Regulatory Mechanisms that Underlie Phenology, Behavior, and Coping with Environmental Perturbations: An Alternative Look at Biodiversity

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PERSPECTIVES IN ORNITHOLOGY

REGULATORY MECHANISMS THAT UNDERLIE PHENOLOGY, BEHAVIOR, AND COPING WITH ENVIRONMENTAL PERTURBATIONS: AN ALTERNATIVE LOOK AT BIODIVERSITY

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OVER ONE HUNDRED years of laboratory research on highly inbred model organisms has greatly advanced our knowledge of how regulatory networks such as the endocrine system work at the cellular and molecular levels. However, an understanding of how these systems play a vital role in mediating the effects of environmental change on morphology, physiology, and behavior must rely on investigations of organisms in their natural environments. To achieve this has meant integrating laboratory and field investigations wherever possible. Field endocrinology, in which free-living birds are captured and sampled for blood, feces, or feathers, has allowed us to assess for the first time how individuals respond to their physical and social environments under natural conditions (Wingfield and Farner 1976, Möstl et al. 2005). Controlled experiments have also made it possible to manipulate hormonal state (Ketterson and Nolan 1999, Ketterson et al. 2009) or social environment (Wingfield et al. 1999) to further expand our understanding of regulatory mechanisms in ecological context. Here, I discuss how regulatory mechanisms, in relation to seasonal events such as breeding, migrations, or environmental perturbations, can have diverse levels of control that we are only beginning to appreciate. Three examples will address territoriality in different seasonal contexts, adrenocortical responses to stress, and thyroid hormone involvement in control of the life cycle.

There is now an urgent need to understand regulatory mechanisms, in the face of massive global changes resulting from anthropogenic influences. For example, loss of biodiversity globally is without doubt one of the biggest issues of our time. Yet we are just beginning to understand how knowledge of the interrelationships among phylogeny, gene–environment interactions, and function may help to facilitate the preservation of remaining biodiversity. Within phenotypes, cells respond in diverse ways to changes in the internal and external environment according to time of day, season, social interactions, and, thus, in how they cope with perturbations. In vertebrates these responses involve perception of the environment through sensory mechanisms, neural transduction within the central nervous system, and neuroendocrine and endocrine cascades to regulate morphological, physiological and behavioral responses of target tissues. This "perception–transduction–response" complex (Fig. 1) involves multiple regulatory mechanisms and is key to predicting how organisms will fare in relation to global change, including direct human disturbance. Furthermore, there are diverse ways in which individuals can respond to the same environmental change, indicating multiple mechanisms (diversity) by which the perception–transduction–response complex can be regulated (Wingfield 2008, Wingfield and Mukai 2009). The traditional view is that selection has favored the persistence of conserved molecular, cellular, and physiological mechanisms of the perception–transduction–response axis over a broad range of populations, habitats, life cycles, and phenology. Evidence is building, however, that there are many variations on this conserved framework that allow individuals not only to survive environmental challenges, but also to successfully reproduce, migrate, molt, and endure a wide range of winter conditions (Wingfield 2008; Wingfield et al. 2011a, b). For example, regulatory networks (e.g., Martin et al. 2011, A. A. Cohen et al.

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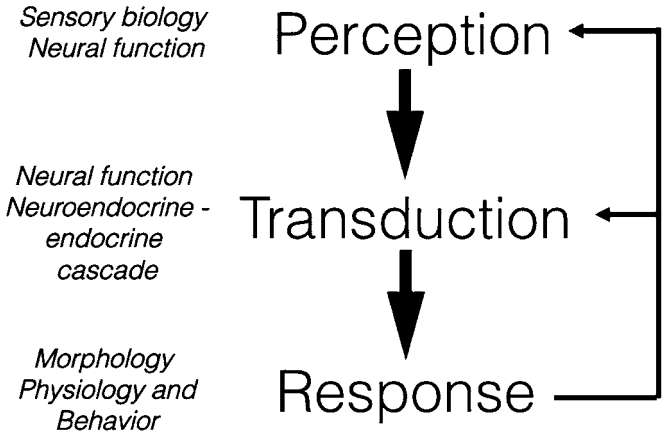

Fig. 1. Perception–transduction–response. Vertebrates perceive their physical, social, and internal environments through sensory receptors that activate neural function. These signals are transduced within the brain and converted to hormonal (neuroendocrine and endocrine) cascades that result in specific hormonal signals that elicit morphological, physiological, and behavioral responses relevant to the environmental change. Note that there are feedback systems (mostly negative) from the response to transduction and perhaps even to perception.

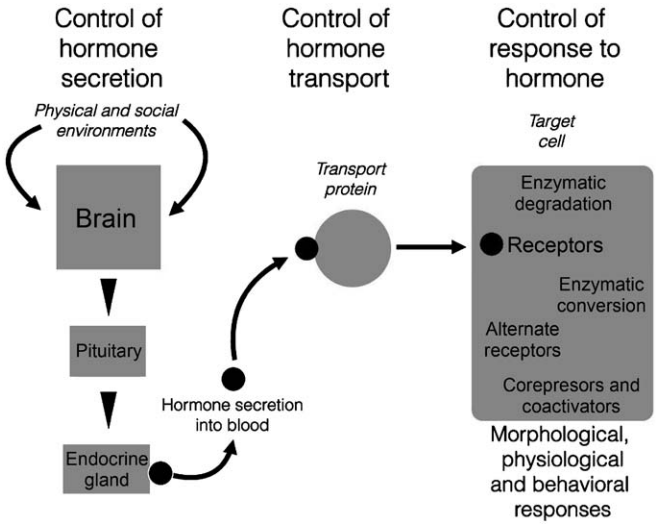

Fig. 2. There are three components of the transduction response that can be regulated in diverse ways. (Left) The perception–transduction–response system triggers the neural, neuroendocrine, and endocrine cascades that result in production of a highly specific signal—hormone secretion. (Center) After secretion into the blood, many hormones (particularly steroids, thyroid hormones, and some peptides) are transported by carrier proteins. (Right) Once the hormonal signal reaches the target cell (e.g., a neuron in the brain), it can act in various ways by binding to membrane or intracellular receptors that trigger extremely complex actions in a cell. Note that all three components are sites of regulation that could change daily or seasonally or vary among individuals, populations, sex, or in response to unique experience of the environment.

unpubl. data) of adaptation or acclimation to environments at high latitudes and high altitudes in the northern and southern hemispheres may seem very similar at behavioral, physiological, and morphological levels but show marked variations at mechanistic levels (Wingfield et al. 2008). Although there are highly conserved molecular and biochemical networks that underlie responses to environmental change, specific cell mechanisms within these networks can be adjusted to "customize" responses of individuals and populations to specific environments, sex, age, and so on (Martin et al. 2011). Frequently, there is more than one way in which individuals may respond to the same environmental challenge: speed up or slow down gonadal development in response to photoperiod under different temperatures or resist a transient stressor. Regulated employment of these alternative mechanisms can enhance fitness (Hau and Wingfield 2011; Martin et al. 2011; Wingfield et al. 2011a, b).

Evidence for such diversity of mechanisms has been put forward in the physiology nexus of Ricklefs and Wikelski (2002) and in the phenotypic flexibility of morphology, physiology, and behavior demonstrated by Piersma and van Gils (2010). Networks of physiological responses that result from developmental experience and environmental influences have also been discussed by Martin et al. (2011) and A. A. Cohen et al. (unpubl. data), including endocrine systems and neural circuits that underlie control mechanisms. Here, I focus on characteristics of endocrine systems that provide regulatory links between environmental change and morphological, physiological, and behavioral responses of the individual. It is important to distinguish the regulatory pathways from the morphological, physiological, and behavioral responses themselves because they are different processes. Neural and endocrine regulatory mechanisms, although they trigger diverse responses, are highly conserved across vertebrates (Wingfield 2005). Nonetheless, there are diverse ways in which this system can be adjusted to customize responses of the individual.

Hormones serve as the signaling molecules following the perception–transduction–response system and circulate in the blood (endocrine actions) from their sites of synthesis and secretion to their targets (Fig. 2). They can also act locally on other cell types (paracrine actions) or provide short loop feedback to the cell of origin (autocrine actions). Therefore, a single hormone can have three major types of action—distant, local, and self-feedback. When circulating in the blood, many hormones, such as steroids, thyroid hormones, and some peptides, are bound to carrier proteins—another point of potential regulation (Fig. 2). When they reach their target organs, they initiate cell responses by binding to specialized proteins called "receptors." The hormone–receptor complex is what triggers responses of the cell that underlie morphological, physiological, and behavioral effects (Fig. 2).

There are two major types of receptors. One is membrane-based, and binding of hormone to the membrane-bound receptor type results in rapid intracellular responses (within microseconds to seconds). The second type involves passage of the hormone across the membrane (intracellular), and when hormones bind they form complexes that function as gene transcription factors up-regulating or down-regulating transcription of many genes. This kind of hormone action is slower, usually on the scale of hours. Some hormones that bind to membrane receptors have rapid effects (the rapid or early cell responses) but can also activate

gene transcription factors (slower or late cell responses). Receptors are almost always highly specific to one hormone, which enables accurate and relevant responses to the hormone signal (for more details, see Nelson 2011). Note that hormone–receptor complexes that are gene transcription factors can be further regulated by other proteins that act as co-activators (enhance gene transcription) or co-repressors (inhibit gene transcription). As one might suspect, these are levels of regulation as well (Shibata et al. 1997, Edwards 2000).

THREE SYSTEMS OF REGULATORY ACTION

Next, it is important to develop the concept that there is more than one way of regulating perception–transduction–response axes in relation to acclimation to environmental change. Diversity in perception systems and central nervous transduction are important to consider, but here I focus on endocrine response systems in natural settings to illustrate potential diversity even within an otherwise conserved system. It is critical to recognize that there are three major components to endocrine control systems (Fig. 2; Wingfield 2005, Hau and Wingfield 2011). First is the regulation of hormone secretion from perception of the environmental stimulus and transduction by the brain, which results in release of neuroendocrine signals from the hypothalamus. This triggers release of tropic hormones from the anterior pituitary gland and, in turn, peripheral endocrine secretions that regulate morphological, physiological, and behavioral responses (Fig. 2). Second, when they have been released into the peripheral blood, transport of hormones such as steroids, thyroid hormones, and some peptides involves binding to carrier proteins (e.g., Breuner and Orchinik 2002, Nelson 2011; Fig. 2). Finally, once the hormone signal arrives at a target cell (e.g., in the brain or liver), there are multiple fates of that hormone that can have profound influences on the type of response (e.g., Wingfield 2005). In some cases the target cell may express enzymes that deactivate the hormone before it can interact with a receptor, or change it to another form that may interact with a very different receptor (Fig. 2).

All components of the perception–transduction–response axes and the resultant cascade of hormone actions (Figs. 1 and 2) are sites of regulation of how an individual can respond to signals from the physical and social environments. Furthermore, combinations of regulatory points enable highly diverse ways for individuals to respond to similar environmental cues. These are part of the suite of phenotypes that may develop under specific environmental conditions. Several phenotypes may have a high degree of fitness in how they respond, and it is not necessarily true that there are only limited ways by which organisms respond to environmental change (Hau and Wingfield 2011). Much more research is needed to explore this fascinating flexibility of individuals in coping with environmental variability, including global climate change.

THREE AVIAN EXAMPLES IN CONTEXT

The three-part system of control of hormone secretion, transport, and responses of target organs is an important concept because it enables consideration of many points of potential regulatory mechanisms. The secretion component on the left of Figure 2 summarizes how sensory information—for example, social information—is transduced into hormone cascades through neural processes that remain largely unknown. After triggering the endocrine cascade, hormone is transported in blood to its target cell, where response is also regulated (Fig. 2). Examples in context are as follows.

Regulation of Territorial Aggression in Birds and Its Seasonal Modulation

Birds have been important models for exploring the control of territoriality, and field and laboratory studies have been key in teasing apart mechanisms. In birds, as in other vertebrates, the hypothalamic–pituitary–gonadal (HPG) axis, neurotransmitter and neuroendocrine secretions such as gonadotropin-releasing hormone (GnRH), and gonadotropin-inhibiting hormone (GnIH) from the brain regulate release of the gonadotropins luteinizing hormone and follicle-stimulating hormone from the anterior pituitary into the blood (e.g., Bentley et al. 2007). Luteinizing hormone circulates to the gonads, where it acts on cells that express steroidogenic enzymes to stimulate secretion of the sex steroid hormone, testosterone (T), in males. Local actions (paracrine) of T in the testis include regulation of spermatogenesis, but it is also released into the blood (endocrine) in many avian species. Among numerous endocrine actions of T are effects on territorial aggression, and negative feedback on neuroendocrine and pituitary secretions.

In birds, T circulates bound weakly to a transport protein, corticosterone-binding globulin (CBG; e.g., Breuner et al. 2003, Swett and Breuner 2008), before entering target neurons involved in the expression of territorial aggression (Fig. 3). Once T has entered a target neuron it has four potential fates. First, it can bind directly to the androgen receptor (AR), a type 1 genomic receptor. Receptors in this family become gene transcription factors once they are bound to T by forming dimerized complexes. Second, T can be converted to estradiol (E2) by the enzyme aromatase. The latter then can bind to either estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ), both of which are genomic receptors that regulate gene transcription, but different genes from those regulated by AR. Third, T can be converted to 5α-dihydrotestosterone (5α-DHT), which also binds to AR and cannot be aromatized, thus enhancing the AR gene transcription pathway. Fourth, T can be converted to 5β-dihydrotestosterone, which binds to no known receptors and also cannot be aromatized, providing a deactivation shunt. A complex system of co-repressors and co-activators of genomic steroid receptor action are also known. Moreover, many neurons in vertebrate brains express all the enzymes required to synthesize T and E2 de novo from cholesterol or from circulating inert steroid hormone precursors such as dehydroepiandrosterone (DHEA), androstenedione, and progesterone. The end result is regulatory action on neural networks that regulate expression of territorial aggression in diverse ways, depending on context, season, and (possibly) individual (e.g., Soma 2006). Several neurotransmitters and neuromodulators, such as arginine vasotocin, vasoactive intestinal peptide (VIP), and serotonin, are also involved at this level (e.g., Goodson et al. 2005). Evidence suggests that the basic secretory, transport, and action mechanisms are conserved across vertebrates. Nonetheless, it is also clear that there are very many points at which the expression

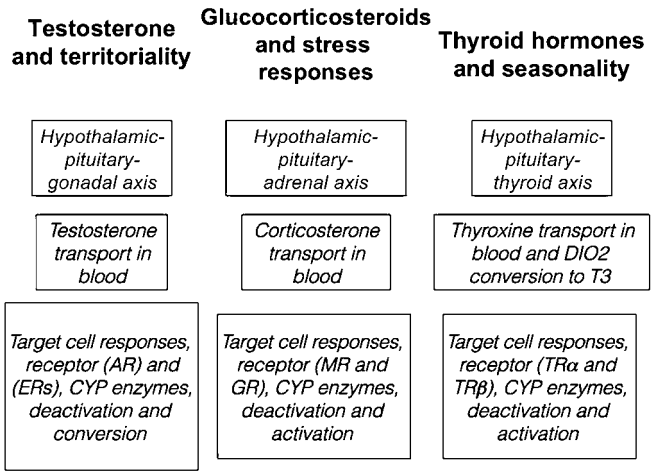

Fig. 3. Three examples of neuroendocrine–endocrine cascades and the different foci of regulatory mechanisms that imbue considerable flexibility in how organisms control their responses to environmental change while maintaining a high degree of conservation of the cellular and extracellular components. (Left) The hypothalamic–pituitary–gonadal axis is regulated by environmental information entering the central nervous system through sensory receptors. This culminates in testosterone secretion into the blood, where it is transported bound to plasma-binding proteins, a second point of regulation (Fig. 2). In the target cell a third level of regulatory mechanisms resides, including different receptor types and modifying enzymes (see text). In some cases (perhaps widespread) during the non-breeding season, sex steroid hormones are synthesized within target cells of the brain, thus avoiding peripheral androgenization at the wrong time of year. (Center) The hypothalamic–pituitary–adrenal axis is part of the stress response; as in the first example, this neuroendocrine–endocrine cascade is regulated at all levels and activated by environmental information entering the central nervous system through sensory receptors. Corticosterone is transported in blood bound to binding proteins; at the target cell, receptor types and converting enzymes can regulate the sensitivity to corticosterone (see text). There is emerging evidence that, as with sex steroids, under certain conditions glucocorticosteroids can be synthesized de novo in the brain. (Right) The third example is a similar cascade in the hypothalamic–pituitary–thyroid axis in regulation of reproduction and metabolism. Once more, binding proteins in blood play an important role and can be regulated. At the target cell, receptor types and converting enzymes provide further flexibility in how metabolism and reproduction can be developed in a changing world. Such flexibility of the three components of hormone secretion and action may be widespread in endocrine systems.

of territorial aggression may be affected, indicating almost limitless combinations of possible regulatory mechanisms.

Hormones have multiple actions when they are secreted at different times of day, season, age, and so on. Yet why and how do the same tissues respond so differently? Secretion of hormones into the blood (endocrine) means that the chemical signal is broadcast throughout the organism. Therefore, cells must be "programmed" to respond differently within an individual by again regulating receptors (type and density; Canoine et al. 2007), transport molecules such as binding proteins (e.g., Breuner et al. 2003), metabolizing enzymes that enhance or reduce chances that the hormone reaches a receptor (e.g., Wacker et al. 2010), and co-repressors and co-activators that can regulate the efficacy of hormone action once it binds to its receptor.

Secretion of hormones locally (paracrine) means that adjacent target cells are influenced directly, and in isolation, without the hormone being transported in the blood and the signal broadcast throughout the organism, thus affecting many other tissues resulting in "inappropriate" responses in a given context. Differential regulation of hormone secretion at endocrine and paracrine levels could be a highly flexible way of maintaining regulatory specificity locally without activating potentially deleterious effects elsewhere in the body. Regulatory mechanisms include local production of hormone and paracrine action; secretion of a circulating precursor that is biologically inert and then is activated enzymatically to active hormone in the tissue; and regulation of receptors locally for that hormone (see Soma 2006, Hau and Wingfield 2011).

An example is the regulation of aggressive territorial behavior in breeding and non-breeding seasons. Control mechanisms for territorial aggression in birds in autumn versus the breeding season pose some problems if the HPG axis remains activated at a time when breeding is not possible. For many avian species, autumn is the non-breeding season and the HPG axis is essentially shut down. There is evidence for some very low-level T secretion that maintains negative feedback, but territorial aggression, when it occurs in the non-breeding season, can be expressed even in the absence of the gonads (e.g., in Song Sparrows [*Melospiza melodia*]; Wingfield 1994). However, all the T response machinery in target cells such as neurons involved in the regulation of territorial aggression may be still fully functional (Soma 2006, Pradhan et al. 2010). In this case, specific neurons appear to be able to express all the necessary enzymes (CYP/HSD) to synthesize T and estradiol (E2) de novo from cholesterol (Schlinger and Brenowitz 2002). There is also evidence that circulating precursor sex steroids such as DHEA may be taken up from the blood and converted within neurons to biologically active sex steroids such as T and E2. In this way, the major pathways regulating territorial aggression in the breeding and non-breeding seasons may have similar or identical bases, but different points of the regulatory pathways are shut down or up-regulated. In these ways, similar behavioral patterns may be partially regulated by a conserved pathway but variably expressed by regulating diverse combinations, or modules, of the components. Assembling these modules as needed may present multiple ways to avoid "costs" of T secreted into the blood at the wrong season while maintaining the same mechanisms at the target neuron.

Seasonal Modulation of Adrenocortical Responses in Relation to Environmental Change

A second example of the three-part regulatory system of secretion control, transport, and hormone responses involves glucocorticoids and daily metabolic needs as well as responses to perturbations of the environment. Modulation of the response to acute stress in which individuals become resistant to acute stressors at certain times of the year avoids potential costs of chronic stress (e.g., Wingfield and Sapolsky 2003). The adrenocortical response of the hypothalamic–pituitary–adrenal (HPA) axis to acute environmental perturbations triggers an emergency life-history stage (ELHS; Wingfield et al. 1999; Fig. 3). Perturbations of the

environment are perceived by sensory modalities, and this information is transduced into neuropeptide secretions such as corticotropin-releasing hormone (CRH), arginine vasotocin (AVT), and mesotocin (MT) that regulate expression of a precursor or pro-peptide hormone, pro-opiomelanocortin (POMC), in the anterior pituitary. The POMC polypeptide can be then cleaved to yield several peptides, including adrenocorticotropin (ACTH). Release of ACTH from the pituitary gland into the blood is also regulated by CRH and AVT (Wingfield et al. 1999). ACTH acts on adrenocortical cells to activate CYP enzymes, including hydroxysteroid dehydrogenases that synthesize glucocorticoids such as corticosterone (Cort). Release of Cort into the blood is a major endpoint of the cascade of events that are part of the adrenocortical response to stress. Once in the blood, Cort circulates bound to a carrier protein, CBG, which is part of the transport part of the system (Breuner and Orchinik 2002). Cort provides negative feedback signals for ACTH release from the pituitary as well as CRH release from the hypothalamus. More than 90% of Cort circulating in avian blood is bound by CBG (e.g., Breuner et al. 2003). On reaching target cells such as liver or neurons in the brain involved in the ELHS, it is thought that only Cort unbound to CBG can enter cells. Once inside the cell, there are two types of genomic receptor that can bind Cort and become gene transcription factors. The mineralocorticoid-type receptor (MR) binds with high affinity and so can be saturated at low circulating levels of Cort. The glucocorticoid type receptor (GR) has a lower affinity and is saturated only at higher concentrations of Cort. Thus, GR has been proposed as the "stress" receptor (Breuner et al. 2003). Note that there is strong evidence in birds for a membrane receptor (non-genomic) that mediates rapid behavioral effects within minutes (e.g., Breuner et al. 2003). The genomic receptors have effects through gene transcription (different genes affected by each receptor type) and thus require up to several hours for biological effects to be manifest.

There are also steroidogenic enzymes expressed in target cells that can modulate how much Cort encounters genomic receptors. There are two isozymes of 11β-hydroxysteroid dehydrogenase (11β-HSD) that apparently play different roles in glucocorticosteroid metabolism (Holmes et al. 2001). Type 1 can be bi-directional in tissue homogenates, but in vivo it acts mostly as a reductase, regenerating active glucocorticosteroids from circulating 11-ketosteroids. Type 2 acts to inactivate glucocorticosteroids. 11β-HSD knockout mice show signs of hypertension arising from activation of MR receptor by glucocorticosteroids in the absence of the protection from the type 2 enzyme (Holmes et al. 2001) and show more subtle effects with reduced glucocorticoid-induced processes such as gluconeogenesis when fasting, and lower glucose levels in response to obesity or stress (Holmes et al. 2001).

Regulation of 11-βHSD activity involves two gene splices and may regulate local production of glucocorticosteroids in neural tissue, immune system, and skin (i.e., extra-adrenal sources; Schmidt et al. 2008; Taves et al. 2011a, b). 11β-HSD 2 converts Cort to deoxycorticosterone, which cannot bind to any known Cort receptor and is a deactivation shunt. 11β-HSD 1 tends to have the opposite effect of enhancing Cort and, thus, the likelihood of binding to MR or GR. Co-repressors and co-activators also are points of regulation for gene transcription and responses that control the ELHS and affect the immune system (Fig. 3). This second example of a three-part system—hormone cascade, transport in blood, and response networks in the target cells—is also well conserved across vertebrates, but the ways in which specific components can be regulated to modulate responsiveness to stress are very diverse. There is growing evidence for regulation of secretion of Cort at the hypothalamic, pituitary, or adrenal-cortex levels, and for regulation of CBG (e.g., Wingfield and Romero 2001, Breuner et al. 2003), but possible regulatory mechanisms of enzymes affecting CORT action within target cells await investigation.

Thyroid Hormones, Metabolism, Reproductive Cycling, Migration, and Molt

The third example involves the multiple actions of the hypothalamic–pituitary–thyroid axis (HPT) and the regulation of seasonal changes in metabolism, reproduction, molt, and migrations (e.g., Yoshimura 2004). Again, a perception–transduction–response system followed by the three components of hormone action emerges. In birds the hypothalamic peptides thyrotropin-releasing hormone and corticotropin-releasing hormone (CRH) regulate expression and release of thyroid-stimulating hormone (TSH) from the anterior pituitary. The latter circulates in blood to the thyroid gland, where it binds to membrane receptors and regulates the synthesis and release of thyroid hormone, thyroxine (T4). This includes expression of key enzymes such as peroxidases and deiodinases (e.g., St. Germain and Galton 1997, Köhrle 1999, Nelson 2011). The process of T4 synthesis and release is complex and beyond the scope of the present discussion. However, each component of this biosynthetic pathway could also be points of regulation. After release, T4 circulates in blood bound to transport proteins transthyretin and prealbumin. As with Cort, it is thought that only unbound T4 can enter cells, although there is also evidence that the binding proteins in blood may also transport T4 into cells. Once inside a target cell, T4 is converted to tri-iodothyronine (T3) by deiodinase-2 (DIO2). Some T4 is converted by DIO2 to T3 in the blood as well. T3 is the biologically active form of thyroid hormone that binds with high affinity to two types of genomic receptor, TRα and TRβ (Vennström et al. 2010). These also become gene transcription factors when bound to T3 and complexed with retinoic acid receptor (type 2 genomic receptors; Vennström et al. 2010). There is evidence for a membrane receptor that mediates rapid effects, whereas genomic receptor binding requires several hours for effects to be manifest. Other enzymes, deiodinases 1 and 3 (DIO 1, DIO 3; St. Germain and Galton 1997, Köhrle 1999), deactivate T4 to reverse T3 that does not bind to any known receptor and, thus, is a deactivation shunt. Cumulative effects of this cascade are to regulate development, molt, reproduction, migration, and seasonal changes in metabolism. Once again, we see that specific components of the HPT, although well conserved across vertebrates, can be regulated in diverse ways (e.g., Yoshimura 2004), resulting in variation among individuals in relation to experience of the environment, sex, and location. Additionally, sites of regulation can vary within an individual with time, which indicates that phenotypic flexibility (sensu Piersma and van Gils 2010) can be great. Future advances will come from focusing on interactions among the three axes if we are to predict how timing of reproduction, response to stressors, and key nonreproductive events of the annual cycle are coordinated in response to global climate change and other major changes such as urbanization, loss of habitat, and invasive species.

Conclusions and the Future

Perception–transduction–response is the first reaction of an organism to any environmental change—physical, social, or internal (Fig. 1). Birds are excellent models to explore these diverse mechanisms because we know so much about their morphological, physiological, and behavioral changes over the life cycle. This, coupled with the recent sequencing of avian genomes, will enable much more sophisticated analyses in the future. However, integration of laboratory and field investigations will still be key. The basic three-part regulation system of hormone secretion, transport, and target cell response (Fig. 2) is probably well conserved across vertebrates, but the combinations of components that are regulated to assemble modules that control overall seasonal and local target effects are very diverse. The three examples given here are probably just a few of many others. We need to understand them more thoroughly if we are to also unravel the many ways in which different species, and individuals, can adjust to environmental change—or not. Future studies will have to address these components, and this will require collaboration of behavioral ecologists, evolutionary biologists, and endocrinologists. The diversity of ways in which an individual can adjust its morphology, physiology, and behavior to environmental change is just the tip of the iceberg. Genomics, bioinformatics, and other "-omics" approaches will be indispensible to flesh out the ways in which hormonal signals help individuals acclimate to change. Collaborations will require considerable outreach and willingness to think broadly and outside one's area of expertise. This does not mean that the ecologist has to become a physiologist or vice versa. The important issue will be to think about integrative ways to bridge the void among disciplines. We should already be teaching undergraduates and graduates such integrative approaches rather than continuing to "canalize" students as molecular or organismal. The results will have far-reaching implications for basic research, education, and outreach.

It should also be borne in mind that many other examples of integrating laboratory and field investigations have been developed, including the use of stable isotopes to assess diet (e.g., Robinson et al. 2010) and data loggers to assess body temperature, exposure to day length, heart rate, and so on (Wikelski et al. 2007, Stutchbury et al. 2009, Robinson et al. 2010). All of these can be combined with field endocrinology to increase our knowledge of why and how individuals respond the way they do to changes in the predictable environment (e.g., seasons, tides, and how climate change may affect this; Wingfield 2008) and the unpredictable, such as weather (Wingfield and Ramenofsky 2011), predators, invasive species, and human distance in general (Wingfield 2008; Wingfield and Mukai 2009; Wingfield et al. 2011a, b). However, despite these exciting advances, considerable challenges present themselves in terms of harnessing new technology to provide instruments and methods that we can apply to field investigations, as well as develop new computational approaches to deal with "big data" and diverse data sets. These data sets span a spectrum from morphological, physiological, and behavioral types to genomic, proteomic, and metabolomic data with images, environmental measures, acoustic information, and so on. Problems and bottlenecks presented by handling big data are enormous, but rapid progress is expected in the next few years (Bryant 2011, Szalay 2011). Future research to integrate new technologies along with frameworks that emphasize different regulatory points in different environmental contexts will be exciting indeed.

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Literature Cited

Bentley, G. E., N. Perfito, T. Ubuka, K. Ukena, T. Osugi, S. O'Brien, K. Tsutsui, and J. C. Wingfield. 2007. Gonadotropin-inhibitory hormone in seasonally-breeding songbirds: Neuroanatomy and functional biology. Journal of Ornithology 148 (Supplement 2):521–526.

Breuner, C. W., and M. Orchinik. 2002. Plasma binding proteins as mediators of corticosteroid action in vertebrates. Journal of Endocrinology 175:99–102.

Breuner, C. W., M. Orchinik, T. P. Hahn, S. L. Meddle, I. T. Moore, N. T. Owen-Ashley, T. S. Sperry, and J. C. Wingfield. 2003. Differential mechanisms for regulation of the stress response across latitudinal gradients. American Journal of Physiology 285:R594–R600.

Bryant, R. E. 2011. Data-intensive scalable computing for scientific applications. Computing in Science & Engineering 13:25–33.

Canoine, V., L. Fusani, B. Schlinger, and M. Hau. 2007. Low sex steroids, high steroid receptors: Increasing the sensitivity of the non-reproductive brain. Journal of Neurobiology 67:57–67.

Edwards, D. P. 2000. The role of coactivators and corepressors in the biology and mechanism of action of steroid hormone receptors. Journal of Mammary Gland Biology and Neoplasia 5:307–324.

Goodson, J. L., C. J. Saldanha, T. P. Han, and K. K. Soma. 2005. Recent advances in behavioral neuroendocrinology: Insights from studies on birds. Hormones and Behavior 48:461–473.

Hau, M., and J. C. Wingfield. 2011. Hormonally-regulated tradeoffs: Evolutionary variability and phenotypic plasticity in testosterone signaling pathways. Pages 349–361 *in* Mechanisms of Life History Evolution (T. Flatt and A. Heyland, Eds.). Oxford University Press, New York.

Holmes, M. C., Y. Kotelevtsev, J. J. Mullins, and J. R. Seckl. 2001. Phenotypic analysis of mice bearing targeted deletions of 11β-hydroxysteroid dehydrogenases 1 and 2 genes. Molecular and Cellular Endocrinology 171:15–20.

Ketterson, E. D., J. W. Atwell, and J. W. McGlothlin. 2009. Phenotypic integration and independence: Hormones, performance, and response to environmental change. Integrative and Comparative Biology 49:365–379.

Ketterson, E. D., and V. Nolan, Jr. 1999. Adaptation, exaptation, and constraint: A hormonal perspective. American Naturalist 154 (Supplement):S4–S25.

Köhrle, J. 1999. Local activation and inactivation of thyroid hormones: The deiodinase family. Molecular and Cellular Endocrinology 151:103–119.

Martin, L. B., A. L. Liebl, J. H. Trotter, C. L. Richards, K. McCoy, and M. W. McCoy. 2011. Integrator networks: Illuminating the black box linking genotype and phenotype. Integrative and Comparative Biology 51:514–527.

Möstl, E., S. Rettenbacher, and R. Palme. 2005. Measurement of corticosterone metabolites in birds' droppings: An

analytical approach. Annals of the New York Academy of Sciences 1046:17–34.

Nelson, R. J. 2011. An Introduction to Behavioral Endocrinology, 4th ed. Sinauer Associates, Sunderland, Massachusetts.

Piersma, T., and J. A. van Gils. 2010. The Flexible Phenotype: A Body-Centred Integration of Ecology, Physiology, and Behaviour. Oxford University Press, Oxford, United Kingdom.

Pradhan, D. S., A. E. M. Newman, D. W. Wacker, J. C. Wingfield, B. A. Schlinger, and K. K. Soma. 2010. Aggressive interactions rapidly increase androgen synthesis in the brain during the non-breeding season. Hormones and Behavior 57: 381–389.

Ricklefs, R. E., and M. Wikelski. 2002. The physiology/life-history nexus. Trends in Ecology & Evolution 17:462–468.

Robinson, W. D., M. S. Bowlin, I. Bisson, J. Shamoun-Baranes, K. Thorup, R. H. Diehl, T. H. Kunz, S. Mabey, and D. W. Winkler. 2010. Integrating concepts and technologies to advance the study of bird migration. Frontiers in Ecology and the Environment 8:354–361.

Schlinger, B. A., and E. A. Brenowitz. 2002. Neural and hormonal control of birdsong. Pages 799–839 *in* Hormones, Brain and Behavior (D. W. Pfaff, A. M. Arnold, A. M. Etgen, S. E. Fahrbach, and R. T. Rubin, Eds.). Academic Press, Amsterdam, The Netherlands.

Schmidt, K. L., D. S. Pradhan, A. H. Shah, T. D. Charlier, E. H. Chin, and K. K. Soma. 2008. Neurosteroids, immunosteroids, and the Balkanization of endocrinology. General and Comparative Endocrinology 157:266–274.

Shibata, H., T. E. Spencer, S. A. Oñate, G. Jenster, S. Y. Tsai, M. J. Tsai, and B. W. O'Malley. 1997. Role of co-activators and co-repressors in the mechanism of steroid/thyroid receptor action. Recent Progress in Hormone Research 52:141–164.

Soma, K. K. 2006. Testosterone and aggression: Berthold, birds and beyond. Journal of Neuroendocrinology 18:543–551.

St. Germain, D. L., and V. A. Galton. 1997. The deiodinase family of selenoproteins. Thyroid 7:655–668.

Stutchbury, B. J. M., S. A. Tarof, T. Done, E. Gow, P. M. Kramer, J. Tautin, J. W. Fox, and V. Afanasyev. 2009. Tracking long-distance songbird migration by using geolocators. Science 323:896.

Swett, M. B., and C. W. Breuner. 2008. Interaction of testosterone, corticosterone and corticosterone binding globulin in the White-throated Sparrow (*Zonotrichia albicollis*). Comparative Biochemistry and Physiology A 151:226–231.

Szalay, A. S. 2011. Extreme data-intensive scientific computing. Computing in Science and Engineering 13:34–41.

Taves, M. D., C. E. Gomez-Sanchez, and K. K. Soma. 2011a. Extra-adrenal glucocorticoids: Evidence for local synthesis, regulation, and function. American Journal of Physiology 301:E11–E24.

Taves, M. D., C. Ma, S. A. Heimovics, C. J. Saldanha, and K. K. Soma. 2011b. Measurement of steroid concentrations in brain tissue: Methodological considerations. Frontiers in Endocrinology 2:1–13.

Vennström, B., H. Liu, and D. Forrest. 2010. Thyroid hormone receptors. Pages 183–201 *in* Nuclear Receptors: Proteins and Cell Regulation, vol. 8 (C. M. Bunce and M. J. Campbell, Eds.). Springer, New York.

Wacker, D. W., J. C. Wingfield, J. E. Davis, and S. L. Meddle. 2010. Seasonal changes in aromatase and androgen receptor, but not estrogen receptor mRNA expression in the brain of the free-living male Song Sparrow, *Melospiza melodia morphna*. Journal of Comparative Neurology 518:3819–3835.

Wikelski, M., R. W. Kays, N. J. Kasdin, K. Thorup, J. A. Smith, and G. W. Swenson, Jr. 2007. Going wild: What a global small-animal tracking system could do for experimental biologists. Journal of Experimental Biology 210:181–186.

Wingfield, J. C. 1994. Control of territorial aggression in a changing environment. Psychoneuroendocrinology 19:709–721.

Wingfield, J. C. 2005. Communicative behaviors, hormone–behavior interactions, and reproduction in vertebrates. Pages 1995–2040 *in* Physiology of Reproduction, 3rd ed. (J. D. Neill, Ed.). Academic Press, New York.

Wingfield, J. C. 2008. Comparative endocrinology, environment and global change. General and Comparative Endocrinology 157:207–216.

Wingfield, J. C., and D. S. Farner. 1976. Avian endocrinology—Field investigations and methods. Condor 78:570–573.

Wingfield, J. C., J. D. Jacobs, A. D. Tramontin, N. Perfito, S. Meddle, D. L. Maney, and K. Soma. 1999. Toward an ecological basis of hormone–behavior interactions in reproduction of birds. Pages 85–128 *in* Reproduction in Context (K. Wallen and J. Schneider, Eds.). MIT Press, Cambridge, Massachusetts.

Wingfield, J. C., J. P. Kelly, and F. Angelier. 2011a. What are extreme environmental conditions and how do organisms cope with them? Current Zoology 57:363–374.

Wingfield, J. C., J. P. Kelley, F. Angelier, O. Chastel, F. Lei, S. E. Lynn, B. Miner, J. E. Davis, D. Li, and G. Wang. 2011b. Organism–environment interactions in a changing world: A mechanistic approach. Journal of Ornithology 152 (Supplement 1):S279–S288.

Wingfield, J. C., I. T. Moore, R. A. Vasquez, P. Sabat, S. Busch, A. Clark, E. Addis, F. Prado, and H. Wada. 2008. Modulation of the adrenocortical responses to acute stress in northern and southern populations of *Zonotrichia*. Ornitologia Neotropical 19 (Supplement):241–251.

Wingfield, J. C., and M. Mukai. 2009. Endocrine disruption in the context of life cycles: Perception and transduction of environmental cues. General and Comparative Endocrinology 163:92–96.

Wingfield, J. C., and M. Ramenofsky. 2011. Hormone–behavior interrelationships of birds in response to weather. Advances in the Study of Behavior 43:93–188.

Wingfield, J. C., and L. M. Romero. 2001. Adrenocortical responses to stress and their modulation in free-living vertebrates. Pages 211–236 *in* Handbook of Physiology, Section 7: The Endocrine System, vol. 4: Coping with the Environment: Neural and Endocrine Mechanisms (B. S. McEwen, Ed.). Oxford University Press, Oxford, United Kingdom.

Wingfield, J. C., and R. M. Sapolsky. 2003. Reproduction and resistance to stress: When and how. Journal of Neuroendocrinology 15:711–724.

Yoshimura, T. 2004. Molecular bases for seasonal reproduction in birds. Journal of Poultry Science 41:251–258.