Measuring Selection on Physiology in the Wild and Manipulating Phenotypes (in Terrestrial Nonhuman Vertebrates)

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ABSTRACT

To understand why organisms function the way that they do, we must understand how evolution shapes physiology. This requires knowledge of how selection acts on physiological traits in nature. Selection studies in the wild allow us to determine how variation in physiology causes variation in fitness, revealing how evolution molds physiology over evolutionary time. Manipulating phenotypes experimentally in a selection study shifts the distribution of trait variation in a population to better explore potential constraints and the adaptive value of physiological traits. There is a large database of selection studies in the wild on a variety of traits, but very few of those are physiological traits. Nevertheless, data available so far suggest that physiological traits, including metabolic rate, thermal physiology, whole-organism performance, and hormone levels, are commonly subjected to directional selection in nature, with stabilizing and disruptive selection less common than predicted if physiological traits are optimized to an environment. Selection studies on manipulated phenotypes, including circulating testosterone and glucocorticoid levels, reinforce this notion, but reveal that trade-offs between survival and reproduction or correlational selection can constrain the evolution of physiology. More studies of selection on physiological traits in nature that quantify multiple traits are necessary to better determine the manner in which physiological traits evolve and whether different types of traits (dynamic performance vs. regulatory) evolve differently. © 2016 American Physiological Society. *Compr Physiol* 6:63-85, 2016.

Introduction

Physiologists have long worked to understand "how" animals work, but rapid technological advances and a greater synthesis with evolutionary biology have resulted in many physiologists also asking "why" animals work the way in which they do (27, 28, 104, 118, 165, 185, 361). The latter set of questions, called ultimate questions, is by definition concerned with the evolutionary history of physiological function. That is, how did a physiological trait or process come to function in the way that it currently does? Is it an adaptation or a byproduct of some other process inherited from an ancestor? Since such ultimate questions are typically framed in an adaptive framework, there is either an explicit or implicit assumption that physiological traits are molded by selection (27, 118, 312, 361). While this assumption is intuitive and has been made for decades (18, 19, 21, 165), two major questions for physiologists are still how selection acts on physiological traits and what the evolutionary consequences of that selection are. One way to answer these questions is to quantify how selection acts on physiological traits in nature by studying how variation in physiology predicts components of Darwinian fitness in nature. An extension of this approach is to manipulate phenotypes experimentally, thus increasing variation, and assessing the impacts on fitness.

Empirical studies of selection in natural populations are valuable to physiologists for a number of reasons, not least of which is that such studies advance our general understanding of the evolutionary process, to which all physiological traits are subjected (12, 54, 99, 217, 227, 228). Selection studies can also tell us what types of selection are operating on the phenotype, what the targets of that selection are, and what the evolutionary response may be. Although natural selection and sexual selection are often approached and quantified in different ways, and the two forces may operate in opposing directions on the phenotype (7, 98, 301), both are types of selection that may, and do, operate on physiological traits to mold the functional phenotype of organisms (59, 171, 188, 219, 226). Knowing how precisely selection operates on physiological traits, and traits correlated to that physiology, can answer several key questions to physiologists. (1) Are physiological traits typically optimized by selection? (2) Are there genetic or phenotypic constraints to physiological function? (3) How much and how easily do physiological traits change over evolutionary time? (4) How did selection lead to the functional diversity present today? (5) Do physiological traits evolve in a manner similar to other phenotypic traits? Understanding the

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answers to these questions can help answer the more general question of “why” animals work the way they do.

In this review, I first provide general information about types of selection and how they can be measured in natural populations. I then discuss more specifically how physiological traits are the targets of, and respond to, selection via the integration of systems. I follow this with specific examples from the literature where selection on a physiological trait was measured in a correlative manner. This is followed by examples of phenotypic manipulation of the phenotype to understand how selection acts on physiology when the range of variation is altered experimentally. Finally, I conclude with a synthesis of what we know about selection on physiological traits and what it can tell us about the evolution of physiology. Throughout, I provide suggestions for future studies, as well as a description of challenges that future investigators face when studying selection on physiology in the wild. As in any review, I have not cited every possible relevant paper, and some important papers are not included. Where relevant I refer readers to other reviews, which provide more complete coverage of a topic. Physiology is interpreted in many ways, but it is in essence the study of how organisms function (155, 272, 286, 308). My definition of “physiological traits” in this review is broad, as animal function can be studied at multiple levels of biological organization. Nevertheless, selection often acts upon suites of traits at the whole-organism levels, so I focus on traits and studies that quantify selection on what are likely the direct targets of selection and result in a direct evolutionary response to physiology.

Measuring Selection

Selection is the evolutionary process whereby individuals that differ phenotypically in a population have differential survival or reproduction as a result of those phenotypic differences (87, 99, 107, 219, 228, 356). For selection to cause evolutionary change in a population, (i) there must be variability in phenotypic traits among individuals, (ii) some phenotypes should have higher fitness than other phenotypes, and (iii) phenotypic variation should reflect genotypic variation; that is, the traits must be heritable. These conditions are met for a multitude of traits in probably most populations in a variety of environments, suggesting that selection should be a common cause of evolutionary change, molding the phenotype over time to the abiotic and biotic environments in which populations occur (99). The response to selection can be characterized with the breeder’s equation, $\boldsymbol{R} = \boldsymbol{h^2 S}$, where $\boldsymbol{R}$ is the response to selection, $\boldsymbol{h^2}$ is the heritability of the trait of interest, and $\boldsymbol{S}$ is the selection differential, or the average deviation of the selected parents’ phenotypic value from the population mean (103). This simple equation elegantly shows how phenotypic change can be large when heritability is high and when individuals with a particular range of trait values have higher fitness than other individuals. Although this equation is often applied to artificial selection (103, 284), where parents are chosen based on their phenotypes, the concept applies to natural populations experiencing selection from predators, environmental variables, or choosy mates. When selection is strong, successive generations will deviate strongly in their phenotypes from the parental generations, and if the traits are heritable, then evolutionary change results. However, some heritable traits that experience directional selection may remain relatively stable over time (255).

Regardless of what trait is being considered, or what factors are causing the selection, there are three basic *forms* of selection that can change the frequency of phenotypic traits that exhibit continuous variation: directional, stabilizing and disruptive (see Fig. 1). Directional selection is the result of a linear relationship between the value of a trait and fitness, and the relationship may be positive or negative. The strength of directional selection can be quantified by the magnitude of the slope (represented as β) of this relationship (i.e., the *selection gradient*; see 54, 192, 228; see Fig. 1). Stabilizing and disruptive selection are the result of curvilinear relationships between values of the trait and fitness, and the strength of such selection can be approximated by the magnitude of the quadratic coefficient (represented as γ). Stabilizing selection is characterized by individuals with extreme values of a trait having lowest fitness, thus favoring individuals with intermediate values. Disruptive selection shows the opposite pattern: individuals with extreme values have the highest fitness. Whereas directional selection shifts the mean value of a trait in a population over time, stabilizing and disruptive selection change variation, with stabilizing selection decreasing variation and disruptive selection increasing it (see Fig. 1). Although one may estimate these forms of selection by comparing trait distributions of individuals in different age classes simultaneously (i.e., “vertical” studies; 110), the most powerful method is to track cohorts of individuals in a population over the course of time (i.e., “horizontal” studies; e.g., 105, 110, 111). To accomplish this, one must measure relevant traits in a large sample of individuals and determine survival, or ideally lifetime reproductive success, of those same individuals (12, 192, 217, 227), a daunting task that has hindered our ability to measure how selection acts on physiological traits (see “Conclusions” section).

Despite the inherent difficulties in measuring selection in nature, there is now a fairly large number of studies that have quantified the form and intensity of selection on phenotypic traits (99, 215, 217, 266), allowing scrutiny of hypothesized patterns of selection in nature. If populations are well adapted to their current environment, we expect stabilizing selection to be common, and both disruptive and directional selection to be less common and weak if detectable (217, 332). A comprehensive database of selection studies in nature on plants, invertebrates, and vertebrates that includes over 1000 estimates of selection across several dozen studies (see 159, 215, 217, 311) has allowed a powerful look at how selection operates in nature. Data on a wide variety of traits clearly indicate that directional selection is common and can be quite strong (215, 217, 270). Stabilizing selection appears no more

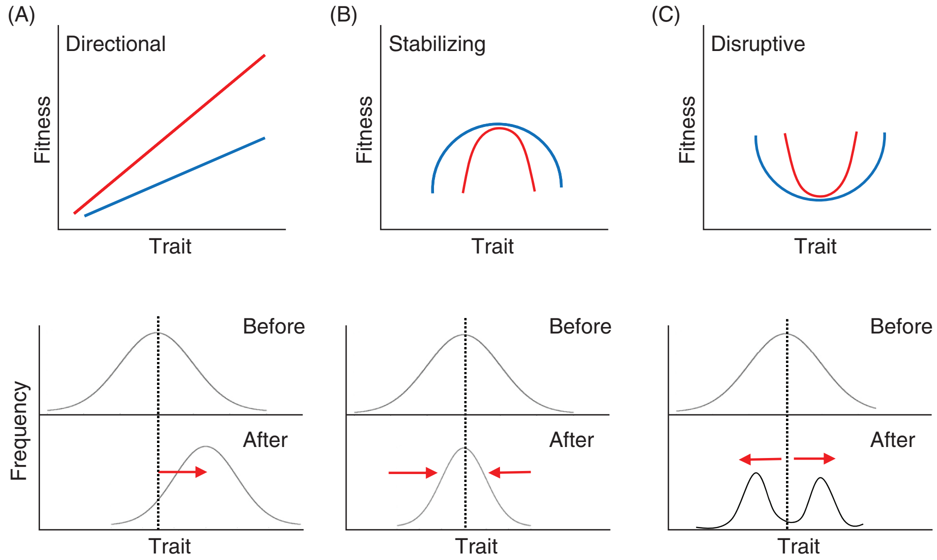

Figure 1 A graphical illustration of the forms of selection that may operate on a continuous trait. The upper panels show the relationship between fitness and values of the trait (the red line indicates stronger selection than the blue), and the lower panels show the frequency of trait values in a population before and after selection. (A) Directional selection results from a linear relationship between fitness and a trait, with the slope of the relationship indicating the strength of the selection. The population mean will shift either positively or negatively, depending on whether fitness is positively or negatively related to trait variation, respectively. (B) Stabilizing selection results from an inverted-U shaped relationship with fitness and causes a decrease in trait variation in the population after selection. (C) Disruptive selection results from a U-shaped relationship with fitness and causes an increase in trait variation in the population after selection.

common than disruptive or directional selection (217, 219), which is surprising from an adaptationist perspective. The finding that directional selection is often as common as stabilizing selection may be due in part to publication bias and low statistical power, but shifting environmental selection and correlational selection (discussed below) may result in patterns of selection that are difficult to predict (217, 219). Examination of the types of traits that have been studied reveals that the vast majority of selection studies in nature have been on morphological traits (including body size) and life history traits (including "phenology"), with very few studies of selection on physiological traits (99, 215, 217, 280). However, there are an increasing number of studies relevant to physiology in recent years, and selection on physiological traits specifically is discussed below (see "Selection on Physiology via Integration" section).

Correlational selection may also occur in populations to mold the phenotype, including physiological traits, in complex ways. Correlational selection happens when the interaction between phenotypic traits (instead of only individual traits) impacts individual fitness (53, 63, 228, 250, 283, 315, 325). This is an important concept because the presence of correlational selection means that selection on any one trait may be highly dependent on other aspects of the individuals' phenotype, including morphology, physiology, or behavior (35, 61, 62). Unfortunately, we know far less about the relative frequency of correlational selection in natural populations, compared to the three forms of selection discussed above, across types of traits and taxa (35). Nevertheless, correlational selection almost certainly operates on physiological traits and is a key concept for physiologists to consider, since selection likely does not act on single traits and correlational selection is a major force leading to phenotypic integration (35, 128, 129, 223). Simultaneously considering multiple traits that do or potentially interact will further our understanding of how correlational selection shapes physiology.

Selection on Physiology via Integration

Physiological traits, just like morphological and biochemical traits, evolve via selection on ecologically and behaviorally realized whole-animal manifestations of those traits: *performance* (18, 20, 28, 165). Arnold (12) described an operational framework for the measurement of on-going selection on suborganismal traits by developing a testable link between Darwinian fitness and phenotypic variation. In this scheme, whole-animal performance represents the link between phenotype and evolutionary consequences (see Fig. 2). This approach, now often referred to as the *Morphology-Performance-Fitness* paradigm, addresses adaptive significance by asking how, proximately, physiology affects performance, and how, ultimately, performance affects Darwinian fitness. Since Arnold's (12) publication, many have provided empirical applications and theoretical refinement to enrich the potential applicability of the concept (2, 28, 67, 96,

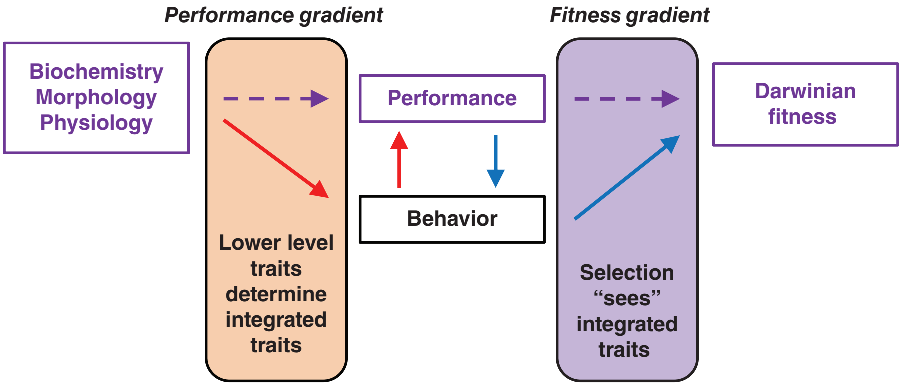

Figure 2 Diagrammatic representation of how selection shapes physiology over evolutionary time, as outlined by Arnold (12), the morphology-performance-fitness paradigm. Variation in lower level traits, such as biochemistry, morphology, and physiology constrains variation in whole-organism performance (the performance gradient), which in turn leads to variation in fitness (the fitness gradient). How individuals use their lower level traits to be manifested in performance (red arrows) may alter the performance gradient (see also Fig. 5), whereas how performance is used in nature (blue arrows) may alter the fitness gradient (67, 118, 120, 184, 185, 225). Since behavior may act as a "filter" between in the performance gradient and fitness gradient, what selection acts upon, and what the evolutionary response will be, is demonstrable only by studying each facet of these hypothetical links. For example, if individuals do not use maximal performance capacity in nature, then selection cannot act on it, and lower level traits that determine it will respond in a straightforward manner.

120, 177, 183, 185, 225, 245, 285, 289, 345). Important to the notion that selection "sees" performance is how one defines performance. Although this may seem a semantic point, it is actually one that is quite important for an understanding of what the evolutionary response to selection on a "performance" trait will be. "Performance" is defined as a quantitative measure of how well an organism accomplishes some ecologically relevant task (12,28,120,165,183,185,189,285). Thus, by definition performance traits are holistic measures of a combination of suborganismal traits and encompass a wide variety of potential quantitative traits. Individuals conduct numerous tasks over the course of their lives that potentially impact fitness, so it is up to physiologists to determine for their study organisms which tasks those are and what processes define them at the suborganismal level. Because performance can encompass such a wide variety of traits, more precise definitions can help in discussions of how selection might act on performance and what the evolutionary response to that selection might be. *Dynamic performance traits* measure movements of the body and constitute most well-studied measures such as sprint speed and bite force that are discussed below. *Regulatory performance traits* measure how well organisms regulate physiological processes within the body or tolerate environmental conditions, and are essential components of maintaining homeostasis in organisms (245, 298). Regulatory performance includes such measures as ion regulation, metabolic rates, thermoregulation, digestive capacity, and immune function, among others. Dynamic and regulatory performance traits are different in many ways, including the fact that dynamic performance traits are typically measured in the context of maximal performance, whereas maximal capacity for regulatory performance may not always be the optimal or most ecologically relevant. Nevertheless, both types of performance represent integrated measures of how well organisms interact with their environment, and are therefore important to fitness. However, the physiological systems and mechanisms involved in these types of performance are likely different, and the way in which selection operates on them may be different (245). Any phenotypic overlap between the two types of performance could lead to nonintuitive evolutionary responses to selection on either of them.

Although it is difficult to conceptually and biologically disentangle "physiology" from "morphology" and "life history" in the context of organismal function and response to selection (12,67,225,313), the distinction tends to be sharper in quantitative studies where the investigator decides on some trait or traits and measures them in individuals. The investigator must decide what aspect of an organism to measure for a selection study, and this generally is determined by the training of the investigator (as well as logistical considerations). Consider a tetrapod's limb. A functional morphologist might measure the linear dimensions of various segments/bones or the multivariate shape of those components (i.e., "morphology"), but a physiologist might measure enzyme rates in muscle (i.e., "biochemistry") or muscle fiber contractile properties (i.e., "physiology"), whereas a biomechanist might measure bone stiffness (i.e., "mechanics"), to determine selection on those traits. All of these measures are represented in the performance of the limb, and the performance is what will ultimately determine fitness. Thus, a review of selection on physiological traits must include discussion of selection on performance traits. Fortunately, there is a great body of literature on the link between morphological/physiological traits and performance, that is, the performance gradient (104,118,218, see

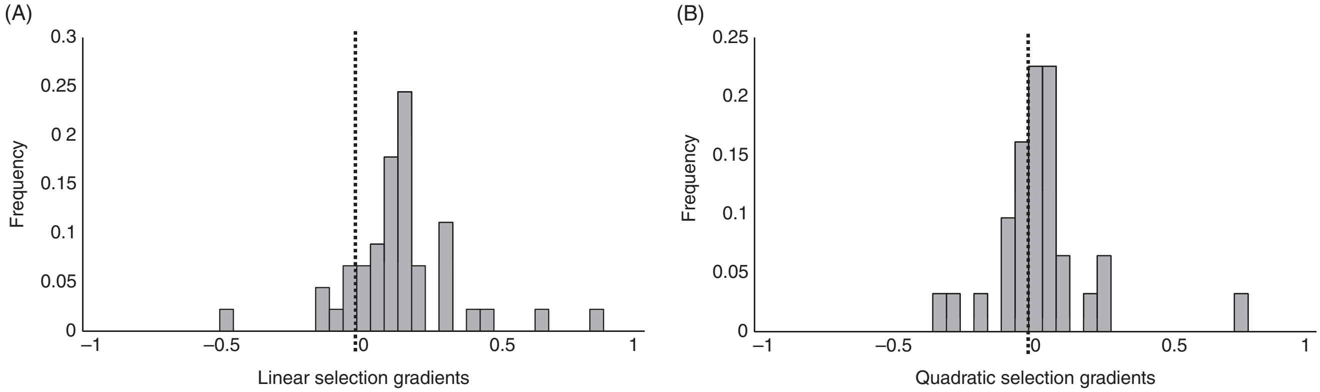

Figure 3 Frequency distributions of selection gradients found in a review of selection studies on whole-animal performance in nature (189). (A) Positive directional selection is common for performance traits, as most linear selection gradients are greater than 0. (B) Stabilizing and disruptive selection are equally common on performance traits, as the distribution of selection gradients is symmetrical around 0.

examples below). However, the vast majority of these studies have been on dynamic performance traits, with selection on regulatory performance traits less well understood.

Despite our understanding of the performance gradient, there is still much to be learned about the fitness gradient. We know far less about selection on physiological and performance traits in nature than we do about morphological and life history traits (see "Measuring Selection" section). However, there are several studies of selection on performance in nature that can help our understanding of how selection acts on physiology. A recent review (189) found 23 studies of selection on physiological performance in nature. Directional selection was common and strong, as is the case for other types of traits (215, 217). Stabilizing and disruptive selection were rare and there was only one study for each of stabilizing and disruptive selection that found statistically significant selection gradients (see Fig. 3). The finding that stabilizing selection is not the most common form of selection on performance matches with results from other types of traits, but it is still not clear why this is the case. Publication bias and inadequate sample sizes or statistical power likely explain the paucity of studies on performance traits that detect nonlinear selection (151, 189, 270). Nevertheless, the available data suggest that positive directional selection is common on performance, but nonlinear selection is not. The evolutionary ramifications for how selection detected on performance trickles down to alter physiology over evolutionary time are still somewhat unclear and are likely complicated by correlational selection (35, 61, 228) and trade-offs (35, 117, 223, 264). Such interactive effects are expected to place constraints on phenotypic evolution, but the evidence so far does not fully support this notion (215). This statement must be framed with the caveat that very few studies have completed the morphology-performance-fitness link in a single study (189, 230).

Examples of whole-organism performance in terrestrial nonhuman vertebrates that represent integration of lower level traits include endurance capacity, maximal sprint speed, and maximal bite-force capacity. These are all well studied, and I discuss selection on these in the next section. Each of these performance traits is, of course, determined by different morphological and physiological systems (25). Maximal sprint speed is among the best studied of organismal performance traits, and lizards have, by far, been the subject of most such studies (23, 41, 120, 168, 169, 183, 185, 189, 234, 257, 261, 334). Sprint speed is highly variable among conspecific individuals (28, 113, 114), and is both repeatable over time (15, 41, 161) and heritable in the broad sense (28, 115, 194, 333, 345, but see 318). Sprint speed is an anaerobic, burst performance trait that has been shown to be determined by hindlimb length, whole muscle size, muscle fiber area, fast-glycolytic muscle fiber area, and proportion of fast-glycolytic muscle fibers (41, 42, 123, 154, 360), among others. Endurance capacity has been studied extensively with regards to its physiological determinants, as well as its fitness consequences, with lizard species again being the most common subjects for these studies (28, 120, 257, 316). Endurance reflects an individual's stamina for fast, sustainable, largely aerobic, locomotion and is constrained by maximal rates of cardiovascular oxygen delivery (25). Reported intraspecific correlates of endurance include maximal rates of oxygen consumption (maximum metabolic rate), heart mass, thigh muscle mass, hematocrit, and lipid metabolism in muscle and liver, among other physiological traits (26, 85, 113, 116, 119, 120, 132, 197, 200). Endurance capacity is also repeatable and heritable in the broad sense where these measures have been estimated (95, 253, 292). Maximal bite force capacity has been correlated with linear morphometric measures of head size and head shape, such as head length, head depth, and head width (143, 148, 178, 232, 336), as well as geometric morphometric measures of multidimensional shape (101, 146, 178, 201). Bite force is also determined by mechanical properties of the jaw apparatus, such as the inlever-outlever proportions of the jaw, the size, insertion points and orientation of the jaw musculature, and the microstructure of muscle fibers (141, 142, 147), as well as physiological properties, such as physiological cross-sectional area and fiber length (88, 134, 144, 335) and muscle fiber types (127). Although bite force is repeatable (6), we know essentially nothing about its heritability. Selection on each of these three well-studied performance traits would result in evolutionary change in a number of morphological and physiological traits: for sprint speed, primarily in the musculoskeletal system of the locomotor apparatus; for endurance capacity, the cardiovascular, respiratory, and musculoskeletal systems; for bite force, primarily the musculoskeletal system of the jaw apparatus.

Studies of whole-organism performance tend to focus on dynamic performance traits, but many have argued either explicitly or implicitly that maintenance metabolism [i.e., basal metabolic rate for endotherms and standard metabolic rate (SMR) for ectotherms] is one of the most ecologically relevant physiological traits for animals, since it is the minimum energy requirement to stay alive and often makes up a large proportion of total daily energy expenditure (DEE) (14, 80, 131, 226, 252). Resting metabolic rates (RMRs) are repeatable (24, 43, 233, 277, 326) as are maximal metabolic rates (MMRs) (71, 137, 233), and they are heritable, though heritability can be low (58, 242, 244, 275, 276, 299, 302). Because metabolic rate is a metric of energy acquisition and transformation into a variety of components throughout individuals' bodies, it is almost certainly important to fitness, either directly or indirectly via its link to other whole-organism traits (65, 67, 118, 221, 222, 226, 252). Metabolism, thus, may undergo evolutionary change from selection on it or through selection on other traits with which it is correlated phenotypically or genetically. Other aspects of metabolism, such as maximum metabolic rate and DEE have also been suggested to be important to fitness (43, 44, 108, 252), and I discuss these below.

Although much of physiological research focuses on mechanisms ("how" questions), we still know surprisingly little about how morphology and physiology integrate to manifest as functional traits on which selection operates. This may be due to several reasons. First, put simply, the multivariate phenotype that selection sees is complex. Multiple skeletomuscular traits and endocrine and physiological pathways interact in a variety of ways to result in what an animal does (Fig. 4). Many of the studies cited in this review have made great strides in understanding this complexity, but more work is needed. Second, in some cases there are evolutionary or energetic trade-offs among components of a higher level trait, as well as positive and negative phenotypic and genotypic correlations among traits. Thus, morphology-performance links are likely more complicated than most studies acknowledge in practice (225, 258, 260, 264). Third, environmental factors, instead of features of the organisms themselves, can have a profound influence on how animals "perform" in nature and how selection then acts on performance and its underlying causes (Fig. 5). Using locomotion as an example, even if there is an appropriate stimulus, such as a predator, for an animal to sprint away at maximal speed, the substrate on which they are currently standing may be suboptimal for their morphology to allow them to reach their full potential speed (78, 186, 199). Even making the initial assessment of whether to run at full speed or not due to a stimulus will also be due to factors unrelated to musculoskeletal design, but instead the integration of sensory systems, neural processing, and sensorimotor integration. The result of these factors that often are not considered in performance studies is that we still do not know exactly how selection acts on whole-organism performance traits. Further work on "how" questions with "why" questions in mind will greatly help.

Selection in Natural Populations

In this section, I highlight studies that quantify how selection operates on physiological traits in nature. Each of these entailed capturing, measuring, marking, and recapturing the same individuals over time to monitor survival. In some cases the individuals' offspring were also captured, measured, marked, and genotyped with molecular genetic techniques to determine parentage and estimate reproductive success. This is no small undertaking for terrestrial vertebrates, but such studies are the only way to understand the form and strength of selection on morphology and physiology. Many of these studies are recent as calls for such data have been growing to compare selection on physiology to selection on other traits (215, 217). Here I use examples of traits that have a long history of study, and which are intuitively linked to fitness. Much of this work has focused on dynamic performance traits that involve movement of the body or its parts or hormone levels. Dynamic performance traits have been favored for selection studies because they often are easier to quantify than regulatory performance traits on large numbers of individuals, which are required for maximizing the possibility of detecting selection in a selection study. A growing number of studies have quantified selection on energy expenditure, especially RMRs, a regulatory performance trait with intuitive links to fitness. Another regulatory performance trait, thermal physiology, has been studied recently, though interest in global climate change will almost certainly increase the number of selection studies on thermal physiology. Finally, circulating hormone levels have been the primary focus in these studies over other aspects of endocrine function, because measuring hormone levels is fairly noninvasive and does not require death, target tissue harvest (such as brains or muscles), or other measures that might alter the fitness of individuals being studied.

Whole-organism performance: Locomotion

"Locomotion, movement through the environment, is the behavior that most dictates the morphology and physiology of animals." Dickinson et al. (93) made this statement, though its prescience would not be known until later that decade when more studies of selection on locomotion were conducted (189). For many terrestrial vertebrates locomotor performance is intuitively linked to survival and reproductive success, because locomotion is used to capture prey, escape predators, and acquire and defend mates (26, 29, 47, 59, 73, 116, 121, 130, 171, 238, 261, 281, 293, 316, 317). There are

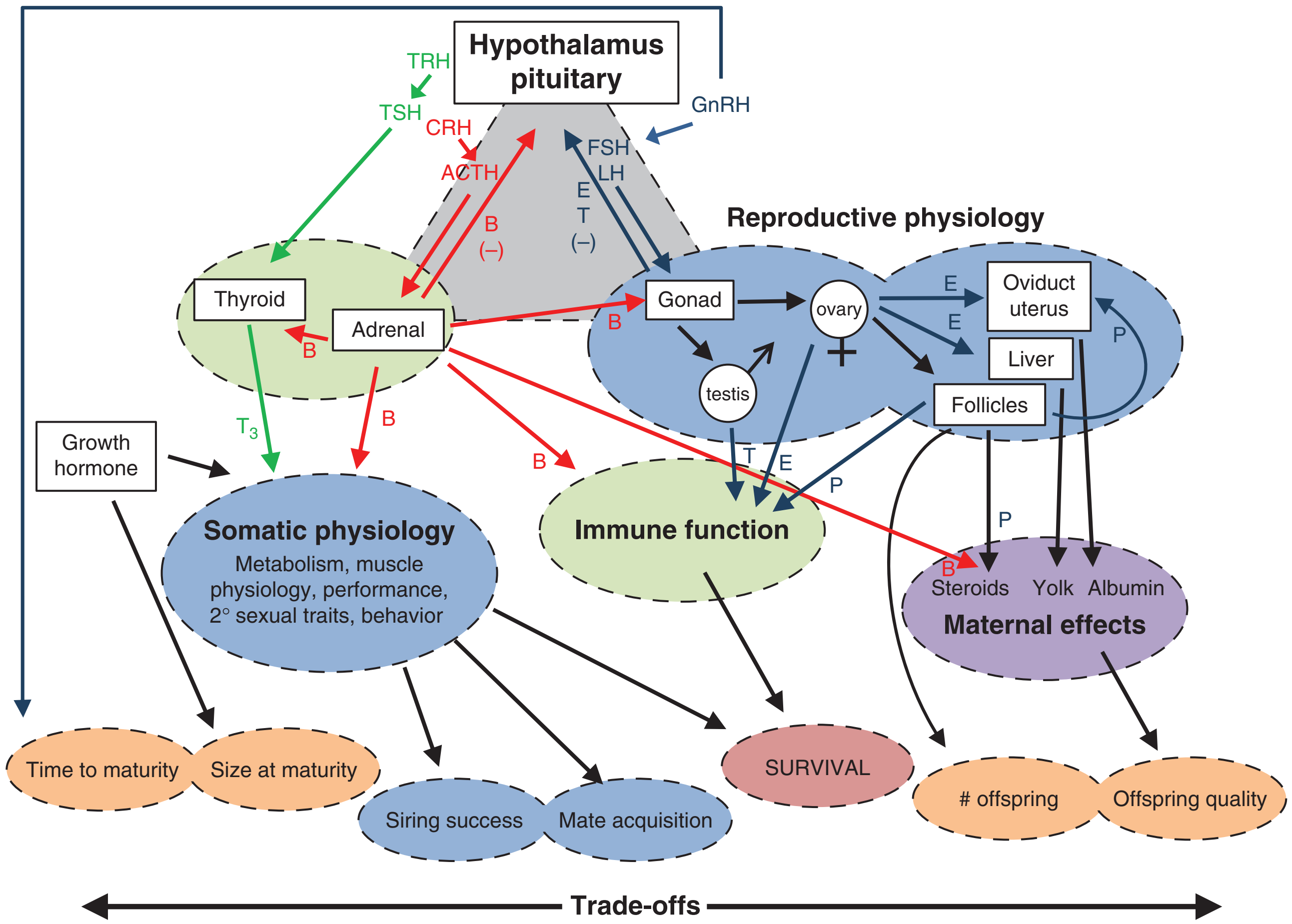

Figure 4 Graphical illustration of trait integration due to endocrine regulation of multiple systems in the vertebrate body. This figure is a modified recreation of Figure 1 in Sinervo and Calsbeek (313) used with permission. The hypothalamic-pituitary-gonadal (HPG) axis and HPA axis (depicted in the top triangle) mediates various physiological and life history traits associated with somatic and reproductive physiology, which contribute to the two major components of fitness, survival (in red) and reproductive success (in orange ovals). Phenotypic and genetic correlations result in trade-offs among traits, such that selection on any one trait can have effects on numerous others. This is a simplified illustration of links known in side-blotched lizards (313) and other vertebrates, but many other links could be added. Hormone abbreviations are as follows: ACTH, adrenocorticotropic hormone; B, corticosterone; CRH, corticotrpin-releasing hormone; E, estradiol; FSH, follicle-stimulating hormone, GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone, P, progesterone; T, testosterone, T_3, triiodothyronine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; (-), negative feedback within the HPA and HPG axes.

now several studies that have documented selection on locomotor performance traits. The earliest such study (195) provided crucial insights into how selection operates in nature on performance traits. Measurement of survival for over 500 garter snakes (*Thamnophis sirtalis*) in two different years revealed positive directional selection on sprint speed for juveniles, but only in one of the 2 years studied. There was also some evidence for weak stabilizing selection on a measure of endurance (distance run until refusing to run further). Subsequent studies on determinants of lizard survival also found directional selection for high sprint speed in juveniles (257, 345) and adults (61, 62, 187), as well as some evidence for weak stabilizing selection (187). Stabilizing selection has also been documented for endurance capacity of female *Uta stansburiana* lizards (259). In this latter case, the burden of gravidity acts indirectly through effects on survival. Several studies have failed to detect significant selection on sprint speed (hatchling *Chelydra serpentina* turtles: 191; lizards: R. Huey, pers. comm. cited in 189; snakes: 53) or endurance capacity (lizards: 74, R. Huey, pers. comm. cited in 189).

One of the most comprehensive studies of selection on performance in natural populations was in collared lizards (*Crotaphytus collaris*), a species in which behavior varies between sexes and during ontogeny. Females do not typically actively defend territories, whereas sexually mature males are socially suppressed their first year and do not defend territories until their second year (16, 17). Hence, whereas prey capture and predator escape may be relevant selective forces for all age classes, selection for territory defense may be more relevant for territorial adult males. Husak and colleagues (168-170, 172) measured selection in a population of collared lizards in Oklahoma, looking at whether maximal sprint speed predicted survival and reproductive success.

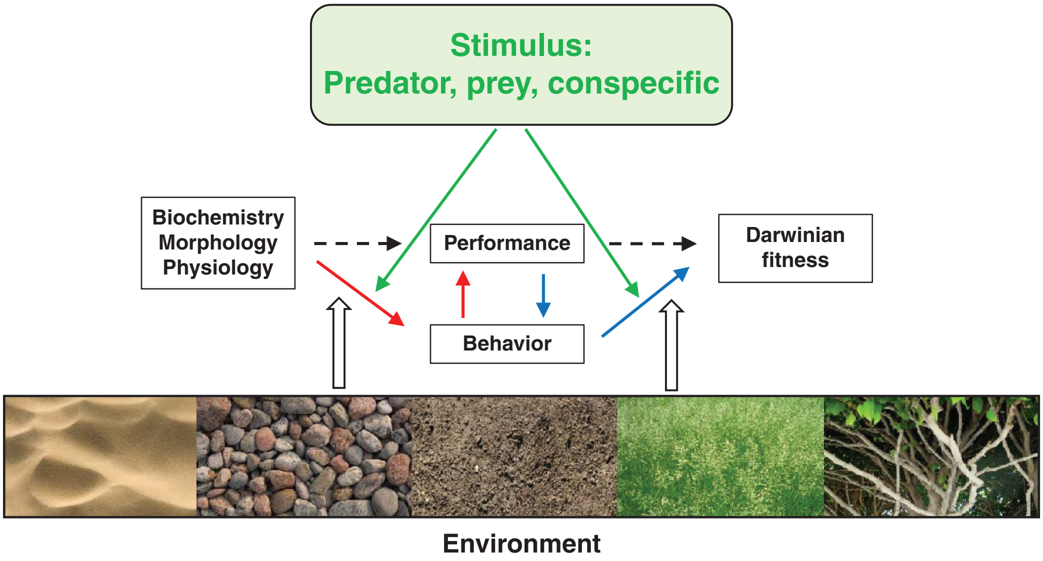

Figure 5 Diagrammatic representation of the environment may alter links in the morphology-performance-fitness paradigm (12). How an organism uses its physiology to perform in a situation may be due to assessment of a stimulus (e.g., run quadrupedally or bipedally) or constraints placed on performance by the physical substrate on which the organism performs (e.g., standing on sand vs. in grass). Both alter how lower level traits predict performance. Similarly, the assessment of how to respond to a stimulus (e.g., run quickly away or hide slowly) and the physical substrate can alter how performance affects fitness. Given these factors, selection studies of physiology in nature should consider traits important to detecting and assessing environmental stimuli (i.e., sensory systems, neural processing, and sensorimotor integration), as well as how performance is altered on relevant substrates (i.e., performance sensitivity, 186) and what lower level traits predict performance on those diverse substrates.

Adult lizards were captured, marked, and measured for maximal sprint speed early in the breeding season and monitored to the next breeding season. They also determined what percentage of their laboratory-measured maximal sprint speed was used in nature (see also 152, 184) while capturing simulated prey, escaping a simulated predator, and responding to a rival introduced into their territory/home range (170). They then determined whether maximal capacity or speeds used in nature predicted survival. In addition, Husak and colleagues also examined selection on maximal sprint speed in hatchling lizards, a group that had not yet been through a round of selection as free-ranging individuals. All individuals were genotyped with molecular genetic techniques to determine reproductive success and whether performance predicted that component of fitness.

Faster sprint speeds provided a survival advantage to hatchling lizards but not adults (168; Fig. 6). However, faster speeds used while escaping a simulated predator provided a survival advantage to adults (169). Speeds used in foraging and responding to consexual rivals did not predict survival. These findings imply that there is selection for an "adequate" speed that adult individuals must attain to effectively escape a predator (169). These results were in agreement with the examination of field speeds: no age class used maximal capacity when capturing prey (25%–45% of maximal used) or escaping a predator (60%–80% of maximal capacity), but adult males used greater than 90% of maximal capacity while responding to an intruding rival male (170). Concordant with this last finding, higher sprint speeds increased the number of mates and reproductive success of adult males (172; Fig. 6). Faster males were better able to defend a larger area with more females while preventing rival males from inseminating defended females, as evidenced by the finding that females defended by faster males had a lower number of offspring sired by males that were not defending them (173). These field selection studies revealed ontogenetic and sex differences in the nature and strength of selection operating on sprint speed, emphasizing the complexity of how selection shapes the underlying morphological and physiological traits that are indirectly affected over evolutionary time.

Studies of selection on locomotor performance in nature have revealed that such traits are in fact targets of selection, but it is unlikely that selection acts solely on the traits measured. That is, fitness is influenced by suites of traits. Work by Calsbeek and colleagues on brown anole lizards (*Anolis sagrei*) in The Bahamas show that correlational selection can be important in the evolution of physiological traits. In the arboreal Caribbean *Anolis* lizards, limb length differences among species has likely resulted from selection on maximizing stability on the portions of trees that each species uses most frequently: longer legs are better on broad-diameter surfaces, whereas short limbs are better on narrow-diameter surfaces (186, 199). Indeed, such selection has resulted in assemblages of anole species with specialized morphologies having reevolved independently across islands in the Greater Antilles (240). Calsbeek and Irschick (62) measured limb morphology, locomotor performance, and survival in Bahamian *A. sagrei*, finding that long-limbed lizards ran faster

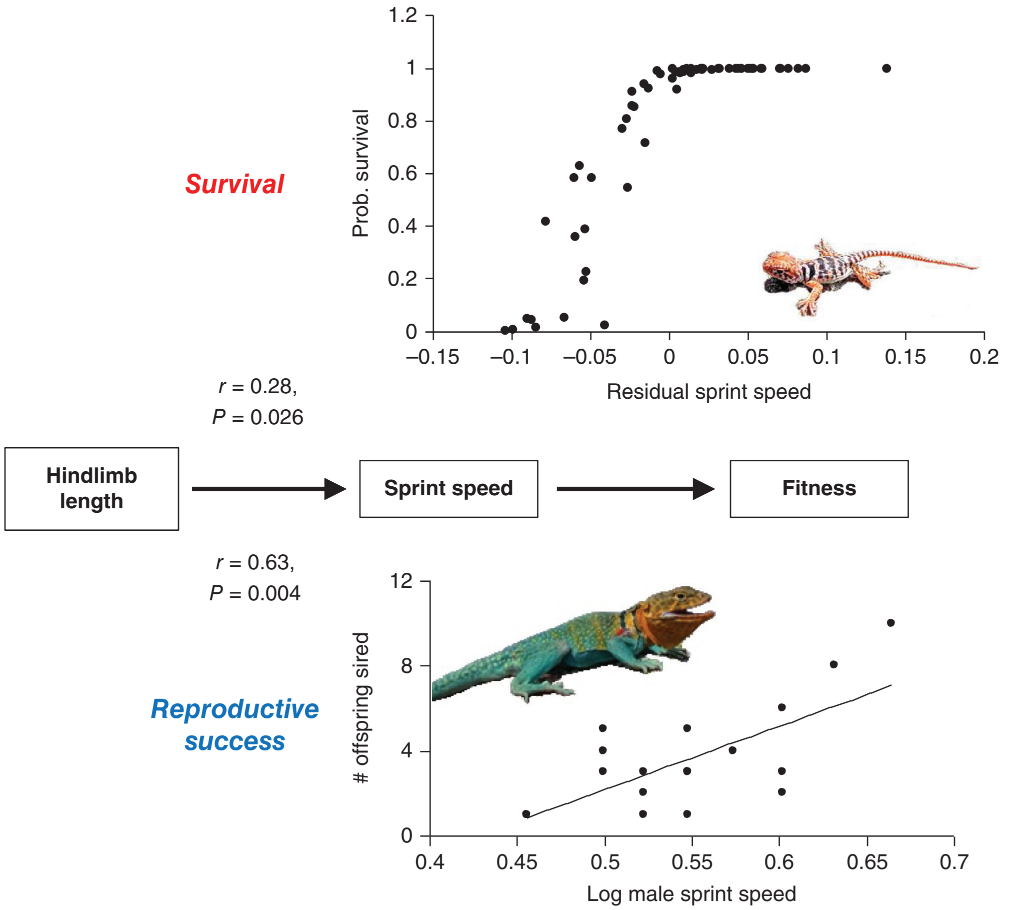

Figure 6 An example of the morphology-performance-fitness gradient quantified in nature in collared lizards (*Crotaphytus collaris*). Size-corrected limb length predicts maximal sprint speed in hatchlings (upper figure) and adult males (lower figure). Survival was only predicted by maximal sprint speed in hatchlings (168), whereas reproductive success of adult males was predicted by maximal sprint speed (172). The evolutionary response to these bouts of selection in nature would not only include limb length, but also other traits that contribute to variation in maximal sprint speed.

on broad surfaces but had decreased speed on narrow surfaces, a phenomenon called sprint sensitivity (186). Accordingly, there was detectable correlational selection for long-limbed lizards that were fast on broad surfaces, and preferred broad substrates, as well as short-limbed lizards that were less sprint sensitive on narrow surfaces, and preferred narrow perches in nature (62). While this pattern was clear in males, there was only weak correlational selection on body size and sprint speed in females, and there was no detectable selection on endurance capacity in males or females (61). This is a clear demonstration that selection can simultaneously act on combinations of morphology, performance, and behavior (see Fig. 2), but more studies are needed to determine how strong such correlational selection is and how common it is in nature.

Whole-organism performance: Bite force

The maximal force that an individual can bite, bite-force performance, is another performance trait that has intuitive ties to fitness. Biting may be important for escaping predators, capturing and processing prey, or fighting rival conspecifics (149, 150, 182, 224, 232, 324). Despite the vast literature on bite force, surprisingly few studies have investigated its fitness consequences, especially survival. The one study that tested whether maximal bite-force performance predicted survival found no such selection in adult male collared lizards, *C. collaris* (176). However, the advantages of bite force during male-male interactions have been extensively studied. Stronger bites have been associated with winning fights in numerous lizard species (138, 175, 182, 224). Work on the Oklahoma collared lizard population described above (see "Whole-organism performance: Locomotion") revealed that adult males in this highly territorial species with a stronger bite have larger territories that overlap more females (231) and sire more offspring (176). Much of the available data thus suggest that species with significant sexual dimorphism in head size and shape have intense sexual selection on bite force, resulting in the evolution and maintenance of dimorphism in morphology and physiology of the trophic apparatus.

An interesting contrast to the growing evidence that increased bite force should increase reproductive success of males (or at least that there should be stabilizing selection), is the work on the Dalmatian wall lizard, *Podarcis melisellensis*, by Huyghe and colleagues, which reveals a different pattern. Males with harder bite forces are more likely to win fights than those with weaker bites during staged interactions (181), but this advantage is not borne out in the wild when reproductive success is determined with molecular genetic techniques. Instead, there was negative directional selection on bite-force performance (and sprint speed), showing that poor performers sire more offspring (180). This paradox is likely better understood with evidence that females, when given a choice in a laboratory setting, prefer males with weaker bites (181; see also 179), but the relative roles of male-male combat and female choice are not resolved, nor are the behavioral strategies of males in the population studied. The authors suggest possible reasons for their results, including two intriguing possibilities. First, perhaps females avoid males with hard bites to avoid injury, since biting is common during copulation. Second, perhaps the strength of sexual selection via female choice of weak biters, regardless of the reason, is stronger than selection for male combat success via strong biting. Whatever the reason in this case, the work by Huyghe and colleagues, as well as the work by others on bite force and locomotion described above, strongly suggests that physiology can be shaped by sexual selection in addition to natural selection (59, 171, 226, 358). What remains to be seen is whether the link between physiology and mating success is straightforward, with high performers enjoying greater fitness, or more complicated, as in wall lizards.

Divergent evolution of Darwin's finches from a common ancestor likely involved strong selection to avoid competition on the Galápagos Islands, and current selection maintains current morphological diversity (124). In the medium ground finch (*Geospiza fortis*), dynamic selection processes maintain a bimodal distribution of beak sizes on Santa Cruz Island. Hendry et al. (140) examined patterns of selection on this island by testing for a relationship between individual beak sizes and interannual recaptures during a prolonged drought. They found disruptive selection on beak size, which reflects bite force capacity (149). However, they also found evidence of selection against extremely large and small beak sizes. These findings suggest that disruptive selection can favor adaptive divergence, but that opposing selection may constrain the functional and morphological outcomes of that selection.

Energy expenditure

All organisms allocate finitely available resources that they acquire to a variety of physiological processes important to fitness, including maintenance, growth, and reproduction, forming the basis for life-history trade-offs (225, 322, 361; see also the "energetic definition of fitness" as developed by 57). Energetic allocation of resources can be considered and investigated as compartments of energy use. One category consists of measures of the lowest rate of metabolism necessary to stay alive (252, 322, 348), but there are subtle differences in what this measure entails across vertebrates. SMR is the lowest metabolic rate at some temperature in a resting, postabsorptive ectotherm, whereas basal metabolic rate (BMR) is measured in endotherms and includes the energetic cost of metabolically maintaining body temperature. RMR is often applied to both ectotherms and endotherms, and is the lowest metabolic rate in a postabsorptive individual at rest (58,252). For simplicity and inclusivity, I use RMR to refer to each of these unless specificity is important to the example. At the other end of the energetic continuum is MMR, which is the maximal oxygen consumption during aerobic activity (252). DEE represents how much energy is used by an individual for any physiological process that occurs in a day, and the magnitude of such measures are strongly influenced by current growth rates and reproductive status, among other things (108, 252).

When one considers how energy allocation might impact fitness, it can help to consider these various components of allocation. For example, if maintenance costs are high in one individual, but resource acquisition is approximately equal to others, then individuals with lower maintenance costs will have more energy to allocate to traits important for survival and reproduction (225, 321, 323, 337). However, this prediction is not as straightforward as it seems upon first consideration, as higher maintenance costs may be due to morphology and physiology that can increase survival and reproductive success (33, 58, 72, 221, 222). Indeed, one can logically argue for both positive and negative relationships between RMR and fitness (43, 58). Individuals with low RMR may have higher fitness because they have more energy to devote to survival and reproduction instead of maintenance (the "compensation hypothesis"). Individuals with high RMR may also have increased mitochondrial production of reactive oxygen species, which could increase cell damage and decrease longevity (the "free-radical" hypothesis of aging; 133). However, there is currently a great deal of debate about whether oxidative damage represents a mechanistic link between high RMR and reduced survival (46, 319, 320).On the other hand, individuals with higher RMR may have larger organs and greater "metabolic machinery" for higher MMRs, allowing greater assimilation of energy for survival and reproduction (the "increased intake" hypothesis). Similarly, it has been difficult to predict the relationship between fitness and DEE. A positive relationship is intuitive, because reproduction is energetically expensive (108), but DEE can be strongly affected by environmental factors (329) and high DEE may be indicative of high physiological costs (94, 361). MMR has been hypothesized to be positively related to survival and reproductive success, since it is linked to locomotion and competitive success, especially in males (108). Such theoretical uncertainty about how metabolism, and energy expenditure in general, affects fitness makes field selection studies invaluable to our understanding of how metabolic rates and energy allocation strategies evolve.

Negative directional selection on RMR, with survival as a measure of fitness, has been reported from natural populations in a bird species (Leach's storm-petrels, *Oceanodroma leucorhoa*; 34) and a mammal species (North American red squirrels, *Tamiasciurus hudsonicus*; 233), while one study found positive directional selection in a mammal (short-talied field vole, *Microtus agrestis*: 190). Stabilizing selection on RMR was found in eastern chipmunks (*Tamiasciurus striatus*; 66). Selection studies on DEE have largely revealed nonsignificant relationships between DEE and fitness (66, 347), though DEE has been associated with increased litter size (30, but see 203) and chick growth rate (269). In North American red squirrels, lactating females with greater DEE had higher annual reproductive success than those with lower DEE (i.e., positive directional selection), but there was no stabilizing, disruptive, or correlational selection (108). It is worth note that the directional selection gradient for DEE ($\beta = 0.47$) is quite strong compared to selection studies on other physiological traits (Fig. 3). In deer mice (*Peromyscus maniculatus*), positive directional selection, but not stabilizing or disruptive selection, on MMR was found with survival as an estimate of fitness (137).

A comprehensive set of selection studies on free-living bank voles (*Myodes glareolus*) in Poland revealed interesting insights into how selection acts on energy expenditure (43, 44). Bank voles are a common forest-dwelling rodent in Europe and Asia, and the study site at which these studies were conducted have cold winters with long periods of snow cover. Thus, energy expenditure may be important to survival in different ways throughout the year, and Boratyński and Koteja (43) tested for selection on BMR and MMR (VO_{2max}) across the breeding season and over winter. Since the study was conducted on an island, survival was unlikely to be confounded by dispersal. They found no directional selection on either trait over any period of the year. However, they did detect significant stabilizing selection on male MMR during the breeding season (but not over winter). Stabilizing selection is likely a result of a trade-off for increased locomotor performance in those with greater MMR and increased mortality with higher activity levels (e.g., 139, 290). That is, individuals with low MMRs may be more likely to be ineffective at escaping predators, but individuals with high MMRs may be more likely to encounter predators with their increased activity. When examining mating success (number of mates) and reproductive success (number of offspring) as metrics of fitness, Boratyński and Koteja (44) found quite different results. Neither BMR nor MMR were consistently related to mating success in males or females. Reproductive success of females was not related to MMR but tended to increase with increasing BMR (though this relationship was not statistically significant). In males, there was a trend for disruptive selection on MMR and positive directional selection on BMR when considering reproductive success as the estimate of fitness. This latter finding was based on a quadratic term, but with higher BMRs having higher reproductive success than lower and moderate BMRs. The finding of no directional selection on MMR in males was surprising, as it was assumed that high MMRs would give males a competitive advantage. As the authors point out, perhaps the disruptive selection has led to different possible strategies for males to maximize their reproductive success. In sum, the authors conclude that their data in general support the "increased intake" hypothesis. Nevertheless, these studies on bank voles combined with other field selection studies on energy expenditure emphasize that much remains unknown about how selection molds metabolic rates and the energetic underpinnings of many life-history trade-offs.

Thermal physiology

Environmental temperature has a profound impact on a variety of physiological variables (9-11, 56, 162, 165, 305). For ectotherms that rely on their environment to modulate their body temperature, thermal physiology is likely under strong selection for individuals to tolerate, and function in, their thermal environment (236). Indeed, recent work predicts that global climate change may have major impacts on populations of ectothermic organisms, even those in the tropics (92, 160, 166, 167, 216, 235, 274, 328, 338). For ectotherms, many aspects of thermal physiology may be the targets of selection. For example, one could study how survival or reproductive success is predicted by the "effectiveness" of individual thermoregulation, which quantifies how far body temperatures deviate from an optimal (preferred) body temperature (T_{set}) relative to how far operative environmental temperatures deviate from that T_{set} (153). Aspects of thermal physiology are often studied relative to some other trait or suite of traits, such as performance (165). The critical thermal minimum (CT_{min}) and maximum (CT_{max}) represent lower and upper bounds respectively in which an organism can function in some capacity (165, 241). For example, loss of coordinated muscle function and the onset of muscle spasms can represent CT_{min} and CT_{max}, respectively (327). Between these extreme values is a *thermal performance curve* (8, 9, 162, 165), which empirically defines how some physiological trait responds to temperature (Fig. 7). Function is highest (maximal performance, P_{max}) at some optimal temperature (T_{opt}), and the range of temperatures in which performance is >80% represents the individual's thermal performance breadth. Each of these components, or a combination of these components, could be a target of selection (9, 163, 237). Unfortunately, little is known about how selection acts on any of these in terrestrial vertebrates.

Using a combination of correlational and experimental data, Logan et al. (237) studied selection on thermal physiology of brown anole lizards (*Anolis carolinensis*) in the Bahamas. First, they measured T_{opt}, P_{max}, and thermal

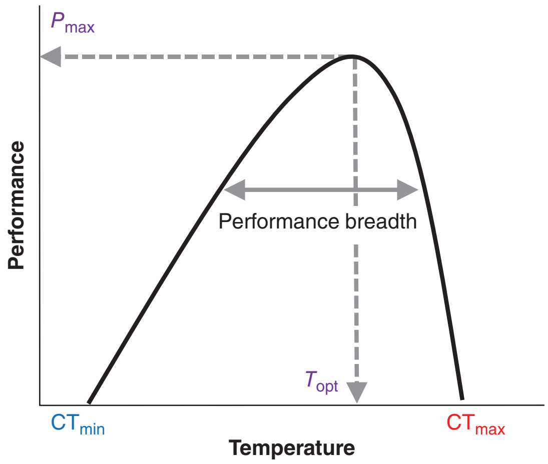

Figure 7 A hypothetical thermal performance curve that shows aspects of thermal physiology that may be targets of selection. The highest level of some function (maximal performance, P_{max}) occurs at the optimal temperature (T_{opt}), with function constrained between some lower (CT_{min}) and upper (CT_{max}) temperature. The range of temperatures in which function is >80% represents the thermal performance breadth. Performance can be broadly defined here to include a variety of physiological traits.

performance breadth (see Fig. 7) of individuals on Kid Cay, Great Exuma Island, monitoring survival over time. Then on another island (Eleuthera), they measured the same variables on individuals and transplanted them to a warmer location elsewhere on Eleuthera to track survival in relation to thermal physiology in a novel, warmer environment. They found evidence for weak, but not statistically significant, positive directional selection on P_{max} at both sites. In the initial reference population, there was no significant directional, stabilizing, or disruptive selection on any of the variables measured. However, the transplanted population experienced strong directional selection for higher T_{opt} and wider thermal performance breadths. It is noteworthy that just a 2.7°C increase in average environmental temperatures resulted in a 1.5°C increase in average body temperatures and strong selection gradients on T_{opt} ($\beta = 0.49$) and thermal performance breadth ($\beta = 0.56$). Thermal performance curves have been shown to be heritable (204, 254, 271), so selection would likely result in evolutionary change in the thermodynamics of enzyme function, which shape thermal performance curves (8, 11, 145). The results of Logan et al. (237) provide strong evidence that selection can shape thermal physiology in changing environments, including changes due to anthropogenic climate change, but they do not provide evidence that selection is currently operating on these aspects of thermal biology. Hence, future studies should seek to understand if and how selection operates on thermal physiology in natural conditions (164, 274).

Hormone levels

Hormones play key roles in coordinating behavior, physiology, and performance, responding to environmental variability, and regulating transitions among life cycle stages (1, 77, 84, 106, 206, 258, 260, 264, 268). Circulating steroid hormones, such as testosterone and corticosterone, produce wide-ranging phenotypic effects in vertebrates, modulating at least in part such disparate traits as reproduction, sexual signals, aggression, parental care, and seasonal changes in energetics, brain structure, and behavior (reviewed in 1, 135, 341), as well as variation in and trade-offs among life-history traits (reviewed in 67, 206, 225, 245, 249, 264, 291, 354, 361, 362). Because of the diversity of integrated phenotypic traits that are regulated by hormones (i.e., “hormonal pleiotropy”), many of which are important to fitness in perhaps different ways, endocrine systems represent a likely target for selection. Multiple lines of evidence indicate that the secretion of hormones, via regulatory effects on traits important to fitness, is shaped by both natural and sexual selection (357). Even though the proximate effects of hormone levels have been studied for decades, we still know remarkably little about how selection operates on circulating hormones and what leads to the incredible interindividual variability observed in natural populations (reviewed in 202, 357). Heritability is necessary for evolutionary change from selection, but heritability of endocrine system components is not well studied (357, 362). Hormone secretion has been shown to be consistent in several species during the breeding season (corticosterone: 76, 306; testosterone: 193,357) and is heritable in some taxa (corticosterone: 102, 196, 278; testosterone: 214, 309), but far more work is needed in this area.

Testosterone (T) in particular has been suggested to act as a critical link between morphology, physiology, performance, and fitness (67, 177, 198, 207, 260, 316; Fig. 4). While different components of an endocrine system may evolve independently (e.g., hormone levels, receptor densities and expression, binding globulins; 1, 135, 206, 249, 300), many have argued that circulating T levels might be key to fitness. For example, average circulating T levels have been shown to be associated with patterns of territoriality and mating systems across species (125, 156-158, 355), as well as breeding season length (birds: 36, 126; amphibians and reptiles: 97). Further, experimental manipulations of testosterone levels in a variety of taxa have revealed consistent effects on traits important to fitness, as well as direct components of fitness themselves (see “Selection on manipulated hormone levels”). Although other components of endocrine systems may well evolve to modulate species differences in behavior, morphology, and life history strategies, empirical data to date are only available for fitness effects of circulating T levels. Selection on receptor expression is problematic, as it is difficult to characterize variation in hormone receptors noninvasively so that selection on that variation can be determined. Much of the research on how testosterone impacts fitness has been through experimental manipulations, which I address below, but there are some studies that have examined the fitness consequences of natural variation in testosterone levels.

Positive directional selection on T, with mating success as a measure of fitness, has been reported from natural populations in some taxa (birds: 4, 45; mammal: 263) but not

Table 1 Total Annual Linear (β) and Quadratic (γ) Selection Gradients for Several Measures of Testosterone Secretion in a Wild Population of Dark-Eyed Juncos (*Junco hyemalis*)

Trait	β or γ	Type of selection
Initial testosterone	0.03	Nonsignificant (+) directional
GnRH-induced increase in testosterone	0.27	(+) directional
(Initial testosterone)^2	−0.13	Nonsignificant stabilizing
(GnRH-induced increase in testosterone)^2	−0.59	Stabilizing
Initial testosterone X GnRH-induced increase	−0.06	Nonsignificant correlational

Note: Squared terms represent quadratic selection, and the cross-product represents correlational selection. Data from McGlothlin et al. (251). Total gradients were calculated by adding selection gradients across survival and reproductive success (number of offspring, number of mates, offspring per mate, within-pair offspring, and extra-pair offspring) components of fitness. Initial testosterone represents circulating levels before a standard GnRH challenge, not baseline levels within a window of time before a stress response.

in others (bird: 55; lizards: 172, 198). The most comprehensive selection study to date on natural T variation was by McGlothlin et al. (251) on the well-studied Mountain Lake Biological Station (Virginia, USA) population of dark-eyed juncos (*Junco hyemalis*), a socially monogamous songbird species. In addition to studying only baseline circulating levels of T, which can be extremely variable within individuals (202,357), McGlothlin and colleagues also measured the magnitude of increase in T levels after experimental challenge with gonadotropin-releasing hormone (GnRH), a repeatable measure that reflects maximal T-secretion capabilities (193, 352). They also looked at a multitude of fitness components, including survival and reproductive success separated into number of offspring, number of mates, offspring per mate, within-pair offspring, and extra-pair offspring. This allowed an examination of how T levels affected each fitness component, but it also allowed the calculation of total selection gradients for each T-related trait summed across fitness components (248, 342). When survival was considered as the measure of fitness, there was detectable positive directional selection and strong stabilizing selection on GnRH-induced testosterone. The results were similar for reproductive success: directional selection on GnRH-induced T increases resulted from greater offspring per mate and within-pair siring success, but selection was mostly stabilizing (with a trend for nonsignificant negative directional selection) when mating success and extra-pair offspring production were the metric of fitness (Table 1). Despite the apparent benefits of higher T levels in males, there are most likely survival costs via suppressed immunity and increased susceptibility to predation (83, 109, 220, 243, 267, 282, 303, 349, 350). More studies are needed to determine how often the costs and benefits of high T levels result in stabilizing selection.

Glucocorticoids (GCs) are a group of steroid hormones with a multitude of functions in vertebrates. At baseline levels they are important for energy intake, metabolism, and mobilization, representing the allostatic load of an individual from the present to the recent past (246, 298), but at acute, stress-induced levels increase food intake, activity, and aspects of immune function, while suppressing growth, reproduction, and parental behavior (136, 295, 298, 304, 354). As part of the "stress response" in vertebrates, it is not surprising that GCs released during chronic stress may have different effects than baseline levels or acutely elevated levels (229, 298, 304). GCs are also important mediators of major developmental transitions (340), as well as life-history trade-offs (136, 260). The importance of GCs, such as corticosterone and cortisol, in so many fitness-related traits makes them obvious candidates to study as a predictor of survival and reproductive success. However, the fact that glucocorticoids do link so many systems has made predicting *how* they should affect fitness difficult. For example, while the "stress response" tends to suppress reproduction in the short term, it also promotes survival. Does this increased survival result in more chances for reproduction over an extended lifespan? The answer may lie in what aspects of GC physiology are studied, as several have been investigated in relation to fitness, each with a potentially different role in determining fitness (see Table 2). The relationship between GCs and fitness have received a great deal of recent attention (39, 51), with three alternative hypotheses

Table 2 Measures of Glucocorticoid Physiology that may be Measured to Determine Their Impact on Fitness

Measure of glucocorticoid	How measured	Interpretation
Baseline	Concentration before "stress response"	Integration of recent activity and stressors
Maximal	Highest concentration measured after stress response	Highest concentration that receptors experience during peak of stress response (often experimentally induced)
Integrated	Area under curve created by multiple sample points	Total quantity that receptors experience during stress response (often experimentally induced)
Fold increase	Maximal level/ baseline level	Proportional increase in concentration that receptors experience during stress response compared to typical, maintenance (baseline) concentration
Efficacy of negative feedback	Lowest concentration after given poststress synthetic GC to simulate feedback	Proportional decrease in concentration after receiving negative feedback

Note: Table and definitions modified from Patterson et al. (280) and Romero and Wikelski (297).

proposed on theoretical grounds and all having some empirical support.

The "cort-fitness hypothesis" (40) predicts that increased baseline GC levels will result in decreased fitness, whether fitness is measured as survival or reproductive success. This hypothesis is based on the observation that baseline GC levels increase with environmental challenges due to energetic demands, and as environmental challenges increase, GC levels rise and fitness decreases. The "cort-trade-off hypothesis" (354) predicts increased survival, but decreased reproduction, with increasing GC levels. Here, GCs are hypothesized to mediate a survival-reproduction trade-off by directing resources away from reproduction and toward survival (5, 280, 354). The "cort-adaptation hypothesis" (39) predicts increased survival and reproduction with increasing GC levels. Here, elevated GCs enhance behavior, such as increased foraging, that promotes both survival and reproductive output. It is important to note that the cort-fitness and cort-adaptation hypotheses apply to baseline GC levels, whereas the cort-trade-off hypothesis includes baseline and stress-induced GC levels. There is much debate about which aspects of GC physiology are most relevant to fitness directly (48, 280, 295) and whether "free" GC concentrations (i.e., not bound to proteins in the plasma) or total concentrations are more relevant, though the majority of studies focus on total concentrations (50, 52, 280, 294). Further, many have pointed out problems with using fold increase in hormone levels calculated from baseline to stressed conditions, as well as absolute change in hormone concentrations calculated from final levels minus initial levels. These variables are often examined as separate traits, but this may not be a valid assumption, and investigators should use caution when using and interpreting these variables (22, 295).

Empirical evidence for the relationship between GCs and fitness are mixed. Studies have mostly examined how GCs predict either survival or reproductive success separately, with one exception to date (280). When survival is the measure of fitness, there is both positive (79, 280) and negative (32, 296) directional selection on baseline GC levels (reviewed in 39) and negative (296) and positive directional selection on stress-induced GC levels (maximal: 60; maximal and integrated GC levels: 280). Romero and Wikelski (297) found that the only measure of GC physiology to predict Galápagos marine iguana (*Amblyrhynchus cristatus*) survival during an El Niño year, when starvation is a high risk, was the ability of individuals to appropriately regulate the termination of the GC stress response (measured as experimentally induced negative feedback with dexamethasone). In their study, survival was not predicted by baseline, stress-induced, or adrenocorticotropin-induced GC levels. When reproductive success is the measure of fitness, there is both positive (198, 280) and negative (40) directional selection on baseline GC levels and negative directional and disruptive selection on fold-increase in GC levels (280; see Table 2 for definitions). The study by Patterson et al. (280) is noteworthy in that all four measures of GCs in Table 2 were examined for both "free" and "total" GC levels as potential predictors of survival *and* reproductive success. Their results supported both the cort-adaptation (higher GC levels increased survival and reproduction) and the cort-trade-off hypothesis (higher GC levels enhance survival over reproduction). However, they caution that their baseline levels were mostly on the low end of concentrations, with very few high values, and their results cannot conclusively determine how moderate-to-high baseline GC levels affect fitness. They also hesitated to conclusively say that there was disruptive selection on fold-increase in free GC levels, as the relationship was from a relatively small sample size ($N = 22$), which can bias estimates of quadratic selection (217). Comprehensive studies such as Patterson and colleagues' (280) are necessary for a better understanding of how selection shapes GC physiology. Romero and Wikelski (297) further emphasize that GCs may impact fitness in a manner that depends on the metabolic state of the individuals. This suggests that we should expect to find correlational selection between metabolism and GCs. The next major advance will be to also incorporate physiological traits that are mediated by GCs to more directly impact survival and reproductive success.

Manipulating Phenotypes: Phenotypic Engineering

Manipulating phenotypes has a long history in physiological research because experimental manipulations can give stronger conclusions about cause-and-effect relationships that correlational studies, including field studies of selection, cannot. The classic experiments by Arnold Berthold (31) on cockerels embody the powerful insights obtainable even from "simple" manipulations: castrated cockerels did not develop combs or have male-typical behavior, but replacing testes, even from another male, in the abdominal cavity restored the male-typical morphology and behavior. Both supplementation and removal experiments have given powerful insights into physiological function, and the use of pharmacological blocking of action at the molecular level has made manipulations more specific and subtle than removing whole organs. Such phenotypic manipulations allow researchers to choose the range of variation for a trait that is studied, including supra- and infraphysiological levels of a molecule (Fig. 8). From an evolutionary perspective, measuring selection on manipulated phenotypes can offer insights about constraints by looking at the consequences of physiological processes at extreme levels that do not occur in nature, thus increasing the power to detect selection (209, 312). Although manipulating phenotypes cannot give estimates of selection on natural variation in nature (and thus how evolutionary processes work), such an approach can provide clearer details on the qualitative form of selection operating on traits of interest, as well as the nature of physiological trade-offs and evolutionary constraints (99, 206, 209, 249, 265, 307, 312, 343). For example, why is a particular hormone level not higher if it has fitness benefits? Conversely, if a physiological process is costly, why

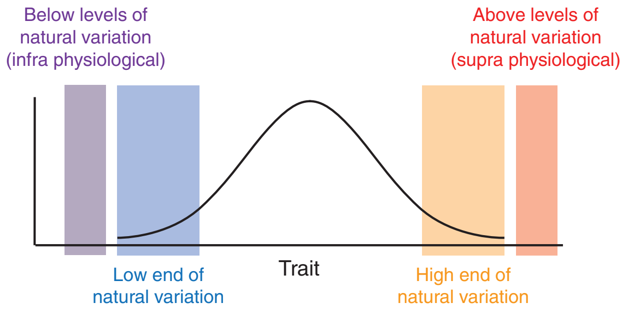

Figure 8 Manipulating phenotypes experimentally can shift the distribution of a continuous trait to what is desired by the investigator to answer a question about the adaptive nature of a physiological trait. Supplements or chemical treatments can be used to shift variation toward the high end of natural variation (orange) or above it into supraphysiological ranges (red). Conversely, organ ablation or chemical blocking actions can be used to shift variation toward the low end of natural variation (blue) or below it into infraphysiological ranges (purple). Studies that use infra- and supraphysiological ranges of variation cannot reveal advantages of current physiology, but they can yield powerful insights into constraints and the adaptive value of current variation.

is it not reduced or absent all together? Such questions can only be answered by manipulating phenotypes and examining the fitness consequences. Manipulation studies may alter a single trait, or suites of traits that are pleiotropically linked. In the latter case, the evolutionary response is likely to be more complex due to potentially different selective contexts that are simultaneously operating on the correlated traits (see Fig. 4). However, an advantage of manipulating phenotypes is that it can be used to reduce collinearity among variables when estimating how selection operates on suites of traits, creating a larger range of phenotypic combinations and eliminating many naturally existing correlations among traits of interest. In this section, I focus on phenotypic manipulations that alter physiological traits where fitness consequences of the manipulations have been well studied. I do not review the plethora of studies that manipulate phenotypes and measure other endpoints, such as the effects of a phenotypic manipulation on other physiological or life-history traits, or those that are conducted in a laboratory setting.

Selection on manipulated hormone levels

Manipulations of hormone levels in free-living vertebrates have provided strong evidence of the fitness consequences of variation in physiology (211, 361). Hormonal implants have been used extensively to determine whether and how hormone levels affect components of fitness, such as survival and reproductive success, as well as proxies for fitness, such as mate choice, aggression, and space use (86, 89-91, 112, 205, 243, 268, 287, 314, 353). More recently, receptor antagonists, such as the anti-androgen flutamide, the antiestrogen tamoxifen, and the aromatase-inhibiting fadrozole, have become more commonly used as a means to decrease endocrine function without ablation of organs or tissues (273,310,344,346,351). Often studies that use antagonists have an experimental design that also includes hormone supplementation to fully explore causation of hormone action on the phenotype and some component of fitness. In this section, I review selection studies that have manipulated the steroid hormones discussed earlier, testosterone and GCs.

Testosterone supplementation studies have revealed the fitness costs and benefits of high testosterone levels (262). Numerous studies that experimentally increased or decreased testosterone levels have shown an increase or decrease, respectively, in male agonistic behavior, growth and body size, and expression of sexual signals across a variety of vertebrate taxa (e.g., 206, 209, 211, 243, 331). Although there are clearly predicted positive effects of higher testosterone levels, especially in males, there are also clear negative effects predicted, phenomena that experimental manipulations may better detect. High testosterone levels have been shown to be associated with decreased survival due to increased activity and conspicuousness to predators or decreased immune function (83, 109, 220, 243, 267, 282, 303, 349, 350). Although the survival cost of experimentally high testosterone levels has been fairly consistently found, the mechanism by which survival decreases is less clear, and future studies that assess *how* high-testosterone individuals succumb will be valuable.

Dark-eyed juncos have served as a model system for examining the fitness effects of experimentally manipulated testosterone levels (see also "Hormone levels" above). The juncos studied by Ketterson, Nolan, and colleagues starting in 1983 have provided a wealth of information on the precise fitness consequences of testosterone levels in male and female individuals (206, 288). In this socially monogamous species, males defend territories during the entire breeding season, and both parents care for young (209), though extra-pair fertilizations are common (213, 287). Many of these traits that are associated with successful reproduction, including territorial aggression and parental care, are mediated by testosterone (206). Experimentally increasing testosterone levels in males increased territorial aggression (205) and extra-pair fertilizations (287, 288), but it also decreased male survival (288), male parental care (211), and growth of nestlings (likely as a function of decreased feeding by the male, 211, 288). What is notable is that the survival disadvantage of high testosterone levels was only present during the breeding season while the treatment was occurring, but not in the winter after treatment had ceased (288). The effects of testosterone on decreasing life expectancy is likely due to the detrimental effects of increased activity and conspicuousness to predators (100), decreased immune function (68), and increased GC levels (212), each of which may directly or indirectly lead to higher mortality than control individuals (288). The high cost of elevated testosterone levels on survival suggests a strong constraint on high testosterone levels, but reproductive success must be considered to fully understand how Darwinian fitness is impacted. Data collected on individual juncos over 7 years revealed that males with elevated testosterone levels had significantly more extra-pair fertilizations than control males (288, see also 287), almost certainly because testosterone-supplemented males had larger home ranges, increased courtship behavior, and were more attractive to females than control males (69, 100). The decrease in survival is more than made up for by an increase in reproductive success before death. These findings suggest that there should be strong directional selection for higher testosterone levels that are not seen in nature (288), a paradox that can be resolved when considering the effects of high testosterone levels in males on offspring and mate quality. Compared to control males, high-testosterone males reduced feeding of offspring, and nestlings had significantly lower growth, and were smaller at fledging, (288), which can lead to detrimental effects on survival and reproduction of those nestlings as adults (3, 64). Females mated to high-testosterone males compensate for the reduced parental effort (205, 211), which can negatively influence the females' condition (68, 359) and immune function (208).

Selection on female testosterone levels may also constrain the evolution of high male levels. Female juncos implanted with exogenous testosterone have delayed egg-laying, decreased parental care for nestlings, and lower rates of daily nest survival (75, 279). Further, in a study designed to examine how female survival and reproductive success was affected by supplemental testosterone, high-testosterone females were less likely to build a nest, laid fewer eggs once they had built a nest, and were less likely to have those eggs hatch (122). Increasing testosterone did not have a detectable effect on extra-pair fertilizations as it did in male juncos. Survival was not affected by testosterone supplementation, so lower fitness in female juncos was due to decreased reproductive success that occurred primarily early in the reproductive cycle (122). These results are mostly consistent with a study of supplemental testosterone in female spotless starlings (*Sturnus unicolor*), where testosterone-implanted females had decreased reproductive success compared to control females (239, 339). Testosterone is likely (though not definitively) genetically correlated between male and female juncos (210), suggesting that selection against high testosterone levels in females may keep male testosterone levels lower than what may be optimal for male fitness due to selection solely on males (213, 249). Such sexual conflict (13, 37, 38, 70, 82) is likely common where the sexes have differing evolutionary interests and may be an important constraint in the evolution of physiological traits (174), but there is still little data to say definitively.

Experimental manipulations of GCs have been important to our understanding of how hormones known for their metabolic and stress-response roles impact fitness. GCs can enhance survival, but they are also known to suppress immune function and reproduction at chronically elevated levels (247, 304; see also "Hormone levels"). Thus, the two primary components of fitness may be affected differently as discussed above. Several studies have shown that corticosterone implants alter fitness-related traits, such as decreased home range size (compared to controls, 89, 90) and male agonistic behavior in male *Uta stansburiana* (91) and *Anolis sagrei* lizards (330), as well as increased locomotor activity in *U. stansburiana* (91) and Gambel's White-crowned sparrows (*Zonotrichia leucophrys gambelii*; 49). These effects make sense if GCs serve to increase survival in the moment at the expense of other functions, such as reproduction (297, 304). Exogenous corticosterone enhanced survival of female *U. stansburiana* in two separate field studies (79, 314), and experimental elevation of female corticosterone in common lizards (*Zootoca* [= *Lacerta*] *vivipara*) resulted in enhanced survival of their juvenile offspring (256). Cote et al. (81) showed that experimental supplementation of corticosterone increased survival of male *Z. vivipara* lizards compared to controls, but this relationship was not found in females. While it appears that elevated levels of GCs may enhance survival, the long-term consequences of variation in the components of GC physiology remain ambiguous and warrant further research. Experimental manipulations appear to provide support for both the cort-adaptation and cort-trade-off hypotheses. The complex manner in which GCs interact with the phenotype at baseline and stress-induced levels to directly and indirectly impact fitness, as well as recent findings that the ability to turn off the stress response might be key (297), leave much to be done. Advancing our knowledge further will require creative manipulations of multiple components of GC physiology to discover which of those components leads to variation in survival and reproductive success.

Conclusion

Selection studies in the wild can reveal evolutionary processes in action, giving us a glimpse of how phenotypes evolve. There are now a large number of studies that have measured selection on traits in nature, but few of them consider physiological traits, especially in comparison to morphological and life-history traits (99, 217). Thus, although physiological systems are the key to organismal function and individual fitness, we know surprisingly little about how physiology evolves. The available data include studies on only a few types of physiological traits (whole-organism performance, metabolic rates, thermal physiology, and hormone levels) but suggest that selection operates on physiology in a manner similar to other traits: directional selection is strong and at least as common as stabilizing and disruptive selection. However, the interconnectedness of physiological systems in particular requires a more integrative approach to selection studies than is typically done. Most selection studies, on physiology or otherwise, consider one trait at a time, or only one component of fitness (survival or reproductive success), but there are exceptions to that strategy that have been particularly illuminating to our understanding of how selection operates on physiology. The interconnectedness of physiological systems that I emphasized in this review means that correlational selection is likely common for physiological traits, but very few studies have taken this approach, and it is not clear how common or strong correlational selection actually is in nature. Studies are needed that quantify multiple traits, each of which may impact fitness, and whose interaction might impact fitness. It is never possible to measure all possible traits, but aiming for multiple traits that likely impact fitness is essential for forward progress in our understanding of how physiology evolves in phenotypes that are integrated units.

Manipulating phenotypes can greatly complement selection studies. Whereas the latter studies give information about patterns of selection in nature, the former can tell us what evolutionary constraints exist for physiological traits. For example, if how effectively one turns off the stress response is important to fitness, then manipulating individuals with hormone implants so that they cannot turn it off would reinforce a correlational selection study. Studies to date have revealed trade-offs between components of fitness, where decreased survival, for example, might be offset by higher reproductive success during a shortened life. Manipulations may also help to reveal other factors that contribute to the evolution of physiology, such as intersexual genetic correlations and sexual conflict, where males and females have different fitness optima for the same physiological traits or systems. Manipulating phenotypes may also break up correlations among traits, thus allowing investigation of specific traits without confounds of another. A research program that uses a combination of selection studies and phenotypic manipulation, which includes high and low ends of natural variation, as well as infra- and supraphysiological levels, can provide strong inferences about what evolutionary processes lead to physiological diversity present today.

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