoroughly in free-living animals can be challenging because it can require collecting tissues (i.e., collecting livers, muscles, or brains is lethal), doing so in a subset of individuals in longitudinal or comparative contexts may provide important insights into how selection acts along the entire HPA-axis rather than on a single component of this regulatory network. By focusing exclusively on circulating glucocorticoids, evolutionary endocrinologists will likely only have an incomplete understanding of how natural selection acts on these hormones in free-living vertebrates.

Circulating glucocorticoid concentrations represent a phenotypically plastic trait, where one genotype (or individual) can give rise to multiple phenotypes (or glucocorticoids titres) across different external or internal contexts (Lendvai et al. 2014). In the case of circulating glucocorticoids, characterizing this plasticity is particularly complex since there are different types of within-individual plasticity which can occur: (i) plasticity in the stress-response (measured as the change from baseline to stress-induced titres) (as in Love and Williams 2008b), or (ii) plasticity within baseline or within stress-induced titres, where either baseline or stress-induced glucocorticoid levels can change across environmental or social contexts (Canoine et al. 2002; Lendvai et al. 2014). These different types of phenotypic plasticity may not only mask our ability to estimate selection on endocrine traits, but it is also possible that adaptive endocrine plasticity itself may be the target of selection (Hau et al. 2016). Researchers have previously highlighted the importance of understanding endocrine flexibility and plasticity (Cox et al. 2016b; Taff and Vitousek 2016), but future research should take care to differentiate between the different types of phenotypic plasticity that occur with respect to circulating glucocorticoids. Future research could address a number of fundamental questions including: (i) is plasticity in circulating glucocorticoid concentrations heritable or correlated to fitness, (ii) does plasticity in circulating glucocorticoids respond to natural selection, and (iii) does plasticity in circulating glucocorticoids differ across populations or species? In a longitudinal context, addressing these questions would require hormone measurements from the same individuals sampled repeatedly through time/environmental contexts, and across generations (Taff and Vitousek 2016). Reaction norms can be employed, where within-individual responses in a flexible trait (i.e., changes in glucocorticoids) are monitored across a

gradient of environmental conditions (Alonzo 2015; Hau et al. 2016). In a comparative context, it has typically been more challenging to study plasticity because hormone titres from individuals across populations or species are not typically sampled repeatedly which gives rise to two issues. Firstly, this represents a methodological concern since a flexible and often plastic trait is assessed from a single measurement at a single time point (Cox et al. 2016b; Hau et al. 2016). Secondly, this limitation makes it difficult to determine whether variation in circulating glucocorticoid concentrations or HPA-axis functioning represent fixed or flexible differences between populations and/or species. Yet, understanding whether circulating concentrations of glucocorticoids are similarly phenotypically plastic across individuals in different populations or of different species remains important for predicting how animals may cope with future environmental challenges (Angelier and Wingfield 2013). One alternative to studying multiple populations or species longitudinally to gain insight into the degree of plasticity of circulating glucocorticoid hormones across populations or species is to use common garden (or transplant) experiments. By rearing animals from different populations in a common captive environment, researchers can assess whether differences in circulating glucocorticoid or HPA-axis phenotypes persist in the absence of environmental differences. Common garden experiments have shown that differences in circulating glucocorticoids from individuals born in differing environments in the wild persisted under a common conditions (Partecke et al. 2006; Angelier et al. 2011). To my knowledge, common garden experiments have never been used to compare whether interspecific differences in glucocorticoids persist under common environmental conditions. Nevertheless, this approach would help to disentangle the contributions of environmental conditions from behavior or life-history in shaping variation in circulating glucocorticoid concentrations across species.

Conclusion

In conclusion, circulating glucocorticoid concentrations represent an important potential mechanism for coping with environmental change. In order to predict how species will respond to novel conditions via glucocorticoid-mediated responses, we need to understand how variation in these hormones arise across individuals, populations, and species (Fig. 1). Understanding how natural selection in a population will contribute to shaping patterns of circulating glucocorticoid variation among populations and species will require that evolutionary endocrinologists replicate microevolutionary studies across contexts and taxa. Importantly, exploring the components of the HPA-axis where selection may act most strongly would represent an important step in determining how variation in glucocorticoid-mediated coping mechanisms is shaped in free-living vertebrates. Phenotypic plasticity in circulating concentrations of glucocorticoids and the HPA-axis likely play an integral role in determining how individuals, populations, and species will adjust to novel conditions, though future research is required to understand patterns and consequences of plasticity in glucocorticoids across these scales.

Acknowledgments

I thank the organizers (Maren Vitousek and Michele Johnson) for inviting me to contribute to this symposium. I also thank the Dantzer, Bergman, and Beehner laboratories for helpful discussion regarding some of the ideas presented in this manuscript. Lastly, I thank four anonymous reviewers for constructive feedback that improved this review.

Funding

My participation in the symposium was sponsored by the Company of Biologists, and the Society for Integrative and Comparative Biology (Divisions of Animal Behavior, Comparative Endocrinology, Comparative Physiology and Biochemistry, and Ecology and Evolution). I am also supported by a Post-Doctoral Fellowship from the Natural Sciences and Engineering Research Council of Canada.

References

Almasi B, Jenni L, Jenni-Eiermann S, Roulin A. 2010. Regulation of stress response is heritable and functionally linked to melanin-based coloration. J Evol Biol 23:987–96.

Almasi B, Roulin A, Jenni L. 2013. Corticosterone shifts reproductive behaviour towards self-maintenance in the barn owl and is linked to melanin-based coloration in females. Horm Behav 64:161–71.

Alonzo SH. 2015. Integrating the how and why of within-individual and among-individual variation and plasticity in behavior. Curr Opin Behav Sci 6:69–75.

Angelier F, Ballentine B, Holberton RL, Marra PP, Greenberg R. 2011. What drives variation in the corticosterone stress response between subspecies? A common garden experiment of swamp sparrows (*Melospiza georgiana*). J Evol Biol 24:1274–83.

Angelier F, Wingfield JC. 2013. Importance of the glucocorticoid stress response in a changing world: theory, hypotheses and perspectives. Gen Comp Endocrinol 190:118–28.

Angelier F, Wingfield JC, Weimerskirch H, Chastel O. 2010. Hormonal correlates of individual quality in a long-lived bird: a test of the "corticosterone–fitness hypothesis." Biol Lett 6:846–9.

Bairos-Novak KR, Ryana CP, Freemana AR, Andersona WG, Hare JF. 2018. Like mother, like daughter: heritability of female Richardson's ground squirrel *Urocitellus richardsonii* cortisol stress responses. Curr Zool 64:153–63.

Bartels M, Van den Berg M, Sluyter F, Boomsma DI, De Geus EJC. 2003. Heritability of cortisol levels: review and simultaneous analysis of twin studies. Psychoneuroendocrinology 28:121–37.

Blas J, Bortolotti GR, Tella JL, Baos R, Marchant TA. 2007. Stress response during development predicts fitness in a wild, long lived vertebrate. Proc Natl Acad Sci U S A 104:8880–4.

Bonier F. 2012. Hormones in the city: endocrine ecology of urban birds. Horm Behav 61:763–72.

Bonier F, Martin PR, Moore IT, Wingfield JC. 2009a. Do baseline glucocorticoids predict fitness? Trends Ecol Evol 24:634–42.

Bonier F, Moore IT, Martin PR, Robertson RJ. 2009b. The relationship between fitness and baseline glucocorticoids in a passerine bird. Gen Comp Endocrinol 163: 208–13.

Breuner CW, Delehanty B, Boonstra R. 2013. Evaluating stress in natural populations of vertebrates: total CORT is not good enough. Funct Ecol 27:24–36.

Breuner CW, Orchinik M, Hahn TP, Meddle SL, Moore IT, Owen-Ashley NT, Sperry TS, Wingfield JC. 2003. Differential mechanisms for regulation of the stress response across latitudinal gradients. Am J Physiol Regul Integr Comp Physiol 285:R594–600.

Breuner CW, Patterson SH, Hahn TP. 2008. In search of relationships between the acute adrenocortical response and fitness. Gen Comp Endocrinol 157:288–95.

Brown KI, Nestor K. 1973. Some physiological responses of Turkeys selected for high and low adrenal response to cold stress. Poult Sci 52:1948–54.

Canoine V, Hayden TJ, Rowe K, Goymann W. 2002. The stress response of European stonechats depends on the type of stressor. Behaviour 139:1303–11.

Carroll ASP, Hendry AP, Reznick DN, Fox CW. 2007. Evolution on ecological time-scales linked. Funct Ecol 21:387–93.

Charmandari E, Tsigos C, Chrousos G. 2005. Endocrinology of the stress response. Annu Rev Physiol 67:259–84.

Cox RM, McGlothlin JW, Bonier F. 2016a. Evolutionary endocrinology: hormones as mediators of evolutionary phenomena. Integr Comp Biol 56:121–5.

Cox RM, McGlothlin JW, Bonier F. 2016b. Hormones as mediators of phenotypic and genetic integration: an evolutionary genetics approach. Integr Comp Biol 56:126–37.

Crino OL, Driscoll SC, Ton R, Breuner CW. 2014. Corticosterone exposure during development improves performance on a novel foraging task in zebra finches. Anim Behav 91:27–32.

Crossin GT, Phillips RA, Lattin CR, Romero LM, Williams TD. 2013. Corticosterone mediated costs of reproduction link current to future breeding. Gen Comp Endocrinol 193:112–20.

Dallman MF, Strack AM, Akana SF, Bradbury MJ, Hanson ES, Scribner KA, Smith M. 1993. Feast and famine: critical role of glucocorticoids with insulin in daily energy flow. Front Neuroendocrinol 14:303–47.

Dantzer B, Swanson EM. 2017. Does hormonal pleiotropy shape the evolution of performance and life history traits? Integr Comp Biol 57:372–84.

Dantzer B, Westrick SE, Kesteren FV. 2016. Relationships between endocrine traits and life histories in wild animals: insights, problems, and potential pitfalls. Integr Comp Biol 56:185–97.

Denver RJ. 2009. Structural and functional evolution of vertebrate neuroendocrine stress systems. Ann N Y Acad Sci 1163:1–16.

Dohm MR. 2002. Repeatability estimates do not always set an upper limit to heritability. Funct Ecol 16:273–80.

Dowle M, Webster KN, Deane E. 2013. Faecal glucocorticoid metabolite concentrations in the free-ranging bandicoots (*Perameles nasuta* and *Isoodon obesulus*) of northern Sydney. Aust Mammal 35:1–7.

Eikenaar C, Husak J, Escallón C, Moore IT. 2012. Variation in testosterone and corticosterone in amphibians and reptiles: relationships with latitude, elevation, and breeding season length. Am Nat 180:642–54.

Evans MR, Roberts ML, Buchanan KL, Goldsmith AR. 2006. Heritability of corticosterone response and changes in life history traits during selection in the zebra finch. J Evol Biol 19:343–52.

Fokidis HB, Deviche P. 2011. Plasma corticosterone of city and desert Curve-billed Thrashers, *Toxostoma curvirostre*, in response to stress-related peptide administration. Comp Biochem Physiol A Mol Integr Physiol 159:32–8.

Fokidis HB, Orchinik M, Deviche P. 2009. Corticosterone and corticosteroid binding globulin in birds: relation to urbanization in a desert city. Gen Comp Endocrinol 160:259–70.

French SS, Fokidis HB, Moore MC. 2008. Variation in stress and innate immunity in the tree lizard (*Urosaurus ornatus*) across an urban–rural gradient. J Comp Physiol 178:997–1005.

Garland T, Zhao M, Saltzman W. 2016. Hormones and the evolution of complex traits: insights from artificial selection on behavior. Integr Comp Biol 56:207–24.

Gesquiere LR, Learn NH, Simao MCM, Onyango PO, Alberts SC, Altmann J. 2011. Life at the top: rank and stress in wild male baboons. Science 333:357–60.

Graham CM, Narayan EJ, McCallum H, Hero JM. 2013. Non-invasive monitoring of glucocorticoid physiology within highland and lowland populations of native Australian Great Barred Frog (*Mixophyes fasciolatus*). Gen Comp Endocrinol 191:24–30.

Hau M, Casagrande S, Ouyang JQ, Baugh AT. 2016. Glucocorticoid-mediated phenotypes in vertebrates: multilevel variation and evolution. Adv Study Behav 48:41–115.

Hau M, Ricklefs RE, Wikelski M, Lee KA, Brawn JD. 2010. Corticosterone, testosterone and life-history strategies of birds. Proc R Soc B 277:3203–12.

Henderson LJ, Evans NP, Heidinger BJ, Herborn KA, Arnold KE. 2017. Do glucocorticoids predict fitness? Linking environmental conditions, corticosterone and reproductive success in the blue tit, *Cyanistes caeruleus*. R Soc Open Sci 4:170875.

Hennin HL, Wells-Berlin AM, Love OP. 2016. Baseline glucocorticoids are drivers of body mass gain in a diving seabird. Ecol Evol 6:1702.

Hofmeister NR, Rubenstein DR. 2016. Environmental variability and the evolution of the glucocorticoid receptor (Nr3c1) in African starlings. Ecol Lett 19:1219–27.

Jaatinen K, Seltmann MW, Hollmén T, Atkinson S, Mashburn K, Öst M. 2013. Context dependency of baseline glucocorticoids as indicators of individual quality in a capital breeder. Gen Comp Endocrinol 191:231–8.

Jenkins BR, Vitousek MN, Hubbard JK, Safran RJ, Jenkins BR. 2014. An experimental analysis of the heritability of variation in glucocorticoid concentrations in a wild avian population. Proc Biol Sci 281:20141302.

Jessop TS, Lane ML, Teasdale L, Stuart-Fox D, Wilson RS, Careau V, Moore IT. 2016. Multiscale evaluation of thermal dependence in the glucocorticoid response of vertebrates. Am Nat 188:342.

Jessop TS, Woodford R, Symonds MRE. 2013. Macrostress: do large-scale ecological patterns exist in the glucocorticoid stress response of vertebrates? Funct Ecol 27:120–30.

John-Alder HB, Cox RM, Haenel GJ, Smith LC. 2009. Hormones, performance and fitness: natural history and endocrine experiments on a lizard (*Sceloporus undulatus*). Integr Comp Biol 49:393–407.

Landys MM, Ramenofsky M, Wingfield JC. 2006. Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes. Gen Comp Endocrinol 148:132–49.

Lendvai AZ, Bokony V, Chastel O. 2011. Coping with novelty and stress in free-living house sparrows. J Exp Biol 214:821–8.

Lendvai AZ, Ouyang JQ, Schoenle LA, Fasanello V, Haussmann MF, Bonier F, Moore IT. 2014. Experimental food restriction reveals individual differences in corticosterone reaction norms with no oxidative costs. PLoS One 9:e110564.

Lessells CM, Boag PT. 1987. Unrepeatable repeatabilities: a common mistake. Auk 104:116–21.

Love OP, Madliger CL, Bourgeon S, Semeniuk CAD, Williams TD. 2014. Evidence for baseline glucocorticoids as mediators of reproductive investment in a wild bird. Gen Comp Endocrinol 199:65–9.

Love OP, Williams TD. 2008. The adaptive value of stress-induced phenotypes: effects of maternally derived corticosterone on sex-biased investment, cost of reproduction, and maternal fitness. Am Nat 172:E135–49.

Love OP, Williams TD. 2008. Plasticity in the adrenocortical response of a free-living vertebrate: the role of pre- and post-natal developmental stress. Horm Behav 54:496–505.

Madliger CL, Love OP. 2016. Do baseline glucocorticoids simultaneously represent fitness and environmental quality in an aerial insectivore? Oikos 125:1824–37.

Madliger CL, Love OP. 2016. Employing individual measures of baseline glucocorticoids as population-level conservation biomarkers: considering within-individual variation in a breeding passerine. Conserv Physiol 4:cow048 (doi:10.1093/conphys/cow048).

Malisch JL, Breuner CW. 2010. Steroid-binding proteins and free steroids in birds. Mol Cell Endocrinol 316:42–52.

Mark MM, Rubenstein DR. 2013. Physiological costs and carry-over effects of avian interspecific brood parasitism influence reproductive tradeoffs. Horm Behav 63:717–22.

Martin LB, Rubenstein DR. 2008. Stress hormones in tropical birds: patterns and future directions. Ornitol Neotrop 19:207–18.

McEwen BS, Wingfield JC. 2003. The concept of allostasis in biology and biomedicine. Horm Behav 43:2–15.

Ouyang JQ, Lendvai Z, Moore IT, Bonier F, Haussmann MF. 2016. Do hormones, telomere lengths, and oxidative stress form an integrated phenotype? A case study in free-living tree swallows. Integr Comp Biol 56:138–45.

Ouyang JQ, Sharp P, Quetting M, Hau M. 2013. Endocrine phenotype, reproductive success and survival in the great tit, *Parus major*. J Evol Biol 26:1988–98.

Partecke J, Schwabl I, Gwinner E. 2006. Stress and the city: urbanization and its effects on the stress physiology in European blackbirds. Ecology 87:1945–52.

Patterson SH, Hahn TP, Cornelius JM, Breuner CW. 2014. Natural selection and glucocorticoid physiology. J Evol Biol 27:259–74.

Pelletier F, Réale D, Watters J, Boakes EH, Garant D. 2009. Value of captive populations for quantitative genetics research. Trends Ecol Evol 24:263–70.

Pottinger TG, Carrick TR. 1999. Modification of the plasma cortisol response to stress in rainbow trout by selective breeding. Gen Comp Endocrinol 116:122–32.

Romero LM, Dickens MJ, Cyr NE. 2009. The reactive scope model—a new model integrating homeostasis, allostasis, and stress. Horm Behav 55:375–89.

Rubenstein DR, Skolnik H, Berrio A, Champagne FA, Phelps S, Solomon J. 2016. Sex-specific fitness effects of unpredictable early life conditions are associated with DNA methylation in the avian glucocorticoid receptor. Mol Ecol 25:1714–28.

Sapolsky RM, Romero LM, Munck AU. 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrinol Rev 21:55–89.

Satterlee DG, Johnson WA, Rouge B. 1988. Selection of Japanese quail for contrasting blood corticosterone response to immobilization. Poult Sci 67:25–32.

Schoech SJ, Romero LM, Moore IT, Bonier F. 2013. Constraints, concerns and considerations about the necessity of estimating free glucocorticoid concentrations for field endocrine studies. Funct Ecol 27:1100–6.

Schoenemann KL, Bonier F. 2018. Repeatability of glucocorticoid hormones in vertebrates: a meta-analysis. PeerJ 6:e4398.

Sepp T, McGraw KJ, Kaasik A, Giraudeau M. 2018. A review of urban impacts on avian life-history evolution: does city living lead to slower pace of life? Glob Chang Biol 24:1452–69.

Sheriff MJ, Dantzer B, Delehanty B, Palme R, Boonstra R. 2011. Measuring stress in wildlife: techniques for quantifying glucocorticoids. Oecologia 166:869–87.

Stedman JM, Hallinger KK, Winkler DW, Vitousek MN. 2017. Heritable variation in circulating glucocorticoids and endocrine flexibility in a free-living songbird. J Evol Biol 30:1724–35.

Taff CC, Schoenle LA, Vitousek MN. 2018. The repeatability of glucocorticoids: a review and meta-analysis. Gen Comp Endocrinol 260:136–45.

Taff CC, Vitousek MN. 2016. Endocrine flexibility: optimizing phenotypes in a dynamic world? Trends Ecol Evol 31:476–13.

Taylor RW, Boon AK, Dantzer B, Reale D, Humphries MM, Boutin S, Gorrell JC, Coltman DW, McAdam AG. 2012. Low heritabilities, but genetic and maternal correlations between red squirrel behaviours. J Evol Biol 25:614–24.

Villanueva C, Walker BG, Bertellotti M. 2012. A matter of history: effects of tourism on physiology, behaviour and breeding parameters in Magellanic Penguins (*Spheniscus magellanicus*) at two colonies in Argentina. J Ornithol 153:219–28.

Vitousek M, Johnson M, Donald J, Francis C, Fuxjager M, Goymann W, Hau M, Husak J, Kircher B, Knapp R, et al. 2018a. HormoneBase: a population-level database of steroid hormone levels across vertebrates. Sci Data 5:180097.

Vitousek MN, Taff CC, Hallinger KK, Zimmer C, Winkler DW. 2018b. Hormones and fitness: evidence for trade-offs in glucocorticoid regulation across contexts. Front Ecol Evol 6:42.

Wingfield JC. 2013. Ecological processes and the ecology of stress: the impacts of abiotic environmental factors. Funct Ecol 27:37–44.

Wingfield JC, Kitaysky AS. 2002. Endocrine responses to unpredictable environmental events: stress or anti-stress hormones?. Integr Comp Biol 42:600–9.

Wolak ME, Fairbairn DJ, Paulsen YR. 2012. Guidelines for estimating repeatability. Methods Ecol Evol 3:129–37.

Zera AJ, Harshman LG, Williams TD. 2007. Evolutionary endocrinology: the developing synthesis between endocrinology and evolutionary genetics. Annu Rev Ecol Evol Syst 38:793–817.

Zhang S, Lei F, Liu S, Li D, Chen C, Wang P. 2011. Variation in baseline corticosterone levels of tree sparrow (*Passer montanus*) populations along an urban gradient in Beijing, China. J Ornithol 152:801–6.