SYMPOSIUM

Evolutionary Endocrinology: Hormones as Mediators of Evolutionary Phenomena

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Introduction

Hormones are agents of biological coordination that circulate systemically to signal diverse cells and tissues, thereby influencing nearly all aspects of the phenotype, including behavior, morphology, physiology, and life history. Hormonal phenotypes can be both heritable and subject to natural selection (Bonier et al. 2009; McGlothlin et al. 2010; Ouyang et al. 2011; Pavitt et al. 2014; Cox et al. 2016, this issue), yet hormones and endocrine pathways have rarely been integrated into evolutionary models and analyses. As Garland et al. (2016, this issue) note this issue, "the seminal papers in modern evolutionary physiology scarcely mentioned the endocrine system." Nevertheless, over the past two decades, the field of evolutionary endocrinology (Zera et al. 2007; Nepomnaschy et al. 2009) has emerged not only as a means of understanding the evolution of the endocrine system itself (Denver et al. 2009), but also as a framework for exploring the roles of hormones in shaping other evolutionary phenomena (Ketterson and Nolan 1999; Adkins-Regan 2008; Husak et al. 2009; Williams 2012). Originally centered on classic quantitative genetic approaches to the study of hormonal phenotypes themselves (Zera and Zhang 1995; Zera and Huang 1999), this field has expanded to include new ideas about the diverse roles of hormones as mediators of a variety of fundamental evolutionary phenomena. This theme of "hormones as mediators of evolutionary phenomena" serves as the organizing concept for this issue and can be illustrated by several examples drawn from the papers that follow.

Hormones as mediators of phenotypic and genetic integration

The field of quantitative genetics arose to provide a mathematical framework for predicting evolutionary responses to natural and artificial selection (Lynch and Walsh 1998). Patterns of genetic variance (e.g., heritability) and genetic covariance among traits (e.g., genetic correlations) provide the statistical basis for these predictions, but they are mathematical abstractions that do not specify underlying mechanisms. As the challenge of mapping from genes to phenotypes has come to prominence, evolutionary biologists have become increasingly interested in the mechanistic basis of these statistical measures. Cox et al. (2016, this issue) illustrate how the hormonal milieu of an individual establishes a local environment for gene expression that can create and break apart phenotypic and genetic covariance by orchestrating patterns of gene co-expression. This implies that selection will act on different patterns of phenotypic and genetic variance and covariance, and thus produce different evolutionary responses, when acting on the same genotypes in different endocrine backgrounds. This idea is an extension (from phenotype to genotype) of the familiar concept of hormonal pleiotropy (Flatt et al. 2005; Williams 2012), in which a single hormone can influence multiple phenotypes, thereby structuring patterns of phenotypic correlation and influencing the trait combinations that are available to selection (McGlothlin and Ketterson 2008; Ketterson et al. 2009). Studies of endocrine mechanism are thus uniquely situated to simultaneously enhance our

understanding of both genetic and phenotypic evolution.

Hormones as mediators of evolutionary conflicts

Evolutionary conflicts can arise at many levels—between parents and offspring, between mates, or between phenotypically divergent sexes, morphs, or ontogenetic stages that share the same underlying genome. Mokkonen et al. (2016, this issue) provide an overview of the many ways in which hormones can mediate these evolutionary conflicts, drawing heavily from their work involving artificial selection for high and low testosterone levels in bank voles, *Myodes glareolus* (Mills et al. 2009; 2012; Mokkonen et al. 2011, 2012). Cox et al. (2016, this issue) demonstrate how the pleotropic effects of testosterone on gene expression in the brown anole, *Anolis sagrei*, may help to reduce genetic correlations for traits that are shared between the sexes, thereby facilitating the evolution of sexual dimorphism and the resolution of intralocus sexual conflict (Rice and Chippindale 2001; Bonduriansky and Chenoweth 2009; Cox and Calsbeek 2009). Other examples in which hormones facilitate the expression of different phenotypes from the same underlying genome include the endocrine regulation of polymorphisms and alternative mating tactics, as illustrated in this issue by several studies of polymorphic insects (Zera 2016, this issue; Zinna et al. 2016, this issue). For example, Zinna et al. (2016, this issue) use a phylogenetic context to show that the effects of juvenile hormone and insulin signaling can differ among lineages with respect to their roles in mediating polyphenisms in some of the most spectacular weapons to be produced by sexual selection—the elaborate horns and mandibles of stag beetles, dung beetles, and rhinoceros beetles.

Hormones as mediators of life-history evolution

Life-history trade-offs are cornerstones of evolutionary theory, and recent work has built on foundational evolutionary perspectives invoking hormones (Finch and Rose 1995) to clarify many of the physiological and genetic mechanisms shaping these trade-offs (Flatt and Heyland 2011). However, this refined mechanistic perspective has yet to be formulated in a way that directly addresses the major predictions of evolutionary theory (Stearns 2011). One major challenge for evolutionary endocrinology is to integrate functional, genomic, and transcriptomic methods for describing the hormonal axes that structure life-history trade-offs (Williams 2012; Schwartz and Bronikowski 2013; McGaugh et al. 2015) with evolutionary theory, quantitative genetic analyses, and artificial selection experiments designed to test predictions about the roles of hormones in shaping life-history evolution (Hau 2007; Zera et al. 2007; Dantzer and Swanson 2012; Davidowitz et al. 2012). Ouyang et al. (2016, this issue) apply a life-history perspective to a wild population of tree swallows, *Tachycineta bicolor*, to examine whether glucocorticoid levels are associated with trade-offs between reproductive investment and physiological aspects of self-maintenance and survival, such as oxidative stress and telomere length. Dantzer et al. (2016, this issue) draw upon their demographic and experimental studies of red squirrels, *Tamiasciurus hudsonicus*, to explore the roles of glucocorticoids as mediators of life-history variation while demonstrating how environmental variation may often complicate our attempts to link endocrine phenotypes to fitness. From a more mechanistic perspective, Schwartz and Bronikowski (2016, this issue) discuss an important endocrine mediator of life-history variation—the insulin and insulin-like signaling network—from a comparative perspective that incorporates new genomic data from reptiles (including birds) to illustrate gene sequence evolution and possible functional changes in this conserved endocrine axis. When it comes to testing predictive theories about life-history evolution, Davidowitz (2016, this issue) argues that it will often be necessary to replace the many small details gleaned from reductionist approaches with more holistic proxies that simplify endocrine complexity into a few key variables, an approach that he illustrates with artificial selection experiments on life-history traits in the tobacco hornworm, *Manduca sexta*.

Hormones as facilitators of and constraints on adaptation

Most of the major axes of the endocrine system are evolutionarily conserved, suggesting a potential evolutionary constraint. Moreover, because hormones often act as pleiotropic regulators of multiple traits (Flatt et al. 2005), changes in hormone production and secretion that are adaptive with respect to one trait may be maladaptive on the whole, due to their deleterious effects on other traits (Ketterson and Nolan 1999; Hau 2007; McGlothlin and Ketterson 2008). However, comparative data are increasingly revealing that the roles of evolutionarily conserved hormones often vary across taxa, and subtle changes in the ways that these hormones are coupled to (and

decoupled from) their downstream targets may actually provide a highly flexible regulatory system with considerable evolutionary potential (Cox and John-Alder 2005; Cox et al. 2009; Hau and Wingfield 2011). For example, Schwartz and Bronikowski (2016, this issue) review recent evidence showing that patterns of molecular evolution in the genes for insulin-like growth factors 1 and 2 vary between mammals and reptiles and suggest that the ontogenetic specificity and developmental significance of IGF2 may also differ between these two lineages. Rosvall et al. (2016, this issue) synthesize the results of common-garden and field studies of two subspecies of the dark-eyed junco, *Junco hyemalis*, to illustrate how recent divergence in several aspects of the hypothalamic-pituitary-gonadal axis and its cross talk with the hypothalamic-pituitary-adrenal axis may underlie population differences in aggression, body size, and ornamentation of males.

Symposium goals, major themes, and future directions

One practical goal of this symposium was to encourage the application of techniques and perspectives from evolutionary biology in studies of endocrine systems. As a starting point, Cox et al. (2016, this issue) introduce the breeder's equation as a conceptual framework for applying two basic evolutionary approaches—phenotypic selection analyses and quantitative genetic analyses—to the study of endocrine traits. Subsequent papers by Ouyang et al. (2016, this issue) and Dantzer et al. (2016, this issue) illustrate many of the potential rewards and challenges associated with linking endocrine phenotypes to fitness in wild populations. Likewise, Cox et al. (2016, this issue) and Zera (2016, this issue) each call attention to the complexities inherent in estimating quantitative genetic parameters for endocrine phenotypes that vary over time. A quantitative genetic foundation is also evident in several contributed papers using artificial selection experiments to explore the endocrine basis of sexual conflict (Mokkonen et al. 2016, this issue), the evolution of life-history traits (Davidowitz 2016, this issue), and the evolution of behavior and other complex phenotypes (Garland et al. 2016, this issue).

A third approach from evolutionary genetics that is featured in many of the contributed papers is the use of RNA sequencing and quantitative PCR to measure gene expression. These methods hold particular promise for evolutionary endocrinology because they can reveal effects of hormones on tissue-wide patterns of transcription, thereby exposing the elusive intermediate steps connecting gene sequences to organismal phenotypes. Topics addressed with this approach include the potential role of testosterone in reducing between-sex genetic correlations by orchestrating patterns of sex-biased gene expression (Cox et al. 2016, this issue), the recent evolution of population differences in gonadal expression of hormone receptor genes between phenotypically divergent subspecies (Rosvall et al. 2016, this issue), the evolution of morph-specific patterns of circadian gene expression associated with polymorphic circadian rhythms for juvenile hormone secretion (Zera 2016, this issue), and the use of comparative transcriptomics to characterize evolutionary changes in the insulin and insulin-like signaling network across major vertebrate lineages (Schwartz and Bronikowski 2016, this issue). With the increasing availability of genomic data for non-model species and the relative ease with which massively parallel sequencing techniques now permit us to assess tissue-wide patterns of gene expression, these approaches should provide answers to an exciting variety of questions at the intersection of endocrinology and genetics. Nonetheless, these relatively newer genomic techniques will be most illuminating when integrated with more traditional evolutionary approaches, such as phenotypic selection analyses, artificial selection experiments, quantitative genetics, and evolutionary developmental biology.

The dynamic tension between reductionist approaches centered on endocrine mechanisms and synthetic approaches seeking predictive utility for evolutionary theory provided a recurring theme throughout the symposium. Nearly every contributed talk involved at least one complex schematic representing an endocrine axis or corresponding gene network, replete with endocrine glands, hormones, receptors, binding proteins, and other biological details. Several of the papers that follow nicely illustrate how this mechanistic complexity can be surveyed so as not to miss the forest for the trees. Morrison and Badyaev (2016, this issue) outline an approach in which the functional utilization of a particular physiological or genetic network, as potentially mediated by hormones, shapes the realized expression and evolution of the network from among the many possible interactions between its component parts. In their view, the network itself is the phenomenon to be explained, but only through quantification of its component parts. Schwartz and Bronikowski (2016, this issue) present the insulin and insulin-like signaling network in impressive mechanistic detail, yet focus their analyses on broad evolutionary patterns

across vertebrates, holistic features of the network itself, and evolutionary shifts in key upstream components of the network. Davidowitz (2016, this issue) argues that predictive utility with respect to evolutionary theory necessitates the use of ''endocrine proxies'' that distill the numerous mechanistic details of endocrine networks into a small number of key variables, though a firm understanding of mechanism will often be crucial for establishing the most informative proxies. Several other papers call for greater mechanistic detail, highlighting the limitations associated with a historical reliance on circulating hormone levels as the primary endocrine phenotypes to be considered in analyses of heritability, field estimates of selection, and artificial selection experiments (Cox et al. 2016, this issue; Garland et al. 2016, this issue). Explicit consideration of the interactions between hormones, binding proteins, and receptors would almost certainly help to move these areas of evolutionary endocrinology forward.

A final goal of this symposium was to identify the emerging questions, biological systems, technological advances, and theoretical perspectives that endocrinologists and evolutionary biologists might reciprocally adopt to foster a true synthesis between these disciplines. Garland et al. (2016, this issue; Table 1) provide an illustrative example of the type of ''emergent questions'' that can arise from the hybridization of endocrinology and evolutionary biology to transcend the usual boundaries of each individual field. Other emergent questions are evident in the conceptual areas discussed above, as are several promising perspectives and methodological approaches (e.g., phenotypic selection, quantitative genetics, artificial selection, transcriptomics, molecular evolution, network theory). Participants also discussed the need to broaden the taxonomic focus of evolutionary endocrinology to include more systems that are amenable to large-scale phenotypic selection studies, quantitative genetic analyses, artificial selection experiments, and genetic and genomic interrogation using reference genomes and associated resources. This hybrid field would also benefit from training future cohorts of endocrinologists as evolutionary biologists (and vice versa) by emphasizing the major unanswered questions in evolutionary biology (and why attention to mechanism can help answer these questions) and techniques in evolutionary analysis (and how they can be adopted by endocrinologists). Finally, we should increasingly attempt to formulate studies of endocrine mechanisms to distinguish among alternative evolutionary hypotheses, so that studies of endocrine pathways transcend reductionism to form the basis of a predictive and testable body of theory centered on the roles of hormones in facilitating and constraining adaptation.

Funding

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