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Common myths of glucocorticoid function in ecology and conservation

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Abstract

Glucocorticoids are popular hormones to measure in both biomedical and ecological studies of stress. Many assumptions used to interpret glucocorticoid results are derived from biomedical data on humans or laboratory rodents, but these assumptions often fail for wild animals under field conditions. We discuss five common assumptions often made about glucocorticoids in ecological and conservation research that are not generally supported by the literature. (1) High acute elevations of glucocorticoids indicate an animal in distress. In fact: because glucocorticoids are needed to survive stressors, elevated concentrations often reflect adequate coping. (2) Low glucocorticoid concentrations indicate a healthy animal. In fact: because glucocorticoids are important in responding to stressors, low glucocorticoid concentrations might indicate the lack of adequate coping. (3) Sustained elevated glucocorticoids indicate chronically stressed animals. In fact: glucocorticoid concentrations by themselves have no predictive value in diagnosing chronic stress. (4) Glucocorticoids mobilize energy to survive short-term stressors such as predator attacks. In fact: glucocorticoids' primary impact on energy regulation is to remove glucose transporters from cell surfaces. Not only is this process too slow to provide short-term energy, but glucocorticoid-induced increases in glucose reflect decreased, not increased, glucose utilization. (5) Glucocorticoid measurements in non-blood tissues (e.g., feces, hair, feathers, etc.) are equivalent to blood concentrations. In fact: these alternative tissues present imperfect reflections of blood concentrations, and it is blood concentrations that interact with receptors to evoke biological change. In summary, proper consideration of these common assumptions will greatly aid in interpreting glucocorticoid data from ecological and conservation studies.

KEYWORDS
conservation physiology, corticosterone, cortisol, stress

1 | INTRODUCTION

Stress is a notoriously slippery concept. Although there have been recent attempts to introduce different ways of thinking about stress in ecological contexts, such as allostasis (e.g., Korte et al., 2005; McEwen & Wingfield, 2003) and reactive scope (Blas, 2015; Romero et al., 2009), most researchers continue to rely upon a general consensus model that is derived from extensive research on humans and laboratory rodents (Romero & Wingfield, 2016). Central to this traditional model is that stress derives from a disturbance of homeostasis (Figure 1a). To restore homeostasis, the body initiates a stress response that consists of a suite of behavioral, physiological, and endocrinological responses. One important part of this integrated response is the release of glucocorticoids, cortisol, or corticosterone, depending upon the species. In a healthy animal, the stress response appropriately balances the disruption caused by the stressor and restores homeostasis (Figure 1b). As important as

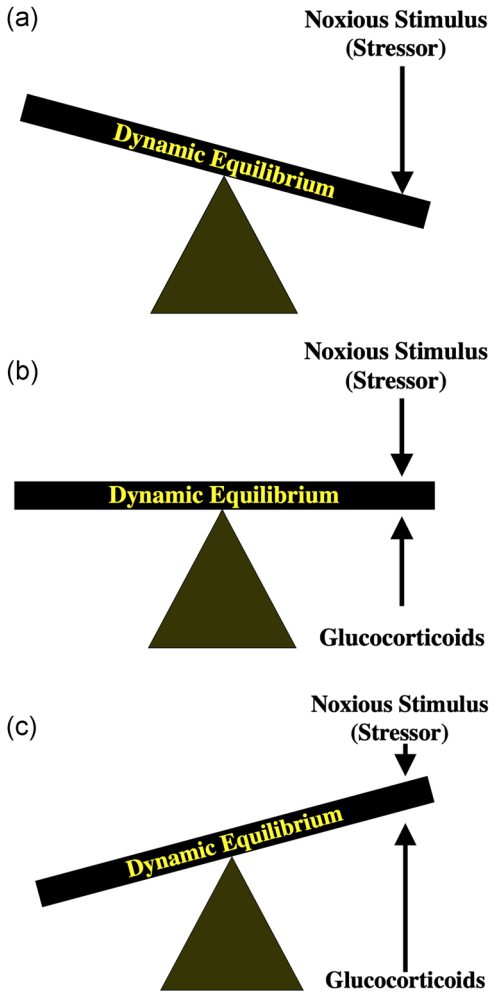

FIGURE 1 Representation of the traditional model of stress. Triangle and bar represent an animal, with a horizontal bar representing an animal in homeostatic balance or dynamic equilibrium. (a) A noxious stimulus, defined as a "stressor," disrupts the animal's dynamic equilibrium. If not corrected, this disruption will result in disease and ultimately death. (b) The stress response in general, and the glucocorticoids specifically, serve to re-establish the animal's dynamic equilibrium. This represents an animal that is adequately coping with the stressor. (c) Chronic stress results when the stress response itself, especially glucocorticoids, are present for too long and/or present in too high concentrations, such that the glucocorticoids themselves disrupt the animal's dynamic equilibrium. This results in stress-induced disease. Figures are adapted from Romero and Wingfield (2016)

glucocorticoids are for counteracting the stressor, however, too high concentrations that are present for too long will also disrupt homeostasis (Figure 1c). The result is chronic stress, or stress-induced disease, where the glucocorticoids themselves become a bigger threat to homeostasis than the original stressor.

Based upon the model above, ecological and conservation researchers became intrigued with the potential of using glucocorticoid titers as a proxy for whether an animal was being exposed to a stressor and an index for the presence of chronically stressed individuals. It has become increasingly clear, however, that the glucocorticoid responses of wild free-living animals do not always match the predictions from the traditional model. New studies do not always incorporate the new data in their interpretations (Vera et al., 2017), leading to the propagation in the literature of several myths of glucocorticoid function.

2 | MYTH 1: HIGH ACUTE ELEVATIONS OF GLUCOCORTICOIDS INDICATE AN ANIMAL IN DISTRESS

The traditional model incorporated extensive biomedical findings that glucocorticoids present in too high amounts or present for too long would result in stress-induced disease. These findings were the primary motivation for depicting chronic stress as in Figure 1c. This made a lot of sense, because humans and domesticated animals rarely run into trouble by having an insufficient response. However, the glucocorticoid increase in response to acute stress is presumed to be necessary to survive a stressor (Sapolsky et al., 2000) and thus serves an adaptive function for wild animals (Wingfield et al., 1998).

Consider the data depicted in the inset to Figure 2. Two populations of animals are tested for their glucocorticoid concentrations and are found to have different concentrations, with Population 1 having lower concentrations than Population 2. These data could be interpreted in two different ways. With Scenario A in Figure 2, Population 1 is having a healthy response whereas Population 2 is having a pathological response. Scenario A is the classic interpretation of data based upon decades of biomedical research. However, Scenario B in Figure 2 is also a possibility. In this case, Population 1 has an insufficient glucocorticoid response to the stressor, whereas Population 2 is having a healthy response. Note that from an ecological or conservation perspective, the conclusions from Scenarios A and B are exactly opposite, and yet Scenario A is generally the default interpretation and Scenario B is infrequently even considered.

Distinguishing between Scenarios A and B often can be quite difficult in studies under natural conditions. As an example, consider two papers recently published on the impact of tourism on marine iguanas (*Amblyrhynchus cristatus*) in the Galapagos. Both papers compared glucocorticoid responses to 30 min of capture and handling in tourist-exposed and undisturbed animals. The initial paper found that tourist-exposed iguanas had lower glucocorticoid concentrations than undisturbed animals (Romero & Wikelski, 2002). In terms of Figure 2, tourist-exposed iguanas correspond to Population 1 and undisturbed iguanas correspond to Population 2. It is unclear, however, how these data should be interpreted. Using Scenario A (Figure 2), tourist-exposed iguanas are the healthy animals and the undisturbed animals are in distress. This interpretation might correspond to the tourist-exposed animals being habituated to human presence (Cyr & Romero, 2009) and therefore coping better with the new human presence of the investigators. In contrast, using Scenario B (Figure 2) leads to the interpretation that the undisturbed iguanas are healthy and the tourist-exposed animals are having an insufficient response to capture and handling. With Scenario B, the iguanas are not coping well with tourism.

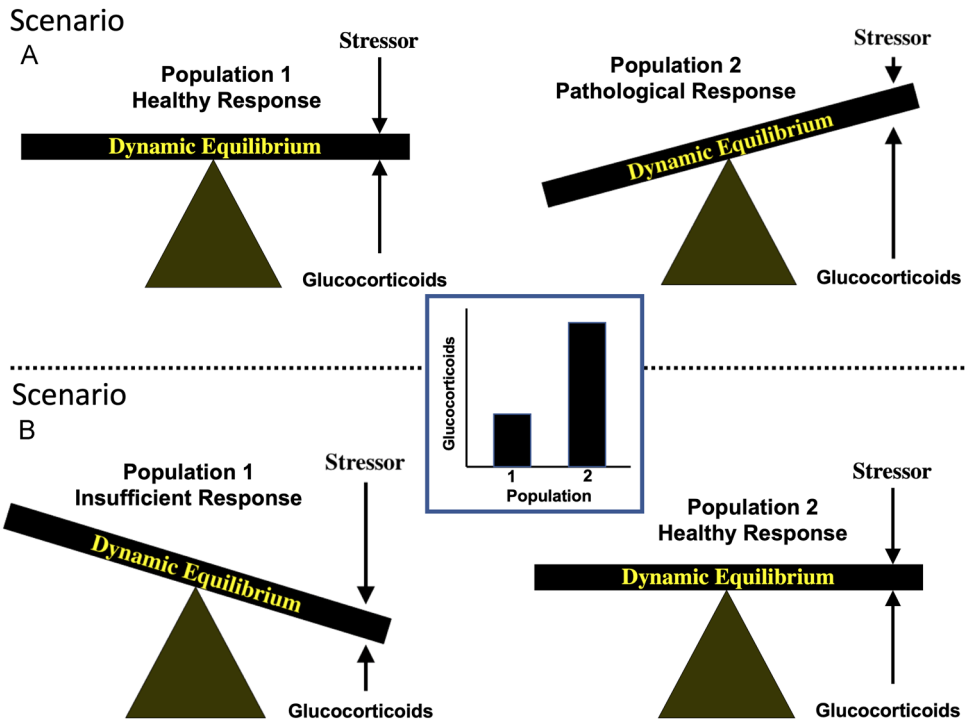

FIGURE 2 Two different scenarios to interpret glucocorticoid data using the traditional model. Representative data from two different populations are presented in the inset. These data could be interpreted with Scenario A, where Population 1 represents a healthy glucocorticoid response and Population 2 represents a pathological glucocorticoid response. Alternatively, these data could be interpreted with Scenario B, where Population 1 represents an insufficient glucocorticoid response and Population 2 represents a healthy glucocorticoid response

Which scenario, A or B, provides a better interpretation of the data is not clear. If we assume that the undisturbed animals show a healthy "normal" response, then Scenario B will be the preferred interpretation. However, "undisturbed-is-healthy" is an a priori assumption that may or may not be justified.

Interpretation becomes even more complicated when we consider the second paper published a few years later. In this case, tourist-exposed iguanas had higher concentrations than undisturbed animals (French et al., 2010). In terms of Figure 2, the populations have now been reversed—Population 1 corresponds to the undisturbed iguanas and Population 2 corresponds to the tourist-exposed animals. Doing the same analysis we did above, interpreting the data through Scenario A suggests that the undisturbed animals are showing a healthy response whereas the tourist-exposed animals are not coping well with tourism. This interpretation would fit well with most people's a priori biases about the impacts of human presence. In contrast, interpretations using Scenario B would suggest that tourism-exposed animals are having a healthy response. This interpretation would fit other data indicating that undisturbed marine iguanas have lost their ability to fully respond to stressors, partly based upon very short flight-initiation-distances that allow potential predators to get lethally close (Vitousek et al., 2010). In this case, exposure to tourists might prime the iguanas to have a more robust and successful stress response.

The two studies above were conducted several years apart and on different islands (and thus different iguana populations), but those differences seem too simple to account for such diametrically opposite data. However, the analyses described above indicate that either scenario from Figure 2 could be used to interpret data from either study—which scenario should be applied to which study is not clear and any specific choice is likely to be based upon preconceived conclusions upon which population represents the "healthy" response. Here lies the problem with Myth 1. Concluding that the population with the higher glucocorticoid concentrations is the population in distress is not supported by theory (Figure 2) or by data (the marine iguana examples).

3 | MYTH 2: LOW GLUCOCORTICOID CONCENTRATIONS INDICATE THAT AN ANIMAL IS DOING FINE

The corollary to Myth 1 is that, if high glucocorticoid concentrations are presumed to be bad for the animal, then low glucocorticoid concentrations must be good. Figure 2 again illustrates the problem. Myth 2 relies exclusively upon Scenario A. Scenario B is not considered. However, the iguana examples cited above again illustrate that Scenario B cannot be easily dismissed and can also provide supportable interpretations.

Interestingly, even though Myth 2 derives from the biomedical literature, there are examples from biomedicine that also do not support this myth. One major example is the Visible Burrow System (VBS). In this experimental design, laboratory rats are housed in multi-male enclosures with all food and water located in a central compartment. One male

quickly comes to dominate access to the food and water, which creates substantial stress in the other, now subordinate, male rats (Blanchard et al., 1995). Intriguingly, however, when these subordinate rats are subjected to restraint stress about 60% show a robust glucocorticoid response. The other 40% show almost no response at all, yet show many other signs of chronic stress (Blanchard et al., 1995). In this case, 60% of the rats correspond to Scenario A in Figure 2, whereas 40% correspond to Scenario B. This is powerful evidence that low glucocorticoid concentrations do not always reflect healthy individuals. Furthermore, in a second example, humans suffering from post-traumatic stress disorder (PTSD) generally have low concentrations of glucocorticoids (Koumantarou Malisiova et al., 2021; Meewisse et al., 2007). In other words, humans with the greatest difficulties coping with stressors often have the lowest glucocorticoid concentrations.

In conclusion, Myth 2 suffers from similar problems to Myth 1. Interpretations that are based on biomedical research do not necessarily apply to wild animals and do not always even apply to biomedical studies. Populations of animals with lower glucocorticoids may in fact be healthier than populations with higher glucocorticoids, but this is not an assumption that should be made a priori.

4 | MYTH 3: SUSTAINED ELEVATED GLUCOCORTICOIDS INDICATE A CHRONICALLY STRESSED ANIMAL

Myths 1 and 2 focused on acute changes in glucocorticoid concentrations, whereas Myth 3 focuses on chronic changes in glucocorticoids. For decades, biomedical research has shown that chronically elevated glucocorticoid concentrations result in many physiological problems, including reproductive dysfunction, metabolic diseases, and immune suppression (Sapolsky et al., 2000). These are the symptoms of chronic stress. A reasonable assumption from these biomedical findings was that wild animals with sustained elevations of glucocorticoids would also show similar physiological problems, and the data mostly support this assumption (Romero & Wingfield, 2016). However, ecologists and conservation biologists then extrapolated from these data to make the reverse assumption. They assumed that chronically stressed wild animals would also have elevated glucocorticoid concentrations, and furthermore, that elevated glucocorticoids could be used as a diagnostic for chronically stressed wild animals.

A recent review tested this assumption (Dickens & Romero, 2013). A literature search revealed 216 studies that examined glucocorticoid concentrations after experimentally exposing animals to sustained and extended stressors to induce chronic stress. The studies spanned a range from highly artificial laboratory studies on domesticated rodents to studies of free-living wild animals in their natural habitats. Furthermore, the 216 studies included work on all five major vertebrate taxa (fish, amphibians, reptiles, birds, and mammals).

The results were very different from the common assumption described above (Dickens & Romero, 2013). Studies that examined changes in baseline glucocorticoids did show a moderate bias toward an increase. Of the 148 studies, 87 documented increases in glucocorticoids, but a substantial minority (47 studies) reported no change with chronic stress, and a small group of studies (18) documented a decrease in glucocorticoids. The situation was even worse with stress-induced glucocorticoids, with 34 studies showing an increase, 34 showing a decrease, and 24 showing no change. The conclusion from these studies is that the literature does not support a generalized glucocorticoid profile for how wild animals respond to chronic stress (Dickens & Romero, 2013). Glucocorticoid concentrations provide no predictive value in determining whether a wild animal is or is not chronically stressed.

The evidence, therefore, indicates that claims that elevated glucocorticoid concentrations indicate a chronically stressed animal do, in fact, constitute a myth. These claims are based entirely on theoretical models derived from biomedicine and not from empirical data from wild animals. Not only will many wild animals suffering from chronic stress show no changes in glucocorticoid concentrations, but decreases may also reflect chronic stress in parallel with the insufficient acute response detailed in Figure 2, Scenario B. Animals with altered glucocorticoid concentrations may be chronically stressed, but the profile will be species-specific and not predictable a priori. A diagnosis of chronic stress requires other corroborating evidence, such as weight loss, changes in fitness, etc.

5 | MYTH 4: GLUCOCORTICOIDS MOBILIZE ENERGY TO SURVIVE SHORT-TERM STRESSORS

It is common in the literature to read statements that glucocorticoids mobilize energy to survive stressors such as predator attacks. The genesis of this claim comes from one of the preeminent physiological outcomes of glucocorticoid increases—the rise of glucose in the blood. Early papers from 60 years ago showed that glucocorticoids stimulated an increase in blood glucose (e.g., Munck & Koritz, 1962), and it made sense that this increase in glucose was intended to provide emergency fuel to working muscles to help survive stressors. However, there are three major problems with this assumption.

First, the time course of glucocorticoid function is not consistent with a role in upregulating blood glucose to help surviving an acute stressor such as a predator attack. A stress response can be divided into immediate and delayed responses (Sapolsky et al., 2000). The immediate response is mediated by the release and actions of catecholamines, epinephrine, and norepinephrine. The catecholamines are released within seconds of the onset of a stressor and one of their main functions is to initiate glycogenolysis, or the breakdown of glycogen (Nonogaki, 2000). Glycogen is the primary short-term storage molecule for glucose and glycogenolysis allows for the immediate production of glucose-6-phosphate. Glucose-6-phosphate is then converted to glucose in the liver, secreted into the blood, and primarily serves to feed the nervous system (Cherrington, 1999), whereas glucose-6-phosphate in muscles is shuttled directly into the glycolytic pathway to produce energy (Nonogaki, 2000; Tank & Wong, 2015). The end result is to quickly mobilize glycogen stores to

get a quick burst of energy. Catecholamines also inhibit insulin release (Taborsky & Porte, 1991) and mobilize fat breakdown (Wajchenberg et al., 2002), further helping to supply energy. The combined effects of the speed of catecholamine release and their major effects on glycogen mobilization make them the preeminent mechanism for providing energy to initiate and sustain a fight-or-flight response—the response most necessary for surviving a short-term stressor such as a predator attack (Romero & Wingfield, 2016).

In contrast to the catecholamines, it takes several minutes in most species before the cascade of the hypothalamic–pituitary–adrenal axis results in measurable increases in blood glucocorticoids (Romero & Reed, 2005). Once glucocorticoids are secreted, they need to interact with receptors to elicit a response. The glucose response elicited by glucocorticoids is thought to result from glucocorticoids binding to intracellular glucocorticoid receptors (GRs) that act as transcription factors to change gene transcription rates (Sapolsky et al., 2000). Although it is possible that glucocorticoid membrane-bound receptors could mediate glucose release (Breuner & Orchinik, 2009), there is, as yet, no evidence that membrane receptors play such a role. When one totals the time to secrete glucocorticoids, the time to travel to target tissues and bind to GRs, the time to initiate transcription, and the time to produce new proteins, a predator attack will be over long before blood glucose begins to rise as a result of glucocorticoid actions.

Second, the extra glucose in the blood does not provide emergency fuel to muscles or the brain. When glucocorticoids bind to GRs, a major protein they induce serves to sequester glucose transporters from the cell membrane (Dimitriadis et al., 1997; Horner et al., 1987). This means that cells that contain GRs (including muscle and brain) take glucose transporters, particularly GLUT4 in mammals, and internalize the transporter so that it is no longer on the cell surface (McCall, 2019). The result is a cell that is taking in much less glucose (Munck et al., 1984). The implications of this response are profound—glucocorticoids regulate blood glucose levels by decreasing cell metabolism. Blood glucose levels rise because cells are no longer using as much glucose, not because the glucose is being preferentially shunted to tissues important to survive predation such as muscles.

Third, glucocorticoids do not always increase blood glucose levels. Most glucocorticoid studies on glucose regulation are performed on fasted individuals. Glucocorticoids are involved in complex pathways and synergies with insulin in regulating blood glucose (Dallman et al., 1993), so experiments with fasted animals were designed to avoid the post-prandial rise in blood glucose to isolate the effects of glucocorticoids. Although this strategy makes a lot of sense, especially in laboratory settings, other studies indicate that glucose regulation is very different in fed animals. Glucocorticoids often fail to alter glucose levels in fed animals (e.g., Remage-Healey & Romero, 2000; Remage-Healey & Romero, 2001). Since predator attacks can occur at any time, even when foraging, wild animals are unlikely to be fasting during every attack. This means that at least some of the time, glucocorticoids are not altering blood glucose levels in response to a stressor.

In conclusion, the premise of Myth 4 is that glucocorticoids are important for increasing blood glucose levels to aid tissues such as muscles and the brain, yet the time course is all wrong, muscle and brain cells have internalized glucose transporters from their surface and are thus unable to take advantage of the elevated glucose, and many times, when animals are fed, the stressor does not even elevate glucose in the first place. Clearly glucocorticoids do not elevate blood glucose to aid in surviving stressors such as predator attacks. If not, then what role does the elevated glucose play? The answer is not entirely clear, but current hypotheses posit that the extra glucose helps the animal recover from the predator attack by replenishing energy stores consumed by the catecholamine response (Romero & Wingfield, 2016), which helps prepare the animal for potential future stressors (Sapolsky et al., 2000). In other words, glucocorticoids are involved in long-term, not short-term, energy maintenance.

6 | MYTH 5: GLUCOCORTICOID MEASUREMENTS IN NON-BLOOD TISSUES (E.G., FECES, HAIR, FEATHERS, ETC.) ARE EQUIVALENT TO BLOOD CONCENTRATIONS

The genesis of this myth seems obvious. Glucocorticoids need to bind to receptors to have any biological effect, and there are no receptors in hair, feathers, and feces. Consequently, concentrations of glucocorticoids in blood and non-blood tissues must correlate for the concentrations in the non-blood tissues to have any biological relevance. The problem is that these correlations are very difficult, if not impossible, to determine from both practical and theoretical grounds.

In terms of theory, consider a typical day in the life of an animal (Figure 3). The animal wakes up with a circadian peak in glucocorticoids, since glucocorticoid concentrations tend to be highest at the beginning of the active phase (Romero & Wingfield, 2016).

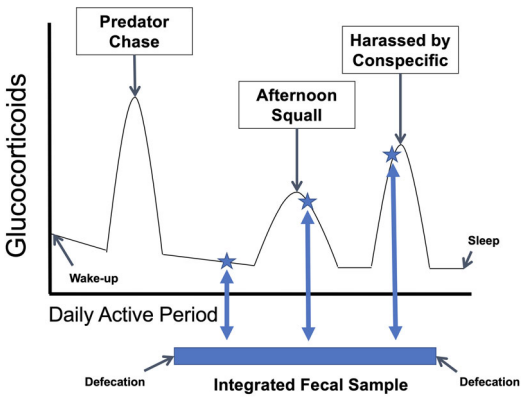

FIGURE 3 Blood glucocorticoid concentrations during a typical day in the life of an animal. Three stressors increase glucocorticoid concentrations during the period from waking up to sleep. The bar below represents a typical fecal sample that integrates glucocorticoid concentrations between two defecation events. Stars represent hypothetical point samples of blood that can be used to correlate blood concentrations with fecal concentrations (represented by arrows)

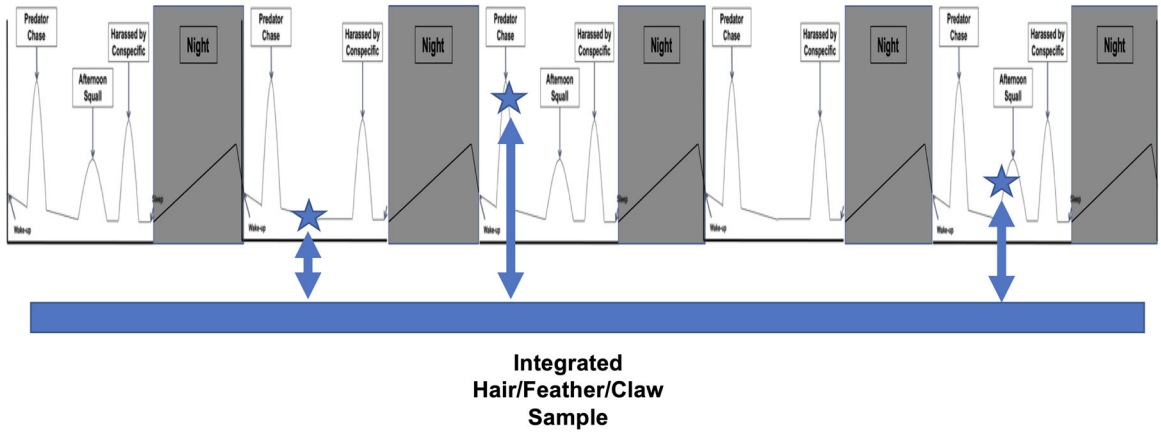

FIGURE 4 Daily fluctuations of blood glucocorticoid concentrations over a 5-day period with various daily stressors typical of a free-living animal. The bar below represents a typical hair, feather, or claw sample that integrates glucocorticoid concentrations while growing. Stars represent hypothetical point samples of blood that can be used to correlate blood concentrations with hair, feather, or claw concentrations (represented by arrows)

Concentrations slowly decrease from that circadian peak until the animal is chased by a predator. The predator chase elicits a large intense glucocorticoid response, but the animal escapes and the glucocorticoid concentrations quickly recover. Glucocorticoid concentrations continue to stay low until a brief afternoon squall elicits another rise in glucocorticoids, this time lower than the response to the predator but lasting for a longer period. Another intermediate rise occurs when the animal experiences a social stressor, but that quickly decreases to the circadian trough just as the animal goes to sleep. In sum, the animal experience three stressors of varying intensity and duration during this typical day.

We can then assume the animal defecates late in the day and the fecal sample is collected by a researcher (Figure 3). The glucocorticoids contained in that fecal sample are an integration of blood concentrations between defecations (Goymann, 2012). Consequently, it is unclear when a blood sample should be taken to correlate blood and fecal concentrations. Consider the three different blood samples represented by the stars in Figure 3. Each sample was taken at different times during the day when the animal was experiencing different stressors. The fecal sample will integrate these three concentrations (as well as the concentrations throughout the inter-defecation period), but will not correlate with any individual blood sample. In fact, Figure 3 indicates that it would be illogical to expect any point sample to correlate with an integrated measure. As an analogy, only by chance would a measurement of rainfall on a single random day correlate with the average daily rainfall for the month. Consequently, from a theoretical perspective, it makes little sense to try to correlate fecal and blood concentrations.

In addition, practical concerns make any connection of fecal to blood glucocorticoid concentrations even more complicated. There is a species-specific time lag before elevated blood glucocorticoids become apparent in the feces, a nuance simplified in Figure 3. Furthermore, fecal content can be altered by numerous processes that do not affect blood concentrations. For example, the water content in the food will alter defecation rates, with longer or shorter periods between defecations providing longer or shorter times for glucocorticoid metabolites to be deposited in the feces, resulting in higher or lower apparent fecal glucocorticoid levels, respectively (Morrow et al., 2002). In another example, bacteria in the gut can modify glucocorticoid metabolites long after the steroids leave the blood, leading to altered apparent concentrations in the feces (Goymann, 2012). The net effect of these processes is substantial variation between different defecations even in animals in controlled environments. In fact, earlier work suggested that even when animals were experiencing no obvious stressors, a minimum of three fecal samples were required to compensate for this variability (Hirschenhauser et al., 2005), something that is rarely done in the literature.

The situation is even worse when considering other biological tissues such as hair, feathers, or claws. Instead of hours between fecal defecations, hairs, feathers, and claws integrate blood glucocorticoid concentrations over days, weeks, and months (Baxter-Gilbert et al., 2014; Heimburge et al., 2019; Romero & Fairhurst, 2016). Figure 4 extends Figure 3 from 1 day to 5 days. Although this is still too short for many of these tissues to complete growth, the problem becomes apparent. Similar to the problem with correlating blood and fecal samples, it is not clear when to take blood samples to correlate with hair, feathers, or claws. Three potential point samples of blood are provided in Figure 4, but none of them will accurately correlate to the integrated measure.

In addition to these theoretical concerns, there are practical issues about correlating glucocorticoids from these tissues as well. For example, field studies rarely sample animals outside of their active period, primarily because active animals are most easily trapped. However, substantial circadian changes in glucocorticoids occur during the inactive period which presumably will contribute to the integrated measure but will not be captured from the blood during normal sampling (Figure 4). In a second example, most studies on hair and feathers rely upon immunological assay techniques for

measurement. Recent work indicates that different antibodies, often associated with different commercial assay kits, provide different glucocorticoid measurements from the same hair (Jewgenow et al., 2020) or feather (Fischer et al., 2021). These are concerns that still need to be resolved.

In conclusion, it remains vital to correlate glucocorticoid concentrations in non-blood tissues with blood concentrations, because it is the blood concentrations that are biologically active. How to makes these correlations, however, is not presently known, but it is clear for both theoretical and practical reasons that taking a "snap shot" from a blood sample is not sufficient.

7 | CONCLUSIONS

As the prior discussions should make clear, glucocorticoid dynamics are very complicated. In summary, stress responses are highly variable within an individual and between individuals, the context of when a stressor occurs (e.g., whether the animal is fed or fasted) can alter the physiological impact of glucocorticoids, and even how to measure glucocorticoids is often unclear. The five myths discussed here primarily derive from simplistic interpretations and extrapolations from these complicated dynamics. The myths also partially derive from reliance on older literature, with current research often doing a poor job of incorporating recent advances in glucocorticoid theory and physiology (Vera et al., 2017). To avoid relying upon these myths, researchers need to embrace the complexity of glucocorticoid physiology. Critical to this process is to recognize that glucocorticoid physiology can be both species- and context-specific, as well as remembering that glucocorticoids are only part of the stress response and have other important non-stress functions as well (MacDougall-Shackleton et al., 2019).

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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