Integrative and Comparative Biology

Integrative and Comparative Biology, volume 58, number 4, pp. 777–789
doi:10.1093/icb/icy046

Society for Integrative and Comparative Biology

SYMPOSIUM

Understanding Context Dependence in Glucocorticoid–Fitness Relationships: The Role of the Nature of the Challenge, the Intensity and Frequency of Stressors, and Life History

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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.

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Synopsis It has been well-established that there is variation in the strength and direction of the relationship between circulating glucocorticoids (GCs) and fitness. When studies demonstrate such variation or the direction of the GC–fitness relationship is unexpected, the results are often attributed to context-dependency. However, descriptors of context can be vague (e.g., "environmental context") and few studies explicitly test how the optimal hypothalamic–pituitary–adrenal (HPA) axis response to stressors varies across specific contexts. Although existing hypotheses create a strong foundation for understanding GC–fitness relationships, many do not provide explicit predictions of how, when, and why the relationships will change. Here, we discuss three broad factors which we expect to shape the relationships between HPA axis activity and fitness metrics: (1) whether the HPA axis-mediated response matches the challenge, (2) the intensity and frequency of challenges, and (3) life history. We also make predictions for how these factors might affect GC–fitness relationships and discuss ways to test these predictions. Observational studies, experimental manipulations of context, and large-scale cross-species comparisons will be critical to understanding the observed variation in GC–fitness relationships.

Introduction

Animals encounter a tremendous diversity of challenges; they face unpredictable environments, defend against predators and parasites, and navigate social interactions, all while managing limited energy stores. The ways animals cope with these challenges affect the likelihood that they survive and reproduce. Glucocorticoid (GC) hormones play a primary role in metabolic regulation and in coordinating the response to challenges in vertebrates, and thus, can influence fitness.

The GC-mediated response to both long-term and immediate challenges is highly conserved among vertebrates. When an animal perceives a challenge, the hypothalamic–pituitary–adrenal/interrenal (HPA) axis initiates a hormonal cascade resulting in the secretion of GCs (primarily corticosterone in birds, reptiles, amphibians, and some rodents; primarily cortisol in fish and most mammals). GCs are integrator molecules, and can mediate a suite of physiological and behavioral changes, including shifts in energy acquisition and mobilization, immune function, growth and development, and reproduction (Sapolsky et al. 2000). They coordinate the expression of such diverse phenotypes through interactions with networks of signaling molecules and multiple physiological systems (i.e., physiological regulatory networks) (Cohen et al. 2012). Thus, the expression of GC-mediated traits relies on multiple components of physiology (e.g., immune cells, nutrient availability), and variation in physiological states (e.g., gestation, starvation) could change the effects of GCs.

Advance Access publication June 7, 2018

In addition to production in the adrenal/interrenal glands, GCs are synthesized in other tissues, including the brain and immune organs. GCs can be measured at systemic, circulating levels in blood components or within specific organs (e.g., skin, brain). Most research evaluating GC–fitness relationships focuses on systemic, circulating levels of GCs. Thus, in this review we also focus on circulating GCs, which can be measured directly in serum or plasma or assessed indirectly via metabolites in waste or tissues (e.g., feces, urine, hair, saliva).

Baseline levels of GCs (i.e., levels not influenced by an immediate threat/acute stressor) are often considered to reflect the overall energetic demands facing an animal because of their primary role in metabolism. Circulating concentrations mediate the expression of physiological and behavioral traits related to energy use, such as body mass, metabolic rate, and foraging behavior. However, the relationships between baseline GC concentrations and these traits can differ among species and contexts (Crespi and Denver 2005; Lendvai et al. 2014; Haase et al. 2016). Baseline GC concentrations are also responsive to other aspects of the physical and social environment (e.g., photoperiod, population density) and fluctuate daily, seasonally, and with life history stage (Reeder and Kramer 2005; Landys et al. 2006). In response to an acute threat or stressor, GC levels increase rapidly and the corresponding changes in physiology and behavior are thought to support immediate survival (Wingfield and Romero 2001; Kalynchuk et al. 2004; Thaker et al. 2009). The GC stress response is downregulated via negative feedback (Myers et al. 2012). Although the overall GC response is highly conserved in vertebrates, the HPA axis' response to challenges varies among individuals and species. There are among-individual and species differences in circulating GC concentrations, both at baseline levels and in response to acute stressors (Hau et al. 2010; Cockrem 2013; Hau and Goymann 2015) as well as in the efficacy of negative feedback (Romero and Wikelski 2010; Bauer et al. 2013; Taff et al. Forthcoming 2018). Furthermore, individual variation in the HPA axis can be associated with variation in survival and reproductive success (Breuner et al. 2008; Bonier et al. 2009b; Romero and Wikelski 2010; Vitousek et al. 2014).

Over the last 40 years, interest in the relationship between GC and fitness measures has grown dramatically. Why has so much effort been dedicated to understanding the relationship between HPA axis activity and fitness? Understanding this relationship will provide insight into how animals cope with challenges and what constitutes a successful physiological response to a challenge (Breuner et al. 2008). Evaluating the direction and intensity of GC–fitness relationships across species, environments, and life history stages can help us understand the evolution of the stress response. In addition, if GCs are associated with both challenges and fitness, they could serve as an indicator of stress as well as individual and/or population health (Dantzer et al. 2014). Because GC levels are relatively easy to measure in many species, there is substantial interest in using these hormones as biomarkers of stress from both the animal welfare and conservation communities (Palme 2012; Dantzer et al. 2014).

In contrast to measuring hormone levels, assessing organisms' fitness is far more challenging. Broadly, fitness is the ability of an organism to pass on genes to the next generation (Orr 2009), which can be estimated as the total number of surviving offspring that an individual produces during its life (lifetime fitness). Quantifying lifetime fitness is not feasible in many study systems; as a result, the two central components of fitness, survival and reproductive success, are often measured as proxies (Barker 2009; Pradhan et al. 2015). Survival is frequently assessed using resightings or recapture of individuals within a limited timeframe. Reproductive success tends to be measured as the number of offspring produced within a specific period (e.g., one breeding season). Hypotheses and predictions about the relationship between GCs and fitness will vary depending on the fitness measure being considered, and thus, it is important to clearly identify the fitness component(s) of interest. Here, we use the term fitness to refer to lifetime fitness, and note explicitly when hypotheses distinguish between survival and reproduction.

Several hypotheses have been developed to explain how GCs might relate to measures of fitness (Table 1). Some propose a very direct, consistent relationship between GC concentrations and fitness. For example, the GC-trade-off hypothesis focuses on stress-induced GCs, and proposes that the hormones mediate a life history trade-off between survival and reproduction. It predicts positive relationships between GCs and survival, and a negative relationship with reproduction (Wingfield and Sapolsky 2003; Breuner et al. 2008). The GC–fitness hypothesis proposes that individuals or populations with elevated baseline GCs are facing greater challenges and/or are in worse condition, and therefore will have lower fitness than those with lower baseline GCs (Bonier et al. 2009a). However, for both stress-induced and baseline GCs, the literature indicates that there are positive, negative, and neutral relationships between

Table 1 Hypotheses and models that make predictions about how the physiological measures responses to challenges relate to fitness (organized by the earliest reference date)

Hypothesis	Relevant HPA axis component	Description	Source(s)
Non-adaptive stress	Baseline and stress-induced GCs	Maintaining high GCs for extended periods impairs reproduction and increases susceptibility to disease.	(Selye 1955; Christian 1980; Boonstra and Boag 1992)
Adaptive stress	Baseline and stress-induced GCs	GCs catalyze energy stores, reducing the need to forage, and thereby allow animals to invest more time in reproduction at the cost of survival.	(Lee and Cockburn 1985; Boonstra and Boag 1992)
Alternative coping strategies	Baseline and stress-induced GCs	Selection maintains proactive and reactive coping styles that are associated with different HPA axis reactivity. Which coping style is positively associated with fitness will depend on the environmental conditions.	(Koolhaas et al. 1999; Korte et al. 2005)
CORT-trade-off	Stress-induced GCs	Stress-induced GCs mediate a life history trade-off between survival and reproduction in favor of survival. Although this hypothesis was initially applied to stress-induced GCs, this role has also been proposed for baseline GCs.	(Wingfield and Sapolsky 2003)
Allostasis model	Baseline and stress-induced GCs	Environmental and life history changes can increase the work required to maintain physiological constancy ("allostatic load"). If the energy demand required to maintain homeostasis exceeds available energy, an emergency life history stage is initiated. If the allostatic load is too high for too long, pathological damage can result.	(McEwen and Wingfield 2003)
CORT-fitness	Baseline GCs	Individuals or populations with elevated baseline GCs are facing greater challenges and/or are in worse condition, and therefore will have lower fitness than those with lower baseline GCs.	(Bonier et al. 2009a)
CORT-adaptation (an extension of the CORT–fitness hypothesis)	Baseline GCs	When individuals face challenges associated with reproduction (e.g., feeding offspring), elevated GCs support increased reproductive effort. Thus, individuals with higher or intermediate GC concentrations will have greater reproductive success than those with lower GCs.	(Bonier et al. 2009a)
Reactive scope model	Baseline and stress-induced GCs, negative feedback	Physiological mediators (like GCs) associated with the stress response have a normal range of activity, called the reactive scope. The reactive scope encompasses baseline circulating levels and stress-induced levels in the range that the mediator does not cause damage to the animal. If hormone concentrations go above or below the reactive scope, the animal accumulates mediator-caused damage that could reduce fitness.	(Romero et al. 2009)
Adaptive calibration model	Total physiological response to stressors (sympathetic and parasympathetic nervous system and the HPA axis)	Organisms have evolved stress response systems that are able to be modified during development and throughout life to match their physical and social environments. Thus, individual variation in stress responsiveness is the result of an adaptive process, and is the best possible response for an organism given their previous experiences.	(Del Giudice et al. 2011)
Scope of flexibility hypothesis	Baseline and stress-induced GCs	If individuals that have a greater scope of flexibility (larger range of potential hormone concentrations) are better able to match the optimal endocrine phenotype across diverse conditions, then they will have higher fitness in variable environments.	(Hau et al. 2016; Taff and Vitousek 2016)
Speed of flexibility hypothesis	Baseline and stress-induced GCs, negative feedback, total vs. free GCs	Changes in environmental conditions will result in a mismatch between the optimal and expressed endocrine phenotypes. In moderately dynamic environments, individuals that can more quickly adjust their endocrine phenotype will generally have higher fitness.	(Taff and Vitousek 2016)

the hormones and fitness (reviewed in Breuner et al. 2008; Bonier et al. 2009a; Sorenson et al. 2017). Furthermore, GC–fitness relationships can vary within a single species among years (Ebensperger et al. 2011; Vitousek et al. 2018), life history stages (Bonier et al. 2009b; Fletcher et al. 2015), sexes (Jimeno et al. 2018), or with resource availability (Ebensperger et al. 2011). Therefore, simple

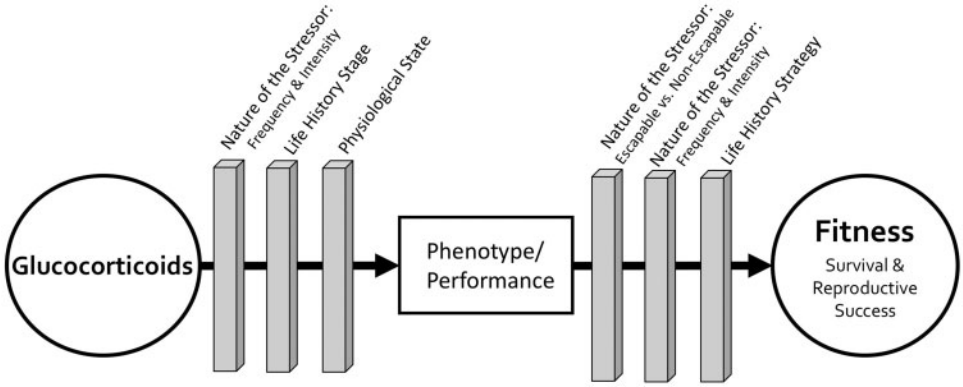

Fig. 1 The relationship between glucocorticoids (GCs) and fitness will depend on (1) factors that affect how GCs influence phenotype and performance and (2) factors that influence the relationship between GC mediated traits and fitness. The effects of GCs on phenotype and performance can vary depending on the frequency and intensity of stressors, the current life history stage (e.g., juvenile vs. adult, breeding vs. nonbreeding), and the animal's physiological state (e.g., starvation, presence of parasite infection). The effect of GC-mediated phenotypes/performance on fitness will depend on whether a stressor is escapable or not, the overall frequency and intensity of the stressors, and life history strategy (e.g., lifespan, value of a reproductive bout).

hypotheses that do not account for context are unlikely to provide realistic, generalizable predictions for GC–fitness relationships (Breuner et al. 2008; Bonier et al. 2009a; Dantzer et al. 2016).

Other hypotheses suggest that GC–fitness relationships will vary across contexts. The GC-adaptation hypothesis, an extension of the GC–fitness hypothesis, considers the type of challenge. It proposes that when individuals face challenges associated with reproduction (e.g., feeding offspring), elevated GCs support increased reproductive effort, and as a result, individuals with higher GC concentrations will have greater reproductive success than those with lower GC concentrations (Bonier et al. 2009a). The most nuanced predictions for variation in the GC–fitness relationship come from the reactive scope model, which allows for consideration of the environmental context as well as seasonal and daily changes in hormone concentrations (Romero et al. 2009). When applied to GCs, this model suggests that individuals have a normal range of GC concentrations called the reactive scope. As long as baseline and stress-induced GCs remain within the reactive scope range, the animal does not suffer damage because of high GC concentrations. The reactive scope of an animal can change seasonally, with life history stages, or with individual quality. Wear-and-tear caused by frequent exposure to stressors can lower the reactive scope, so that stronger or more frequent GC responses are more likely to cause damage. Whenever the reactive scope has a smaller range, greater or longer elevations of GCs are more likely to reduce fitness. Because the safe/healthy range of GCs can change across multiple contexts, so will GC–fitness relationships (Romero et al. 2009; Romero 2012).

Although many researchers have suggested that relationships between HPA axis activity and fitness should vary across contexts, there are few studies that explicitly test when and why we observe variation in GC–fitness relationships. GC–fitness relationships will depend on factors that influence both the way GCs affect phenotype and how GC-mediated phenotypes correlate with fitness (Fig. 1). Here we discuss three major factors that we expect to influence the direction and intensity of the relationship between GCs and fitness metrics: (1) whether the HPA axis-mediated response matches the challenge, (2) the frequency and intensity of challenges, and (3) life history strategy, specifically longevity and the relative value of survival and reproduction for lifetime fitness. We also discuss methods for testing the effects of these factors within and across species.

The match between the challenge and the physiological response

Although animals encounter diverse stressors and participate in many energetically demanding activities, the highly conserved HPA axis responds similarly to a wide range of challenges (Selye 1937). Whether or not the HPA axis helps individuals cope will depend on how well the physiological response and its downstream effects match the challenge. An HPA axis-mediated response to a challenge will only promote fitness if the resulting physiological and behavioral changes enable the animal to successfully escape, avoid, or overcome the challenge. However, if a challenge is inescapable or there is a mismatch between the response and the challenge, then the changes in HPA axis activity are likely to

have either a negative effect or no effect on fitness. In addition, we might also see no relationship between HPA axis activity and fitness if components of physiology and behavior that are most important to maximizing performance are not regulated by GCs. Here we discuss specific examples to illustrate how the relationship between HPA axis activity and fitness depends on the nature of the challenge, focusing on when (1) the challenge is escapable or inescapable, (2) the HPA axis supports a successful response to the challenge and when it does not, and (3) environmental change or range shifts present animals with novel challenges.

The nature of the challenge: can it be escaped, avoided, or overcome?

Mounting a GC stress response is predicted to be relatively more beneficial in organisms facing challenges that can be escaped or mitigated. For example, food limitation or poor body condition are escapable challenges when energetic resources remain available, but become inescapable challenges when both internal and environmental energy sources are depleted. GC concentrations can increase in response to low food availability (Kitaysky et al. 1999; Jenni-Eiermann et al. 2008) or poor body condition (Kitaysky et al. 1999; Moore et al. 2000) and promote survival by both increasing the intensity or efficiency of foraging behavior (Lohmus et al. 2006; Cottin et al. 2014) and mobilizing existing energy stores (Challet et al. 1995; Sapolsky et al. 2000). During starvation, GCs increase both resource mobilization and activity. For example, an experimental study in rats demonstrated that fasted adrenalectomized rats were less active and had lower net protein break-down than controls, but both were restored in adrenalectomized rats treated with GCs (Challet et al. 1995). These actions of GCs (increased locomotion/food-seeking and increased short-term energy mobilization to support this behavior) are likely to increase the ability to cope with food limitation if some food remains accessible (Wingfield et al. 1998; Wingfield 2013). However, when no food is available, the challenge becomes inescapable. In this case, increased energy expenditure and GC-driven energy mobilization from limited, unreplaceable stores could accelerate mortality. As a result, individuals mounting a stronger or longer GC response could have lower fitness. This is the case for Galapagos marine iguanas (*Amblyrhynchus cristatus*) which are at high risk for starvation during El Niño climatic events when their sole food source becomes scarce (Romero and Wikelski 2010). Iguanas that were less able to terminate an acute increase in GCs (i.e., weaker negative feedback) were less likely to survive an El Niño event than iguanas that were better able to downregulate the acute GC response, indicating a cost of maintaining high GCs. When the challenge of low food availability can be overcome, we can observe positive relationships between GCs and performance. However, we are more likely to see negative or neutral relationships if, as with the marine iguanas, the challenge cannot be escaped.

The nature of the challenge: can the HPA axis support phenotypic changes that match the challenge?

The GC stress response is a non-specific response activated by a variety of different challenges to homeostasis. The multifaceted phenotypic changes induced by this response help organisms to cope with and recover from many of these stressors. However, the GC response can also be activated by challenges that are not best dealt with by many of its classic effects (e.g., increased energy mobilization, changes in life history investment). Increases in GC concentrations are more likely to be associated with higher fitness when the physiological and behavioral changes mediated by the hormones match the specific challenges an animal is facing. For example, when amphibian larvae encounter a stressor during metamorphosis, the resulting increase in GCs accelerates the rate of development (Denver 2009). Whether this is adaptive or not could depend on the specific challenges the larvae are facing. When facing pond desiccation, accelerating metamorphosis allows animals to escape the drying environment, and thus GC secretion can increase fitness (Denver 2009). However, accelerating metamorphosis when facing energetically demanding challenges, such as mounting an immune response, may be maladaptive. Because both mounting an immune response and metamorphosis can be energetically costly, larvae that develop more rapidly could be less able to defend against infections (Gervasi and Foufopoulos 2008; Warne et al. 2011). However, these effects are likely to depend on the specific parasite and the magnitude of the GC response (Kirschman et al. 2018). Thus, the HPA-axis response could have remarkably different fitness consequences depending on the challenge.

The activation of the HPA axis in response to social stress—particularly chronic social stress—could also represent a stressor type mismatch. In many species, social challenges result in the

activation of the HPA axis (reviewed in Creel et al. 2013). Yet in most species, social challenges do not represent a direct threat to survival—the situation where an acute GC response is predicted to be the most beneficial. Social challenges can have significant fitness consequences (e.g., when losers are evicted from a social group or their reproductive success declines precipitously); thus, in some cases mounting an acute GC response to social threats could still be beneficial—enabling individuals to mobilize energy needed to face the challenger, or to recover from wounds inflicted during combat. However, in many social species, ongoing conflict can result in the long-term activation of the HPA axis and chronic stress (see reviews in birds [Goymann and Wingfield 2004] and primates [Cavigelli and Caruso 2015]). The impact of social challenges has been well documented in different taxa—for example, GC levels can be chronically elevated in individuals of certain social ranks or at higher population densities (Creel et al. 2013). Likewise, the deleterious consequences of chronic social stress can be profound (Jasnow et al. 2001; Gilmour et al. 2005; Bartolomucci 2007; Archie et al. 2012). For example, social stress is frequently associated with reduced immunity and greater disease risk. In male Syrian hamsters (*Mesocricetus auratus*), both acute and chronic exposure to social challenges resulting in defeat reduce the antibody response to an immune challenge (Jasnow et al. 2001). Similarly, baboons of lower social rank are less able to heal after illness or injury than high ranking baboons (Archie et al. 2012), and lower ranking cynomolgus monkeys (*Macaca fascicularis*) are at greater risk for upper respiratory viral infections than higher ranking group members (Cohen et al. 1997). In all of these examples, greater social stress was also associated with higher GCs. Thus, we predict that highly social species in which social challenges result in the repeated activation of the HPA axis may be more likely to suffer a mismatch between the nature of the stressors to which they are frequently exposed and the activation of this generalized physiological stress response.

The nature of the challenge: novel challenges may increase the likelihood of a mismatch between the challenge and HPA axis response

Human-driven environmental change has created new challenges that can activate HPA axis-mediated changes in physiology and behavior. GCs might be less likely to support a response that matches the challenge because there has been little time for selection to shape physiological responses to novel challenges. There is some evidence that HPA axis activation can have negative consequences in the face of novel challenges (Dantzer et al. 2014). For example, noise pollution alters HPA axis function (Kight and Swaddle 2011) and is associated with lower reproductive success in multiple species (Francis and Barber 2013; Kleist et al. 2018). Similarly, artificial light at night can increase GC concentrations (Ouyang et al. 2015) and have additional physiological consequences, such as an increase in disease prevalence (Ouyang et al. 2017). Although novel challenges such as light and sound pollution can cause animals to change GC concentrations, the HPA axis may not support changes in behavior or physiology that will help them cope (Kight and Swaddle 2011).

The intensity and frequency of challenges

The frequency and severity of stressors may also have substantial impacts on optimal GC responsiveness. In habitats where organisms face intense stressors that are best responded to—at least initially—with elevated GCs, mounting a robust GC response will likely benefit survival (matched stressors, i.e., when the HPA axis response is appropriate to the challenge). In contrast, in relatively benign environments (where the likelihood that the GC stress response will be triggered by a major threat to survival is lower), the cost of mounting a stronger GC response may outweigh its potential benefit. Thus, in risky environments where GCs can support a successful response to the present stressors and/or prime an individual for successful responses to future stressors, we predict a stronger positive relationship between the GC response and survival than in more benign environments. The presence and nature of relationships between the GC response and reproductive success may also be context-dependent. While a robust GC stress response can negatively impact reproduction (Wingfield and Sapolsky 2003), in riskier environments, responding effectively to threats could enable organisms to better maintain ongoing reproductive attempts in addition to increasing their survival (Jaatinen et al. 2014; Vitousek et al. 2018).

Environmental risk is frequently invoked as a driver of GC concentrations (Wingfield 2013; Dantzer et al. 2014), but very few studies have explicitly compared hormone–fitness relationships across populations that differ in risk. The few studies that have directly compared stress responsiveness and fitness in different environments have generally

supported this prediction. Among American redstarts (*Setophaga ruticilla*), stress-induced GC levels positively predict survival in birds overwintering at low-quality sites with limited and unpredictable food availability, but not in more benign environments (Angelier et al. 2009). GC–fitness relationships are also context-dependent in breeding female eiders (*Somateria mollissima*), which are subject to large annual fluctuations in predator pressure. When predation risk is high, individuals that mount a stronger GC stress response have higher hatching success, whereas the opposite relationship is seen under low predation risk (Jaatinen et al. 2014). Comparisons across studies and species are harder to interpret, but findings are generally consistent with the prediction that stronger GC responders have higher survival in riskier environments (e.g., Cabezas et al. 2007; Patterson et al. 2014) and lower survival in more benign environments (e.g., Cabezas et al. 2007; Jimeno et al. 2018). However, patterns can vary. As discussed previously, stronger GC stress responses did not predict the survival of Galapagos marine iguanas during challenging El Niño conditions, but survival was predicted by the ability to terminate the acute GC response (Romero and Wikelski 2010).

Although the fitness benefit of variation in baseline GCs is also likely to be highly context-dependent, we do not predict that baseline GC–fitness relationships will vary consistently across environments based on the level of environmental challenges. In riskier or more energetically demanding environments, elevated baseline GC levels may help organisms to prepare for the challenges that they will face (Lattin et al. 2016, but see Fletcher et al. 2015). In such environments, positive baseline GC–survival relationships may be more common. However, because elevated baseline GCs are also often seen in individuals struggling to cope with challenges, riskier or more demanding environments may be more likely to contain individuals with higher baseline GCs, and lower fitness (Bonier et al. 2009a). Few analyses have directly compared baseline GC–fitness relationships across environments; among those that have, relationships are highly variable. In both risky and benign habitats, baseline GC is unrelated to survival in American redstarts (Angelier et al. 2009). Baseline GCs are negatively associated with reproductive success among eiders breeding in predator-exposed nests, but not at sheltered sites (D'Alba et al. 2011). Similarly, baseline GCs are negatively associated with the reproductive success of female tree swallows (*Tachycineta bicolor*) under poor conditions (low food availability), but not under more benign conditions (Vitousek et al. 2018).

In addition to the relative risk posed by different environments, the frequency with which organisms face major unpredictable stressors, and the duration of these events, may be important factors in predicting GC–fitness relationships. Mounting a stress response is believed to cause wear and tear—often referred to as allostatic load (McEwen and Wingfield 2003) or a narrowing of the reactive scope (Romero et al. 2009). Some animals downregulate their response to acute stressors when they are facing chronic stress, possibly to avoid this wear-and-tear (Jeffrey et al. 2014; Arlettaz et al. 2015). However, more prolonged stressors, or stressors that occur so frequently that they allow insufficient recovery time between stressful events, are more likely to induce pathological damage (e.g., Hau et al. 2015; Raynaud et al. 2015; Valenzuela et al. 2018). Thus, if all else is equal, we predict more negative GC–fitness relationships when stressors are extremely frequent or prolonged. Stressor frequency is also likely to be a particularly important factor shaping selection on negative feedback efficacy (Romero et al. 2009; Romero 2012). For organisms facing severe and frequent stressors, the combination of a robust stress response with strong negative feedback may be particularly beneficial (Breuner et al. 2008; Taff et al. Forthcoming 2018). A related but relatively unexplored concept is the extent to which multiple stressors have interacting effects. Although most conceptual models and experimental studies of GC–fitness relationships focus on single stressors (but see, e.g., Clinchy et al. 2004; Romero et al. 2009), in reality, stressors are often experienced concurrently or in succession, and it has been well-documented that exposure to one stressor can substantially influence the response to subsequent stressors (e.g., through acclimation, facilitation; Romero 2004). A few recent reviews have begun to provide graphical models of the impacts of multiple stressors (Romero et al. 2009; Taff and Vitousek 2016). While we expect the nature of multiple interacting stressors could have significant impacts on GC–fitness relationships, a full predictive framework is beyond the scope of this review because of the complexity of these interacting effects.

Life history strategy: the importance of residual reproductive value and longevity

Life history strategy could drive variation in GC–fitness relationships among individuals, populations,

and species. GCs support transitions between life history stages, underlie phenotypic variation in life history traits, and mediate life history trade-offs (Wada 2008; Crespi et al. 2013; Solomon-Lane et al. 2013; Dantzer et al. 2016); as a result, GCs are inextricably linked to both fitness and life history strategy. At the core of life history theory is the classic trade-off between survival and reproduction (Stearns 1992). Whether individuals prioritize investment in survival or reproduction varies with overall life history strategy (e.g., pace-of-life, r- vs. K-selected species), and with life history traits like sex and age (Stearns 1992). Organisms that prioritize survival will generally have a high residual reproductive value—the potential for successful reproductive bouts in the future. Organisms with limited future reproductive opportunities, or low residual reproductive value, are more likely to prioritize reproduction over survival. Here, we discuss two ways that life history strategy might influence the optimal GC response to challenges: (1) differences in residual reproductive value could alter how GCs mediate the trade-off between survival and reproduction and (2) variation in longevity could change the costs of high GCs. It is important to note that GC–fitness relationships can also vary across life history stages, but this has been discussed in detail elsewhere (Bonier et al. 2009a, 2009b; Vitousek et al. 2018).

Residual reproductive effort may influence the way GCs mediate life history trade-offs

Because the fitness benefits that an individual will accrue by investing in survival and reproduction vary according to their residual reproductive value, the role of GCs in mediating components of fitness could also vary with residual reproductive value (Breuner et al. 2008; Bókony et al. 2009; Hau et al. 2010). If organisms with a high residual reproductive value encounter a challenge, they should allocate resources to ensure survival and future reproductive opportunities, even if it reduces reproductive success in the short term. Therefore, among individuals with a high residual reproductive value, selection might favor those in which GCs shift investment away from reproduction and toward survival, whereas among individuals with low residual reproductive value, selection should nearly always favor those that invest heavily in reproduction. As a result, species, populations, or individuals with high residual reproductive value are more likely to have more positive GC–survival relationships and more negative GC–reproduction relationships than species with low residual reproductive value. Although there are few empirical tests of this hypothesis, there is some evidence that the relationships between GCs and fitness measures follow this pattern. Experimental elevations of GCs in black-legged kittiwakes (*Rissa tridactyla*) caused a decrease in nest attendance and chick survival in populations that have a longer lifespan, and thus higher residual reproductive value (Schultner et al. 2013). In populations with shorter lifespans and lower residual reproductive value, increasing GCs has the opposite effect: an increase in nest attendance and chick survival (Schultner et al. 2013). We need additional evidence to determine if similar patterns exist for endogenous GCs and fitness metrics across life history strategies as well as in response to other acute and long-term challenges.

The negative consequences of high GCs may vary with longevity

If the physiological costs of high GC concentrations are cumulative, high GCs could have more negative consequences for long-lived animals than for short-lived animals. Elevated GC concentrations could result in damage that builds over time through several mechanisms. First, GCs can increase the rate of oxidative damage or oxidative stress and alter telomere dynamics, both of which can be associated with accelerated senescence (Haussmann and Marchetto 2010; Costantini et al. 2011; Angelier et al. 2018). Second, GCs can alter brain physiology and function, and in some cases, cause long-term structural damage (Sapolsky et al. 1990; McEwen 2008). Furthermore, work in a variety of vertebrates has shown that GCs can increase the risk of exposure and susceptibility to parasites (Malisch et al. 2009; Gervasi et al. 2016), and both the resulting infection and immune response can harm host tissues (Graham et al. 2011; Schoenle et al. 2018). The accumulation of damage across time could ultimately reduce both survival and reproductive success, and could come at a higher cost for organisms with greater longevity. Longer-lived organisms will both have more time in which to accumulate costs and their lifetime fitness will be more affected by reductions in survival. We predict that in long-lived animals, higher GCs will be associated with lower survival and reproductive success than in short-lived animals. We know of no studies that explicitly test the relationships between variation in GCs, tissue damage, and fitness metrics among species that vary in longevity or pace of life. Comparative analyses focused on circulating GC concentrations suggest that life history is important to the evolution and expression of the endocrine stress response

(Bókony et al. 2009; Hau et al. 2010). Similar large-scale, comparative analyses of GC–fitness relationships across species will be important for disentangling how life history strategy shapes the endocrine response to challenges.

Conclusions and future directions

One of the most fundamental gaps in our understanding of the endocrine response to stressors relates to when and why we observe differences in the relationships between HPA axis activity and fitness. When studies find that GC–fitness relationships vary across years or the direction of the relationship is unexpected, the results are often attributed to context-dependency. Yet there are few studies that explicitly test how the optimal response to challenges changes with context. As we discuss here, one major context that is largely unexplored is the nature of the stressor, and how fitness changes as stressors vary in the extent to which the HPA axis can support a successful response and whether the stressor can be escaped or mitigated. Experimental manipulations exposing individuals to different stressors and subsequent assessment of HPA activity and fitness measures will help clarify the effect of stressor type. In observational studies, it will be important to consider the specific nature of the challenges individuals are facing and include that information in statistical models. For example, in many group-living primates, both dominant and subordinate males at the extremes of the social hierarchy maintain relatively high circulating levels of GCs relative to middle-ranking males, and that is thought to be associated with their social rank and resulting social interactions (Cavigelli and Caruso 2015). The fitness consequences of high GCs could vary substantially with social status, and thus should be considered when evaluating GC–fitness relationships. Experimental manipulations of stressors would also be helpful in understanding the effects of stressor intensity and frequency, as would comparisons of GC–fitness relationships across environments that pose different challenges. Evaluating the role of life history in influencing these relationships could be achieved by comparisons both within and among species. To date, studies addressing the role of life history have primarily been done within a species, and involve manipulating GCs across groups with different life history strategies (Lancaster et al. 2008; Schultner et al. 2013). Because GC manipulations do not always yield the same effects as comparable levels of endogenous GCs (Fusani 2008), it will also be important to conduct observational studies. Ultimately, we recommend working toward an integrative framework that incorporates the nature, intensity, and frequency of stressors with life history and environmental factors. Empirical studies manipulating stressors and GCs across environments and/or life history stages could provide insight into the complex interactions that may influence GC–fitness relationships (e.g., Gabor et al. 2018). Meta-analyses and cross-species analyses incorporating phylogeny will help us understand how GC–fitness relationships vary on larger scales. Mathematical models that simulate the interactions between GCs, environmental conditions, and organismal traits to predict fitness could be used to test existing hypotheses and identify generalizable patterns for GC–fitness relationships.

Studies addressing the relationship between the endocrine stress response and fitness have almost entirely focused on GC levels, either circulating in the blood or metabolites in feces, fur, or feathers. Other components of the HPA axis—such as corticosteroid plasma binding proteins and the distribution and densities of GC receptors—are often neglected, but could have important effects on fitness (Romero and Wikelski 2010; Breuner et al. 2013; Lattin et al. 2016). For example, receptor number—which can vary among life history stages—influences how tissues respond to GCs, and as a result, can shape how animals cope with challenges (Lattin et al. 2013, 2016). In addition, there is growing interest in measures that describe the dynamic nature of HPA axis activity, including negative feedback and flexibility of the HPA axis. Individuals that can rapidly adjust their endocrine phenotype to match the optimal phenotype for the environment might have higher fitness in dynamic environments (speed of flexibility hypothesis, Table 1) (Taff and Vitousek 2016). Likewise, individuals that can access a greater scope (range) of GC levels might be better able to match the optimal endocrine phenotype under a broader range of environmental conditions (scope of flexibility hypothesis, Table 1) (Taff and Vitousek 2016). A reaction norm approach can be used to measure the endocrine scope across different environmental gradients. Individuals can vary in their endocrine scope (Lendvai et al. 2014; Fürtbauer et al. 2015), but to our knowledge no studies link these reaction norms to measures of survival or reproduction. Measuring endocrine reaction norms requires an intense data collection effort, including repeated measures from individuals across time. As a result, describing the relationships between fitness metrics and endocrine reaction norms is challenging, and not always feasible, particularly in free-living populations. However,

evaluating endocrine flexibility as reaction norms across environments, life history stages, and in response to different challenges will be critical to understanding how selection shapes endocrine traits (Bonier and Martin 2016).

In conclusion, characteristics of both organisms and the challenges they face can have profound effects on the direction and strength of GC–fitness relationships. To understand how selection shapes the endocrine response to stressors, we need to address the ways the HPA axis affects survival and reproduction in specific contexts.

Acknowledgments

We thank the SICB DCE, DAB, DCPB, and DEE divisions and the Company of Biologists for supporting the symposium "Understanding the Evolution of Endocrine System Variation through Large-Scale Comparative Analyses." We thank other members of the HormoneBase Consortium for discussions on this topic.

Funding

L.A.S. was supported by NSF grants IOS-1656618 (to L.B. Martin) and IOS-1656551 (to C.J. Downs). M.N.V. and C.Z. were supported by NSF grant IOS-1457251 (to M.N.V.).

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