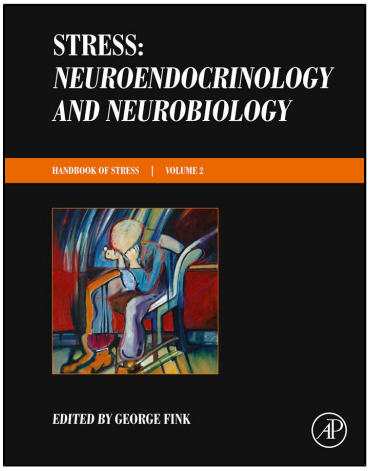

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CHAPTER

42

Seasonal Rhythms

L.M. Romero, C.M. Bauer, R. de Bruijn, C.R. Lattin

Tufts University, Medford, MA, United States

OUTLINE

Abstract

Many free-living species show seasonal rhythms in baseline and stress-induced glucocorticoid release. Glucocorticoid titers, as well as glucocorticoid-binding proteins (CBG) and intracellular glucocorticoid receptors, vary with different life history stages over the course of the year. Concentrations are often highest during breeding. Seasonal glucocorticoid rhythms appear to be regulated by a mixture of hypothalamic, pituitary, adrenal, and glucocorticoid feedback mechanisms. Three hypotheses have been proposed to explain why seasonal glucocorticoid rhythms exist: to mediate seasonally different energetic needs, to initiate seasonally appropriate stress-induced behaviors, and/or to prepare for subsequent stressors whose frequency varies seasonally. Future work distinguishing between these hypotheses will help us understand how seasonal glucocorticoid rhythms likely aid the short-term survival of free-living animals. Finally, biomedical studies that ignore seasonal variation in glucocorticoid responses miss the rich variation in these responses that likely affect humans as well.

EVIDENCE FOR SEASONAL GLUCOCORTICOID RHYTHMS

Glucocorticoid secretion in response to noxious stimuli is so common that it is often used as a working definition of what stimuli are stressors. In a laboratory setting, the magnitude of glucocorticoid secretion to stressors applied in similar circadian, developmental, and psychological contexts within the same species is remarkably consistent despite individual variation. In the majority of free-living species studied to date, however, glucocorticoid release is modulated seasonally.[23] In other words, the magnitudes of both basal and stress-induced glucocorticoid concentrations vary throughout the year. An example, for white-crowned sparrows (*Zonotrichia leucophrys*), is presented in Fig. 42.1.

In studies of free-living wild animals, glucocorticoids are measured by directly sampling from freshly caught individuals. Because glucocorticoids start to increase 2–3 min after initiation of a stressor, plasma samples collected within a few minutes of capture are assumed to reflect prestress, or baseline, glucocorticoid concentrations. These initial samples are usually referred to as "baseline" rather than "basal" because the immediate past history of a wild animal is rarely known, thereby making a true basal sample, as defined in laboratory

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studies, impossible. Stress-induced glucocorticoid concentrations then reflect the animal's response to capture, handling, captivity, etc. and are assumed to be a measure of the hypothalamic-pituitary-adrenal (HPA) axis's ability to respond to a stressor. This "capture-stress" protocol can then be used to compare glucocorticoid responses across individuals, species, and seasons.[33]

These studies provide clear evidence that a majority of reptilian, amphibian, avian, and mammalian species seasonally modulate glucocorticoid concentrations.[23] Males and females of the same species sometimes differ in whether they show seasonal rhythms, and occasionally a species will show a seasonal rhythm in baseline but not stress-induced glucocorticoid concentrations (or visa versa). However, approximately 75% of all species that have been studied have at least one sex with a seasonal rhythm of glucocorticoid release.

The evidence for an annual glucocorticoid rhythm is generally much stronger for baseline than stress-induced concentrations, primarily because more studies have focused on this time point. Furthermore, avian species often show a seasonal rhythm in baseline but not stress-induced glucocorticoid concentrations, suggesting that baseline and stress-induced glucocorticoid concentrations are regulated differently. Laboratory studies indicate that baseline and stress-induced glucocorticoids have different regulatory mechanisms and serve different physiological functions that are mediated by separate receptors (e.g., Ref. 6). It is not surprising, therefore, that the HPA axis might be regulated differently under baseline and stress conditions and that these separate regulatory pathways can show different annual cycles.

Of those species that do show a seasonal rhythm, the seasonal peak is usually during the breeding period. There are three notable caveats. First, the most robust rhythm in birds is a nadir during the prebasic molt when they replace their feathers. The effect is often very pronounced, with many animals essentially failing to secrete glucocorticoids during molt (Fig. 42.1). This is thought to protect the bird from the protein catabolism effects of glucocorticoids during the protein mobilization of feather replacement.[7] The current hypothesis is that the downside for long-term survival of glucocorticoid-induced degradation of growing feathers outweighs any short-term survival benefits of secreting glucocorticoids in response to an acute stressor. Second, desert-breeding birds show a seasonal glucocorticoid peak concurrent to the rainy season, suggesting that seasonal rhythms can be timed to seasonal environmental cues as well as seasonal physiological cues (e.g., Refs. 8,35). Third, even though most mammal species show a seasonal rhythm, there is no consensus season when mammals tend to have elevated glucocorticoid concentrations.[23] This may result from the often-dissociated timing of mate selection, copulation, pregnancy, and lactation. A systematic study of the impact of these different life history periods on seasonal glucocorticoid release has not yet been attempted for wild free-living mammals.

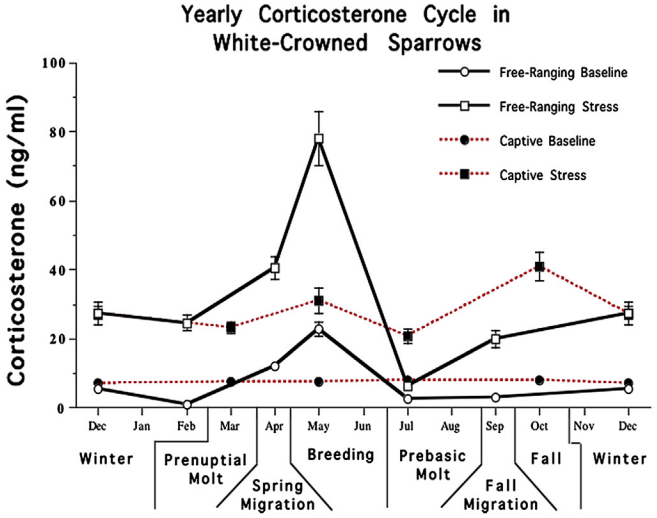

FIGURE 42.1 Seasonal rhythm of baseline and stress-induced corticosterone from free-living and captive white-crowned sparrows. *Reprinted with permission from Romero LM, Wingfield JC. Alterations in hypothalamic-pituitary-adrenal function associated with captivity in Gambel's white-crowned sparrows (*Zonotrichia leucophrys gambelii*).* Comp Biochem Physiol. *1999;122B:13–20.*

KEY POINTS

- There is increasing evidence that glucocorticoids, and their regulatory system the HPA axis, show annual rhythms in free-living species.
- Glucocorticoids are thought to modulate the response to environmental changes, and as such are expected to adapt to seasonal changes in energy needs, behavioral responses, and exposure to stressors.
- To further our understanding of how glucocorticoids help animals survive, there is a need for a cohesive hypothesis that integrates the different aspects of glucocorticoid physiology, and has explanatory power across all life history stages.
- Seasonal modulation of glucocorticoids often disappears in captive and domesticated animals, which is important to consider when working with laboratory models of stress.

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Many wild species held in long-term captivity also show seasonal rhythms, but these rhythms do not usually match what is found in free-living animals (e.g., Ref. 9). This likely reflects that both domestication and captivity alter HPA axis function in ways that are different for each species, making it difficult, if not impossible, to ascertain natural annual variation from these populations.

EVIDENCE FOR SEASONAL RHYTHMS DOWNSTREAM OF GLUCOCORTICOID RELEASE

Glucocorticoid release is only one aspect of glucocorticoid physiology. After release, the steroids must be transported to the target tissues and bind to the appropriate receptors in those tissues. The impact of glucocorticoids on the animal is an integration of these three steps (release, transport, receptor binding), as well as others.[32] Seasonal changes in glucocorticoid-binding globulins (CBGs), mineralocorticoid receptors (MRs), and/or glucocorticoid receptors (GRs), could potentially augment or counteract any seasonal variation in glucocorticoid titers. Current evidence suggests that these aspects of glucocorticoid function do indeed vary seasonally, but the overall impact of these changes is not yet clear.

The capacity of CBG has been found to vary seasonally and to be regulated by gonadal testosterone.[4] Free steroids, the glucocorticoids unbound to CBG, are able to diffuse across cellular membranes and bind to intracellular receptors and thereby initiate physiological changes. This implies that free steroid concentrations may be more biologically relevant than total steroid concentrations.[2] CBG titers often increase or decrease in parallel to glucocorticoid titers, so that when total and free steroid concentrations are compared, the seasonal rhythm in total glucocorticoids often changes or disappears entirely.[2] On the other hand, CBG may act as a long-term reservoir that can extend glucocorticoid availability.[18,30] If CBG does primarily act as a reservoir, increases in CBG that parallel glucocorticoid increases would thereby augment glucocorticoid access to receptors. Current research is attempting to distinguish between these possibilities.

There are also seasonal changes in the density of GR and MR in different target tissues, although when the peak in receptor density occurs appears to be tissue-, species-, and even population-specific.[3,12,16] Receptor concentrations do not track glucocorticoid titers in a straightforward manner—that is, receptor density is not merely low when hormone titers are high, nor are receptor concentrations always high when plasma hormone levels are high. One set of studies examined seasonal patterns in GR and MR binding in 13 different tissues of wild-caught house sparrows and found only two overall patterns across different tissue types.[15–17] First, GR was more likely to show seasonal modulation than MR. Second, receptor concentrations in several tissues peaked immediately prior to breeding. Increased or decreased receptor density during certain times of the year may be due to animals' needs to augment or moderate glucocorticoid effects on specific tissues during different life history stages. Studies in a wider range of free-living animal species should help clarify how seasonal modulation of downstream components of the HPA axis alters the effects of seasonally varying plasma hormones.

MECHANISMS REGULATING ANNUAL RHYTHMS OF GLUCOCORTICOIDS

Progress is just beginning in understanding how HPA axis function is regulated seasonally. What induces these changes, be it photoperiod, temperature, food availability, etc., is currently unknown. Plasma glucocorticoid concentrations often are correlated with adrenal mass, and early studies showed increases in adrenal mass during breeding (e.g., Ref. 31). Consequently, the ability of adrenal tissue to respond to ACTH changes seasonally. A few studies in birds indicate that there are multiple regulatory points in the HPA axis. Some species seasonally regulate glucocorticoid release from the adrenal, others seasonally regulate ACTH release from the pituitary, and still others regulate CRH and arginine vasotocin (the avian congener of arginine vasopressin) release from the hypothalamus.[23] There is also some evidence that the efficacy of negative feedback changes seasonally.[14] These regulatory control points may be related to how sensitive each species is to adverse environmental conditions.[26]

Glucocorticoids also interact with the gonadal system. Although glucocorticoids inhibit gonadal hormone release, exogenous testosterone elevates glucocorticoids in at least one free-living bird species.[29] This suggests a complex interaction between the gonadal and adrenal systems, with glucocorticoids downregulating gonadal androgen release concurrent with gonadal androgens elevating glucocorticoid release. Gonadal androgens, therefore, could potentially be an important physiological regulator of seasonal glucocorticoid rhythms.

WHY DO SEASONAL GLUCOCORTICOID RHYTHMS EXIST?

Modulation of glucocorticoid release presents us with an interesting paradox: if glucocorticoid release is so important for survival, then how do animals survive stressors at certain times of the year when they essentially fail to release glucocorticoids (see Fig. 42.1)? Three major hypotheses have been proposed to explain seasonal glucocorticoid rhythms (Fig. 42.2).

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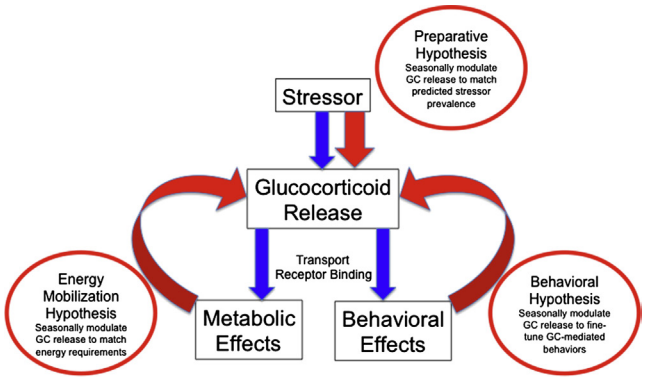

FIGURE 42.2 Summary of the three major hypotheses proposed to explain why glucocorticoids vary seasonally. The standard response to a stressor is depicted in blue and the proposed regulatory mechanisms are depicted in red. *GC*, glucocorticoids.

1. The Energy Mobilization Hypothesis focuses on the metabolic effects of glucocorticoids. Glucocorticoids play an important role in energy mobilization, especially during chronic stress,[28] so glucocorticoid concentrations should be highest during energetically costly times of the year. Under this hypothesis, high glucocorticoid concentrations during breeding result from breeding exerting the highest energetic demands during the year. Females of many species, for example, expend substantial energy during breeding, and breeding males of many species have increased energy costs associated with testosterone and territorial defense. Moreover, increased energy mobilization could explain seasonal peaks during nonbreeding periods if these periods are more energetically costly than breeding.
Two examples, however, mammalian hibernation and avian molt, highlight the insufficiency of the Energy Mobilization Hypothesis in providing a universal explanation for seasonal glucocorticoid rhythms.[23] Hibernating mammals require dramatically increased fat stores to survive the winter, but it is not clear that these energy requirements for accumulating and depositing these fat stores are greater or less than lactation. Furthermore, the Energy Mobilization Hypothesis would predict that hibernators that accumulate fat would have higher glucocorticoid titers than hibernators that rely upon cached food, but data suggest the opposite may be true.[25] Second, feather replacement during molt in birds requires substantial energy expenditure,[20] yet this period is the nadir of the annual rhythm. The Energy Mobilization Hypothesis can be a powerful explanatory mechanism for certain species during some times of the year, but it clearly is insufficient to fully explain seasonal glucocorticoid rhythms.

2. The Behavior Hypothesis focuses on glucocorticoid's behavioral effects (Fig. 42.2). It posits that annual glucocorticoid rhythms result from different requirements for expressing (or not expressing) glucocorticoid-mediated behaviors at different times of the year. For example, an important glucocorticoid-mediated behavior in wild animals might be fleeing an area and relocating during storms. This may be an excellent strategy for most of the year, but could be catastrophic for an individual's overall fitness when relocation requires abandoning young. Consequently, the Behavior Hypothesis suggests that the need to seasonally regulate the expression, or nonexpression, of those behaviors drives glucocorticoid rhythms.
There can also be subtle differences between species. There is good evidence that the degree of parental care in birds negatively correlates with baseline glucocorticoid concentrations.[1] In addition, short-lived species with few potential breeding attempts tend to have lower glucocorticoid concentrations than long-lived species that have many potential breeding opportunities.[11] Alternatively, species with limited breeding opportunities appear to decouple glucocorticoid release with glucocorticoid impact on the reproductive system.[33] Extreme examples of this include species that have only one breeding attempt in their lifetimes, such as several salmon species, where glucocorticoid concentrations are extraordinarily high yet breeding progresses as normal, but there are many less extreme examples.[34] Studies on glucocorticoid effects during breeding led to the proposal of the Brood Value Hypothesis[1] that posits that individuals will modulate glucocorticoid responses depending upon how many broods they likely have remaining during their life. Individuals will upregulate glucocorticoid release, and thus bias personal survival, with many remaining reproductive attempts, whereas individuals will downregulate release, and thus bias offspring survival, with few remaining reproductive attempts.
The Behavior Hypothesis, however, does not fit a more general annual rhythm in glucocorticoid concentrations. Glucocorticoid titers are highest in most species during breeding (e.g., Fig. 42.1), exactly when glucocorticoid concentrations should be lowest if seasonal glucocorticoid rhythms were primarily to regulate the behavioral consequences of glucocorticoid release. Consequently, this hypothesis may be useful in explaining modulation of glucocorticoid concentrations within a single season, but not across seasons.

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3. The Preparative Hypothesis focuses on the coordinating aspects of glucocorticoid physiology and posits that seasonal rhythms in glucocorticoid concentrations serve to modulate the priming of other stress pathways during periods with different potential exposure to stressors (Fig. 42.2). Glucocorticoids are only one part of the stress response. Other hormones (especially epinephrine and norepinephrine), neurotransmitters (e.g., 5-HT, CRH), opioid peptides, cytokines (e.g. IL-6), as well as other brain functions, exert their effects rapidly with the onset of stress without involving the pituitary or adrenals. However, glucocorticoids have a permissive effect on many of these systems and thereby facilitate better performance under stress. Higher baseline glucocorticoid concentrations may augment the priming effects on these systems in preparation for further stressors. This is the traditional explanation for timing the circadian peak for the beginning of the active period. These permissive effects may help prepare the organism for subsequent stressors.

If the Preparative Hypothesis is correct, higher glucocorticoid concentrations should coincide with seasons where animals can predict that stressors will be more likely to occur. The available data fit this prediction moderately well. The risk of exposure to many stressors in wild animals likely varies seasonally. During the breeding season, for example: predation risk may increase when caring for young; competition for mates, with the risk of frequent fights, increases during breeding; and disease may become more prevalent when breeding individuals congregate. Consequently, glucocorticoid concentrations may vary seasonally in order to mediate changes in preparedness in the nonglucocorticoid pathways of the stress response. Evidence for the Preparative Hypothesis is slowly building (e.g., Ref. 25).

The three explanatory hypotheses presented above are derived from different aspects of glucocorticoid physiology (Fig. 42.2). The Energy Mobilization Hypothesis emphasizes glucocorticoid's metabolic effects in compensating for increased energetic demands, or the allostatic load, experienced by the animal. The Behavior Hypothesis emphasizes the desired acute behavioral effects of glucocorticoids, specifically the importance of avoiding stress-induced behaviors that will interfere with breeding. The Preparative Hypothesis emphasizes the regulatory role glucocorticoids have in preparing other stress systems for times of the annual cycle when there is a high likelihood of experiencing stressors. Integrating these hypotheses into a cohesive physiology will provide the foundation for understanding how elevated glucocorticoid concentrations aid in survival.

AVIAN MIGRATION: TESTING SEASONAL GLUCOCORTICOID RHYTHM HYPOTHESES

Migratory birds undergo two migrations per year: a fall migration to wintering grounds and a spring migration to breeding grounds. While birds travel the same total distance during both migrations, spring migration is usually faster with fewer stops in between. Therefore, we can assume that spring migration is more energetically expensive than fall migration (Fig. 42.3). Because inclement weather and low food availability are more common during spring migration, we can also assume that migrants have an increased chance of encountering predictable stressors during spring versus fall migration (Fig. 42.3).

In general, migratory birds tend to have higher corticosterone (CORT) levels at stopover sites during spring migration compared to fall migration.[21] We ask which of the three seasonal glucocorticoid hypotheses best explains this pattern:

The Energy Mobilization Hypothesis predicts that baseline CORT is highest during energetically expensive times of year. Therefore, we would expect baseline CORT to be higher during the spring stopovers and that high baseline CORT during spring migration enhances hyperphagia and fat deposition. However, the majority of lab and field studies have not found a positive effect

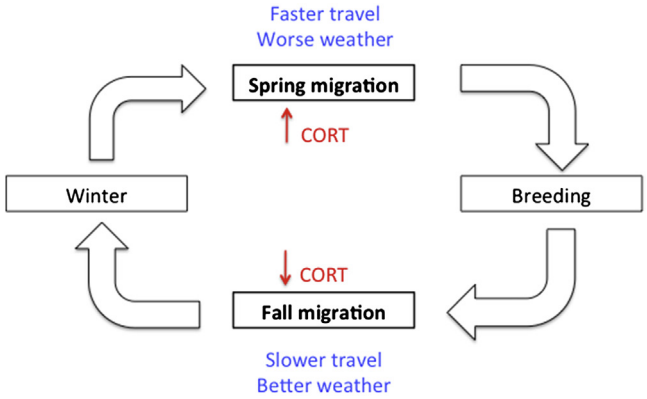

FIGURE 42.3 Seasonal schedule for migratory birds. Compared to fall migration, spring migration is often faster and more direct since early arrival to breeding grounds is advantageous. Because of this, spring migration can be considered more energetically expensive than fall migration. Inclement weather and low food availability are also more common during spring vesus fall migration. Therefore, migrants are more likely to encounter predictable stressors during spring migration than fall migration. The majority of studies have found that corticosterone (CORT) levels are higher in migrants during spring versus fall stopovers.

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of baseline CORT on food intake and lipogenesis in migrating birds.[10,22]

The Behavior Hypothesis predicts that CORT is highest during the times of year when glucocorticoid-mediated behaviors increase survival, as glucocorticoids can have permissive effects on survival-promoting behaviors, such as fleeing severe storms. While high CORT during spring migration might help birds prioritize survival over reproduction before significant reproductive investment has occurred, increased CORT might also delay arrival to breeding grounds, which can result in reduced reproductive output. Therefore, the Behavior Hypothesis makes no clear a priori predictions about CORT levels during spring versus fall stopovers.

The Preparative Hypothesis predicts that CORT is highest during times of year when predictable stressors are more likely. Therefore, we would predict that CORT is higher during spring stopovers, as there is a higher chance of encountering inclement weather during spring versus fall migration. In conclusion, the Preparative Hypothesis best explains seasonal patterns in migratory CORT levels, but this has yet to be empirically tested and will need confirmation that migratory CORT levels are not intermediate points during life history stage transitions (see Fig. 42.1).

ADAPTIVE SIGNIFICANCE

Proper concentrations of glucocorticoids seem crucial for survival. Too little and even mild stressors will kill animals, but too much can lead to suppressed gonadal and immune function, and ultimately disease. Consequently, a balance must be struck between needing glucocorticoids to survive stressors and modulating glucocorticoid secretion to prevent deleterious exposures. What is becoming clear is that there is a seasonal rhythm in what is the "right amount" of glucocorticoids. Understanding why the "right amount" changes seasonally will help us understand why glucocorticoids are released, both basally and during stress, and how they help animals survive.

Seasonal variation in glucocorticoid concentrations, however, presents two challenges to our understanding of the role of glucocorticoids in the stress response. The first challenge is to the major assumption that release of glucocorticoids helps animals survive stressors.[28] For many species, there is a period during the year when glucocorticoids have a dramatically damped response to stressors. Whether or not this damped response threatens survival is currently unknown. The second challenge is in understanding why glucocorticoid titers are usually at their seasonal peak during the breeding season. Breeding often requires substantial energetic resources, which fits with newer concepts of allostasis, reactive scope, and especially allostatic load, as explanations of glucocorticoid release.[19,24] However, there are other energetically costly periods during the annual cycle that are not coincident with elevated glucocorticoids. A better understanding of these seasonal changes is likely to lead to a better understanding of why glucocorticoids are secreted during stress.

IMPORTANCE FOR BIOMEDICAL RESEARCH

Species routinely adjust their physiology to cope with different life history stages (e.g., pregnancy, migration, hibernation) and it is perhaps not surprising that seasonal adjustments in glucocorticoid release and function occur as well. In fact, it appears to be a general phenomenon shared by many free-living species. However, much of this rich seasonal variation in responses disappears when animals are brought into captivity, likely masked by the chronic stress of captivity itself (see example in Fig. 42.1; Ref. 5). Furthermore, domestication can exert profound effects on HPA function, including glucocorticoid release (e.g., Ref. 13). This could have an impact on many common laboratory models of stress, including studies on laboratory rodents. Focusing solely on a 12:12 light:dark cycle, as is the default light cycle for housing most laboratory animals, will provide only a partial view of the role of glucocorticoid release during a stress response. Without an understanding of the natural seasonal variation in glucocorticoid release, it will be difficult to integrate glucocorticoid titers into a full picture of the physiology of a species.

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