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REVIEW

Conserved and convergent mechanisms underlying performance–life-history trade-offs

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ABSTRACT

Phenotypic trade-offs are inevitable in nature, but the mechanisms driving them are poorly understood. Movement and oxygen are essential to all animals, and as such, the common ancestor to all living animals passed on mechanisms to acquire oxygen and contract muscle, sometimes at the expense of other activities or expression of traits. Nevertheless, convergent pathways have also evolved to deal with critical trade-offs that are necessary to survive ubiquitous environmental challenges. We discuss how whole-animal performance traits, such as locomotion, are important to fitness, yet costly, resulting in trade-offs with other aspects of the phenotype via specific conserved and convergent mechanistic pathways across all animals. Specifically, we discuss conserved pathways involved in muscle structure and signaling, insulin/insulin-like signaling, sirtuins, mitochondria and hypoxia-inducible factors, as well as convergent pathways involved in energy regulation, development, reproductive investment and energy storage. The details of these mechanisms are only known from a few model systems, and more comparative studies are needed. We make two main recommendations as a framework for future studies of animal form and function. First, studies of performance should consider the broader life-history context of the organism, and vice versa, as performance expression can require a large portion of acquired resources. Second, studies of life histories or mechanistic pathways that measure performance should do so in meaningful and standardized ways. Understanding proximate mechanisms of phenotypic trade-offs will not only better explain the phenotypes of the organisms we study, but also allow predictions about phenotypic variation at the evolutionary scale.

KEY WORDS: Life history, Mitochondria, Muscle, Performance, Reactive oxygen species, Trade-offs

Introduction

Life-history theory is essential for explaining phenotypic expression and variation. Finite resources render trade-offs inevitable, including the ubiquitous survival–fecundity trade-off, but shared mechanistic pathways may also drive phenotypic trade-offs independent of energy availability. Despite decades of life-history research, we do not fully understand how phenotypic trade-offs occur across the integrated organismal phenotype and whether such trade-offs, and the mechanisms that govern them, are fundamentally the same across species (Braendle et al., 2011; Wingfield, 2018). Life-history traits pertain to organismal life cycles, and include fecundity, longevity and age at first reproduction. Although these appear so diverse that shared underlying mechanisms of expression seem unlikely, many ecologically relevant features of the integrated organismal phenotype are subject to trade-offs with others. The causal factors driving such trade-offs include both proximate, such as shared endocrine signals, and ultimate factors, including the genetic architecture and antagonistic selection regimes (Finch and Rose, 1995; Hau, 2007; Zera and Harshman, 2001; Ricklefs and Wikelski, 2002; Hau et al., 2010). Importantly, the ubiquity of specific life-history patterns across the animal kingdom strongly suggests that mechanisms governing them might be highly conserved. However, ancient divergence of animal lineages could preclude shared mechanisms, because those mechanisms had not yet evolved in a common ancestor. Identifying causal pathways implicated in common life-history trade-offs could offer both predictive and mechanistic insight into other, related trade-offs that impinge upon those traits either within or across species.

Whole-organism performance traits refer to quantitative measures of how well organisms conducting dynamic, ecologically relevant tasks such as sprinting, flying or jumping (see Lailvaux and Irschick, 2006; Husak and Fox, 2008 for discussion of the reasoning behind this definition). Performance traits affect survival but are also energetically costly to develop, maintain and use, rendering them integral components of life histories and subject to trade-offs with other life-history traits (Ghalambor et al., 2003). Performance–life-history trade-offs are likely common, yet typically demonstrated only in specific study systems or as isolated studies (Lailvaux and Husak, 2014). For example, experimental immune challenges alter reproductive output (Metcalfe and Graham, 2018; Adamo, 2017) and performance capacities (Zamora-Camacho et al., 2015; Husak et al., 2021; Hudson et al., 2021), whereas increasing investment in locomotion via 'exercise training' reduces reproductive output (Husak et al., 2016; Minter et al., 2018) and alters immunocompetence (Chapman et al., 2015; Wang and Husak, 2020; Altizer et al., 2011). Performance costs are still seldom integrated into the broader aspects of life history despite the energetic costs, relevance to fitness and integrative nature of performance. Furthermore, the possibility of trade-offs involving performance caused by proximate factors other than resource allocation is not commonly considered.

In this Review, we explore links between whole-organism performance and other life-history traits, emphasizing that if one or the other is ignored, then evolutionary conclusions regarding either can be misleading. We show that several conserved mechanisms link performance to 'classic' life-history traits, and that convergent interspecific mechanisms modulate trade-offs under common environmental stimuli. This prospective Review is intended to link disparate systems that will be of interest to integrative biologists aiming to understand the various mechanisms governing phenotypic expression, which we define generally here as any aspect(s) of the measurable phenotype. Although we focus primarily on whole-organism performance traits and traits to which

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performance is linked, the insights into the mechanisms underlying these trade-offs are likely to be general and thus relevant to the broader field of integrative biology. The diversity of these systems precludes an exhaustive review, and we cite other review papers where possible. For brevity, we simplify some pathways, realizing that more nuance is required in future studies. Finally, although we refer to both proximate and ultimate causes of life-history variation, consideration of the specific mechanisms – particularly those involving gene expression and gene products – blurs the boundaries between these two causal categories (e.g. Wittman et al., 2021).

Conserved life-history mediators

Several molecular/hormonal pathways integrate life-history traits through both the action of conserved endocrine factors, and the production of intermediate proteins. Below, we focus on several such integrator pathways with either demonstrated or likely links to performance that are common to all metazoans owing to shared ancestry. These ancient pathways reflect the importance of movement, oxygen acquisition and resource availability to all animals.

Muscle structure and myokines

Muscle is costly to build and maintain, and muscle growth requires a positive dietary protein balance. Consequently, both whole-organism performance and other life-history traits that are associated with performance incur energetic costs associated with producing, maintaining and using skeletal muscle (Husak and Lailvaux, 2017). The biochemical processes underlying muscle contraction are highly conserved, and the mechanical principles governing muscle arrangement are universal. As such, muscle function constitutes a direct link among performance abilities from arthropods to vertebrates. Further, shared muscle composition across animals means that the maintenance and production costs are likely to be comparable across all animals. We focus on endocrine effects of muscle, but the abundance of mitochondria in muscle, as well as the production of reactive oxygen species (ROS), also links performance to numerous pathways described below.

Muscle is a secretory tissue that maintains metabolic homeostasis in many organs and tissues (Pedersen, 2011, 2013; Rai and Demontis, 2016). Myokines are peptide cytokines synthesized and released by muscle in response to muscular contractions (Pedersen et al., 2007), and they are conserved across metazoans (Zhao and Karpac, 2017; Piccirillo, 2019). Humans exhibit over 600 myokines, mostly of unknown physiological function, but the primary role for those characterized is to promote muscle cell proliferation, differentiation and growth to maintain muscle mass and function, as well as fatty acid oxidation (Lee and Jun, 2019). Aerobic and anaerobic activity elicit differential myokine secretion, with aerobic myokines stimulating anti-inflammatory responses [via interleukin 6 (IL-6), IL-10 and IL-1ra, among others] and mitochondrial biogenesis, and anaerobic myokines stimulating muscle hypertrophy and myogenesis, albeit with some overlap (Piccirillo, 2019; Lee and Jun, 2019). Myokines directly connect muscle activity and metabolism via adipose tissue and the liver (Leal et al., 2018), but studies from mammals and *Drosophila* have also revealed many systemic effects of myokines (Demontis et al., 2013), ranging from the ability to release insulin (via IL-6 and IL-1β) to stimulating muscle growth and repair (via musculin, myostatin, IGF-1, LIF and CXCL-1), regulating lipid and glucose metabolism (via FGF-21, myonectin, ANGPTL4, irisin, IL-15, myostatin and IL-6), and promoting angiogenesis (enhanced by VEGF-B, which is also stimulated by the HIF pathway described below). Alterations in myokine signaling have consequently been linked to a variety of human diseases, including diabetes mellitus, heart failure, cancer and chronic obstructive pulmonary disease, as well as aging (Piccirillo, 2019). Although the metabolic effects of myokines have clear links to allocation and availability of energy (Pedersen et al., 2007), there is also evidence that aspects of the immune system, including lymphocyte numbers and activity, can be altered by myokines such as irisin (Pedersen and Hoffman-Goetz, 2000; Pedersen, 2011; Myint et al., 2021), depending on the intensity and duration of activity (Lee, 2006). The realization that muscle used for movement also acts as a large endocrine organ that affects other systems is still new, and comparative studies that incorporate myokines into a life-history framework are needed. This is especially true in light of ROS-stimulating release of myokines in contracting muscles (Scheele et al., 2009), thus linking myokine effects to other downstream effects of ROS (described below). Myokines, therefore, are an understudied yet promising avenue of research for those who wish to study performance–life-history trade-offs across diverse animal taxa.

ILS and mTOR

The insulin/insulin-like growth factor signaling pathway (ILS) is a nutrient signaling pathway that coordinates development and growth with resource availability. Both the ILS and the associated downstream mTOR (mechanistic target of rapomycin) pathways are responsible for toggling between energetically costly anabolic and energy conserving catabolic processes. Because growth represents the largest component of variation in resource allocation, promotion or suppression of growth is therefore a major aspect of variation in life-history strategies, and the ILS pathway regulates the classic survival–reproduction trade-off.

The vertebrate ILS pathway ligands include insulin and insulin-like growth factor (IGF-1), two key anabolic hormones that promote glycogenesis/lipogenesis, DNA replication and growth, while also inhibiting proteolysis and autophagy. Growth is therefore promoted by activation of ILS, whereas downregulating this pathway suppresses growth and reproduction and induces both catabolic processes and processes such as ROS repair that have collectively been shown to increase lifespan. Evidence links variation in circulating levels of IGF-1 directly with variation in life-history strategies in mammals, such that increased levels of plasma IGF-1 are associated with ‘faster’ life histories characterized by increased growth and reproduction, and shorter lifespans (Dantzer and Swanson, 2012; Swanson and Dantzer, 2014). Insufficient comparative data exist connecting circulating IGF-1 directly to performance traits; however, Lailvaux and Husak (2017) showed that mammal species on the ‘fast’ end of the fast–slow life-history continuum – i.e. those with generally high levels of IGF-1 – also spend less of their total daily energy budgets on locomotor performance, suggesting that performance likely trades off against growth, reproductive capacity and, possibly, longevity.

The ILS pathway is highly conserved. Arthropods lack insulin and IGFs, but rely on insulin like proteins (ILPs) and insulin receptors, as well as ecdysone and juvenile hormone, to regulate growth. In all cases, these hormonal signals connect to the downstream mTOR pathway – insulin, IGF-1 and ILPs all act as regulators of mTOR. The mTOR pathway is of special interest to gerontologists because it mediates the relationship between dietary restriction and longevity. First demonstrated more than 80 years ago in laboratory rats (McCay and Maynard, 1935), dietary restriction (defined as a reduction in food intake without malnutrition) acts via mTOR to extend lifespan at the cost of reduced capacity for

reproduction in a wide range of taxa (Mair and Dillin, 2008; Speakman and Mitchell, 2011). By diverting energetic resources away from reproduction and toward somatic maintenance, damage to DNA from free radicals and waste product accumulation in cells can be repaired even under limited resource conditions. Dietary restriction initiates these repair processes by altering the phosphorylation of mTOR's FOXO transcription factors, and that phosphorylation in turn is prompted by decreased upstream insulin signaling. Recent evidence suggests that ILS/mTOR not only affect traits that are directly linked to survival and fecundity, but also the timing and extent of expression of sexually selected ornaments or weapons, and the condition-dependent nature of those traits (Emlen et al., 2012; Casasa and Moczek, 2018). Given this scope for the ILS/mTOR network to influence secondary sexual traits, which are frequently linked to fitness, survival and performance (Lailvaux and Irschick, 2006) – and which may also affect performance even in the sex that does not bear the sexual trait (Husak and Swallow, 2011; Husak and Lailvaux, 2014) – our understanding of the multivariate phenotype is likely to be greatly enhanced by testing for putative links between ILS and performance.

Despite being conserved, there is evidence for specialization in certain aspects of ILS and mTOR pathways, although relevant data in many cases are sparse. For example, there are at least six different kinds of IGF binding proteins (IGFBPs), all of which bind with high affinity to IGF-1 and a second primary hormone of the ILS, insulin-like growth factor 2 (IGF-2), but not insulin (Clemmons, 2018). These tissue-specific IGFBPs both carry and regulate the bioavailability of IGFs. As such, they modulate interactions with IGF receptor molecules on specific tissues depending on the IGFBP (Dell et al., 1999). For example, IGF signaling exerts anabolic effects on mature bone growth in mice and humans, but also influences the development of osteoblasts during ontogeny (Beattie et al., 2018). The IGFBPs therefore constitute a mechanism for fine-tuning bone growth and development (Clemmons, 2018), which is highly relevant to performance (Arnold, 1983). The development and maintenance of skeletal muscle is also regulated by both endocrine and autocrine secretion of IGFBPs, such that serum concentrations generally correlate negatively with muscle mass (Lang et al., 2003). Beatty and Schwartz (2020) also show that IGFBP expression is ubiquitous across both tissue type and developmental stage in the lizard *Anolis sagrei*, an important step in expanding our understanding of these mechanisms to other animal taxa. Finally, IGFBPs also have effects independent of IGFs through a variety of poorly understood processes (Clemmons, 2018).

Despite the emphasis placed on homology with regard to ILS, it is noteworthy that our understanding of various functional aspects of IGF signaling (and IGFBPs in particular) is derived primarily from work on humans, mice or rats, despite important interspecific variation in the action of key components of ILS. For example, IGF-2 is both paternally imprinted and not produced post-natally in mice (Carter et al., 2002); however, the *IGF2* gene is not only expressed in adult reptiles without imprinting (Schwartz and Bronikowski, 2016), but in green anole females it is also expressed at higher levels in calorie-restricted animals compared with controls (Marks et al., 2021). The implications for performance are currently unknown, and we still have much to learn about the action of these important signaling molecules that might affect investment in growth and reproduction versus survival in different species.

Regan et al. (2020) argue that the ILS pathway is not merely nutrient-sensing, but a general mediator between intrinsic growth and a variety of external environmental inputs, ranging from circadian effects to temperature and humidity. However, our knowledge of the effects of these various other sources of environmental variation on the expression of whole-organism performance traits is almost entirely lacking. For example, among the environmental cues to which the ILS network is sensitive is water availability, via the *Ppk28* (*Pickpocket28*) gene (Waterson et al., 2014; Regan et al., 2020). Only a handful of studies have investigated the influence of water availability on performance abilities (usually in frogs; Gatten and Clark, 1989; Moore and Gatten, 1989; Rogowitz et al., 1999; but see Lailvaux et al., 2017), and consequently elucidating general patterns is challenging. It is clear that although whole-organism performance research has long been a cornerstone of physiological ecology, we still have a great deal to learn regarding the influence of external environmental conditions on performance expression.

Sirtuins, AMPK and dietary restriction

Sirtuins (silent information regulators) are a group of NAD^+-dependent protein deacetylases that regulate stress and metabolism, but also longevity (Sauve et al., 2006). Sirtuins are activated by the phosphorylation of FOXO (activated by reduced IGF-1 levels during, for example, caloric restriction), and are thus an important part of the signaling chain that initiates cellular repair. Indeed, sirtuin deletion eliminates the longevity-enhancing effect of dietary restriction. Sirtuins are a highly conserved signaling protein family, with homologous coding genes in organisms ranging from insects to vertebrates. Seven sirtuins exist in humans and mice, of which three occur in the mitochondria, three in the nucleus and one in the cytoplasm. Although the conserved histone acetylase SIRT1 has received the most attention owing to its connection with longevity, the mitochondrial SIRT4 is associated with both aging and locomotor performance. For example, *Drosophila melanogaster* experimentally lacking the sirtuin dSIRT4 (the analogue of mammalian SIRT4) exhibited markedly reduced lifespan and climbing performance independent of diet treatment compared with dSIRT4-intact controls, an effect that became more exaggerated as the flies aged (Parik et al., 2018). Given the role of mitochondrial sirtuins (SIRT3, 4 and 5, and analogues) as metabolic sensors and modulators of metabolic enzymes, they constitute a promising link between performance and other energetically costly life-history traits.

Attempts to induce the longevity benefits of dietary restriction without first inducing dietary restriction have focused interest on several compounds, such as resveratrol, thought to activate sirtuins independent of the action of the ILS/mTOR network. The effect of resveratrol on aging and longevity, if any, is controversial, but some recent studies have tested for such effects in conjunction with performance measures, with mixed results. Staats et al. (2018) found no influence of life-long dietary resveratrol on lifespan, oxidative stress or climbing performance in *D. melanogaster*, nor did resveratrol affect the expression of genes related to longevity or antioxidant activity compared with controls. However, dietary resveratrol did enhance both median and maximum lifespan and delay the onset of locomotor senescence when supplemented over the adult lifespan of a naturally short-lived fish (*Nothobranchius furzeri*) (Valenzano et al., 2006), and short-term dietary resveratrol supplementation restored circadian locomotor activity rhythms that are disrupted in older *Microcebus murinus* lemurs such that they were comparable to those of younger animals (Pifferi et al., 2013).

Sirtuin activity is associated with the activation of peroxisome proliferator-activated receptor gamma coactivator (PGC-1α), a master regulator of mitochondrial biogenesis and function (Liang

and Ward, 2006; Fernandez-Marcos and Auwerx, 2011) that also controls the expression of mitochondrial antioxidant genes such as manganese superoxide dismutase and uncoupling protein-2, and thus shields against oxidative injury (Rius-Pérez et al., 2020). PGC-1α is also highly expressed in tissues experiencing high energetic demand (Jung and Kim, 2014; Rius-Pérez et al., 2020). Exercise induces PGC-1α activation in muscle, and overexpression of PGC-1α in skeletal muscle increases endurance by activating mitochondrial oxidative metabolism and the formation of new blood vessels (Yang et al., 2020), in addition to mitochondrial biogenesis (Schnyder and Handschin, 2015; Bloise et al., 2018). Furthermore, PGC-1α is implicated in promoting remodeling of muscle to a more oxidative fibre type composition in mammals (Liang and Ward, 2006; but see Lira et al., 2010). Therefore, sirtuins constitute an important link between ILS and mitochondrial function, although caution should be taken in using PGC-1α activity as a proxy for mitochondrial activity (see below).

Mitochondria

Metabolism and metabolic rates describe the rate at which organisms use energy acquired from the environment, and thus also the relative allocation of that energy to various life-history traits. The main process by which animals convert stored energy into useful ATP is aerobic respiration in the mitochondria. Mitochondria thus constitute an essential link among various energetically costly aspects of the phenotype, and their action and efficiency (measured as the ratio of ATP generated to oxygen consumed; Bishop et al., 2019) are central subcellular mechanisms of interest in determining performance expression. Mitochondria are dynamic organelles, breaking apart, recombining, and changing size and structure in response to increased aerobic demands (Heine and Hood, 2020), which has consequences for mitochondrial function, and likely for organismal function as well. Despite the implications of mitochondrial activity for locomotor performance in particular (e.g. Seebacher et al., 2003), and the relevance of mitochondrial function to life history (see Gangloff et al., 2020; Heine and Hood, 2020), few empirical studies have directly linked mitochondrial state and/or efficiency directly to performance capacity, most likely because of the difficulty in doing so (but see Schaeffer et al., 1996, who showed that rattlesnake tailshaker muscle exhibits higher mitochondrial density than skeletal muscle elsewhere in the animal). However, the positive link between locomotor endurance performance and mitochondrial function and biogenesis is confirmed by exercise studies (Hood, 2009; Steiner et al., 2011), although the specific effects of types of training on mitochondrial structure, remodeling, quality and respiratory function remains unclear (Bishop et al., 2019).

Mitochondrial function produces potentially damaging ROS, although it is not the only way by which oxidative stress is induced (Zhang and Wong, 2021). Oxidative stress affects phenotypic trade-offs over both the short- and long-term, often owing to allocation-based trade-offs driven by the energetic cost of ROS repair processes (Monaghan et al., 2009). ROS and oxidative stress affect performance specifically in many possible ways, depending on several factors, making the relationship between oxidative stress and performance not at all straightforward (Monaghan et al., 2009). Furthermore, the extent to which ROS are produced by mitochondria specifically is also variable, and depends on both the structure and behavior of the mitochondria in question, as well as the energetic state, activity level and life-history strategy of the whole organism (Heine and Hood, 2020; Koch et al., 2021; Bishop et al., 2019). At ecological scales, the details of mitochondrial function are complex and sometimes

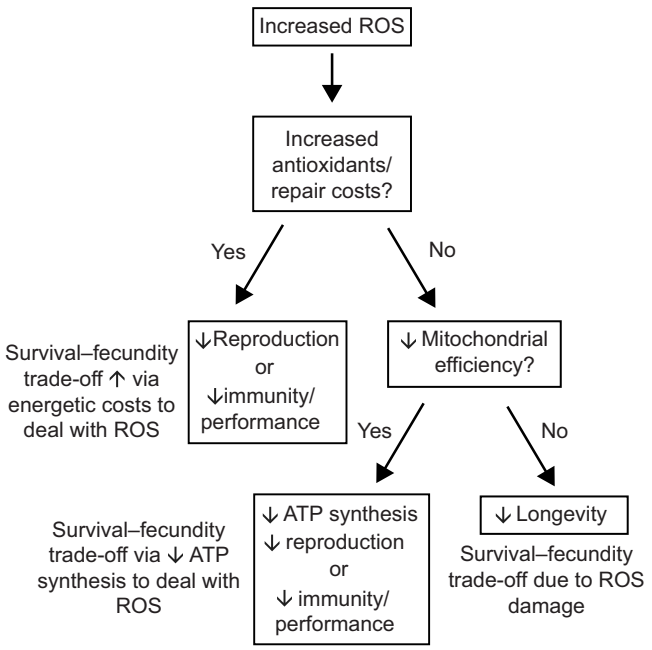

Fig. 1. When reactive oxygen species (ROS) increase, expression of life-history traits will depend on whether antioxidant mechanisms are also increased to deal with ROS (Monaghan et al., 2009), as well as how mitochondria change in their efficiency to reduce production of ROS or ATP (Koch et al., 2021).

counterintuitive, especially with regard to ROS. Koch et al. (2021) note that while increasing metabolic rate during increased locomotor activity might be expected to increase ROS production, the opposite often occurs. For example, increased oxidative stress is associated with migratory flight in bats (Constantini et al., 2019) and with elevated physical activity in humans (Pontzer et al., 2015), yet endurance exercise lowers ROS levels in three out of four male *Ctenophorus pictus* lizard color morphs (Friesen et al., 2021). Koch et al. (2021) show that intra- and inter-individual life-history variation in mitochondrial efficiency of ATP production can drive different patterns of ROS generation, and the possibility exists that similar variation in life-history strategies may be structured accordingly, especially when antioxidant systems are alternative ways of modulating ROS effects on life-history trait expression (Speakman et al., 2015). This phenomenon has important implications for how we conceive the relationship between performance and ROS in particular, but also for integrating performance and life histories given that the 'decision' to switch between survival and reproductive life-history strategies often hinges on the need to either tolerate or repair ROS-induced damage to cellular and sub-cellular processes (Speakman et al., 2015) (Fig. 1).

Hypoxia-inducible factors

Animals require sufficient oxygen for cellular respiration, and the hypoxia-inducible factor (HIF) pathway evolved to sense oxygen levels in tissues and cause both tissue-specific and systemic effects to increase oxygen delivery under hypoxic conditions (Wenger, 2002; Schofield and Ratcliffe, 2004; Kaelin and Ratcliffe, 2008; Semenza, 1998). The transcription factor HIF-1α targets numerous tissues for a variety of physiological roles (Maxwell, 2005), but deals primarily with hypoxia resulting from low environmental oxygen availability (e.g. high elevations) or oxygen depletion in tissues during increased activity (Ameln et al., 2005). Prolyl hydroxylase domain (PHD) enzymes are evolutionarily conserved

enzymes across metazoans that hydroxylate HIF-α subunits for proteasomal degradation in normoxic conditions (Wong et al., 2013). In hypoxic conditions, HIF-α subunits are not degraded and act as transcription factors (dimerized with HIF-β subunits) to alter expression levels of hundreds of genes involved in oxygen delivery and energy metabolism (Kaelin and Ratcliffe, 2008). These changes include a decrease in oxidative phosphorylation and an increase in glycolysis, as well as angiogenesis and erythropoiesis in vertebrates (Kaelin and Ratcliffe, 2008) and tracheal tube formation in insects (Marden et al., 2013). Human athletes activate this pathway by training at high elevations in hypoxic conditions, resulting in enhanced performance at lower elevations owing to HIF-induced changes that increase oxygen delivery to tissues (Hoppeler and Vogt, 2001). Furthermore, human populations at high altitudes show adaptations in HIF alleles that are advantageous in hypoxic conditions (Julian and Moore, 2019).

Marden et al. (2013) showed that polymorphism in the succinate dehydrogenase (SDH) gene, part of the HIF pathway, is associated with variation in tracheal oxygen delivery, flight metabolic performance and mitochondrial aging in the butterfly *Melitaea cinxia* (hinting at a relationship between this pathway and aging/longevity). Increased mitochondrial succinate (among other metabolic intermediates) inhibits PHDs, resulting in activation of the HIF pathway (Marden et al., 2013, 2021). Hence, low SDH activity was associated with higher HIF expression and, consequently, greater cross-sectional area of tracheoles in flight muscle, and better flight performance; however, mitochondrial cristae damage increases owing to the formation of ROS. Furthermore, a dominant allele for SDH in these butterflies resulted in reduced larval growth rate and metabolism (reduced larval fitness), but high adult flight capacity (increased adult fitness), revealing a clear case of antagonistic pleiotropy (Marden et al., 2021). Similar phenomena were observed in *Drosophila*, with a pronounced detriment to longevity (Walker et al., 2006). Consequently, variation in SDH and HIF alleles can have far-reaching impacts on endurance performance, growth and longevity in addition to cell- and tissue-level effects to deal with hypoxia (Marden et al., 2021). PHDs are also known to impact macrophage production via decreased NFκB signaling, thus affecting wound-healing abilities (Takeda et al., 2010; Palazon et al., 2014), but the broader life-history implications of this remain unknown.

Convergent life-history mediators

Arthropods and vertebrates have been on separate evolutionary trajectories for over 500 million years (Pisani et al., 2004; Peterson et al., 2008) and thus evolved additional convergent mechanisms to mediate many key phenotypic trade-offs. Indeed, the convergent evolution of life-history mediators that link 'classic' life-history traits to metabolism and performance emphasizes the evolutionary importance of such trade-offs across phylogenetically diverse taxa. Although differences between vertebrate and invertebrate endocrine regulation exist, the two groups use hormones as integrating systems in similar functional ways.

Energy regulation: adipokinetic hormones, octopamine, catecholamines, glucocorticoids and glucagon

Free-living animals have evolved mechanisms coordinating responses to environmental challenges (McEwan and Wingfield, 2003) that typically affect energy use and availability to increase function in certain tissues and systems while decreasing function in others. In vertebrates, the classic 'fight or flight' response serves this purpose (Sapolsky et al., 2000). Here, catecholamines (epinephrine, norepinephrine) are released from the nervous system and the adrenal glands to break down stored glycogen and triglycerides into usable glucose and fatty acids (Tank and Wong, 2015). Catecholamines also increase cardiac output to increase delivery of oxygen and the newly available energy. The hypothalamus–pituitary–adrenal (HPA) axis enhances these processes by prompting the release of glucocorticoids from the adrenal glands. Like catecholamines, glucocorticoids break down storage molecules and inhibit anabolic reactions such as protein and lipid synthesis. Norepinephrine is also an important regulator of locomotor activity, in conjunction with the action of biogenic amines such as dopamine (Fishman et al., 1983) and glucocorticoids of the HPA axis (Goossens et al., 2020). Glucagon, a hormone secreted by pancreatic alpha cells, also mobilizes energy by promoting glycogenolysis, lipolysis and lipid oxidation (Habegger et al., 2010). All of these hormones increase after increased activity (Khoo et al., 2010), linking performance to energy availability and use. Importantly, these energy-mobilizing hormones also impact other life-history traits; glucocorticoids suppress many components of the immune system and decrease reproductive output (Sapolsky et al., 2000; Hau et al., 2010; Demas et al., 2011).

Invertebrates lack norepinephrine but instead have an equivalent catecholamine messenger, octopamine (OA), which affects not only muscle contraction and locomotion (Malamud et al., 1988; Lorenz and Gäde, 2009), but also aggression (Hoyer et al., 2008; Bubak et al., 2014), experience effects during social interactions (Stevenson et al., 2005), energy availability (Roeder, 2020) and heart rate (Goossens et al., 2020). There is also evidence of close association between OA receptors and a region of the insect brain called the mushroom bodies, which are themselves linked to locomotion in flies and orthopterans (Martin et al., 1998). The direct neural connections between OA receptors, mushroom bodies and the antennal lobes suggest that performance expression can potentially be affected or modified by sensory input or recent experience, in addition to energetic state (Condon and Lailvaux, 2016; A. N. Bubak, J. G. Swallow, F. I. Adeola and S. P. Lailvaux, unpublished results). OA therefore constitutes a potential direct link between metabolism and performance that is also affected by social context, and thus an opportunity for the modulation of performance via behavior that might simultaneously affect other aspects of the integrated phenotype by altering metabolism. Thus far, few studies have directly manipulated OA (or other biogenic amines) to test for performance and life-history effects in insects.

Invertebrates also lack glucagon and glucocorticoids, but these roles are played by adipokinetic hormones (AKHs). Neuropeptides from the insect brain stimulate the nearby neuroendocrine corpora cardiaca to secrete AKHs, which primarily target the fat body (Kodrík, 2008). Similar to their vertebrate analogues, AKHs mobilize energy from stored lipids and carbohydrates and inhibit synthesis of storage molecules (Kodrík, 2008; Lorenz and Gäde, 2009). AKHs also power flight, a very energetically expensive task. Even in flightless insects, supplemental AKH raises lipid levels in hemolymph and increases activity (Kodrík et al., 2002). Interestingly, stressors other than flight (e.g. exposure to insecticide or constant darkness) can increase AKH levels, but also ROS production, although AKH is also known to enhance antioxidant production (Kodrík, 2008). AKH is involved with other phenotypic trade-offs as well, such as a general decrease in protein synthesis that may result in decreased anti-microbial activity of hemolymph (Kodrik and Goldsworthy, 1995), and in the 'oogenesis-flight syndrome' where flight, even minor distances, is restricted to pre-reproductive periods (Johnson, 1969; Rankin et al., 1986). Flight muscles are broken down to supplement energy provided by

the fat body to fuel oogenesis, resulting in decreased flight abilities (Zera and Denno, 1997). Despite its generality, this classic trade-off in orthopteran insects is complicated. AKHs inhibit fat body synthesis of proteins, lipids and glycogen for egg yolk in locusts and other species (Glinka et al., 1995), and decrease vitellogenin in females, thus reducing ovary mass and oocyte maturation (Lorenz, 2003). Interestingly, chronic high-fat diets increase AKH signaling, and impair lifespan and fecundity (Liao et al., 2021). Nevertheless, Lorenz and Gäde (2009) caution against viewing AKH as an 'inhibitor of reproduction' because AKH also plays a permissive role in reproductive events. Taken together, AKHs, released during increased flight, appear to act as 'stress hormones' that mobilize energy, but at a potential cost to immunocompetence and reproduction. Although the metabolic effects of AKH are similar to glucagon, the phenotypic trade-off effects are similar to glucocorticoids. How generalizable the trade-offs regulated by AKH are across invertebrate taxa remains unknown. Additionally, although glucocorticoids are often studied as 'stress hormones' (Gormally and Romero, 2020), a major function of their actions is to modify physiological systems to prepare for subsequent stressors (e.g. increased sensitivity to catecholamines; Sapolsky et al., 2000). It is unknown whether AKHs have similar preparatory effects in invertebrates.

Development: juvenile hormones and thyroid hormones

In vertebrates and some marine invertebrates, lipophilic, iodinated thyroid hormones (THs) regulate development, metamorphosis, metabolism, mitochondrial function, immune function and life-history transitions (Flatt et al., 2006). TH secretion is stimulated by thyrotropin (TSH) from the anterior pituitary, which is stimulated by thyrotropin-releasing hormone (TRH) from the hypothalamus in the brain. In endothermic vertebrates, THs increase basal metabolic rate and decrease mitochondrial efficiency (by increasing expression of uncoupling proteins) to generate heat by increasing proton leak in the electron transport chain (de Lange et al., 2001). Increased activity in the form of aerobic exercise training elevates systemic TH levels in mammals, but also increases expression of deiodinase enzymes in muscle tissue, which increase local TH levels and actions (Bloise et al., 2018). One consequence is upregulated expression of PGC-1α and thus mitochondrial biogenesis (Bocco et al., 2016). In insects, some of these roles are accomplished by juvenile hormone (JH) (Dingle and Winchell, 1997; Shpigler et al., 2020) and ecdysteroid hormones (Tibbetts et al., 2020) such as 20-hydroxy-ecdysone. JH and ecdysteroids are critical for insect development and metamorphosis (Ables and Drummon-Barbosa, 2010), and have been linked to memory, lifespan, stress resistance (Flatt et al., 2006; Uryu et al., 2015) and immune function (Flatt et al., 2005; Contreras-Garduño et al., 2009). Although insects have neither a thyroid gland nor presumably produce endogenous THs, THs have pleiotropic effects when experimentally administered (Flatt et al., 2006), mimicking many of the actions of JH. Just as THs are important for promoting reproduction in vertebrates, especially females (Ables and Drummon-Barbosa, 2010; Silva et al., 2018), JH also increases fecundity (Flatt and Kawecki, 2007; Roy et al., 2018). Intriguingly, long-duration flight increases JH in the migratory grasshopper *Melanoplus sanguinipes*, though apparently not due to increased AKH, suggesting a direct stimulation of JH release by flight (Min et al., 2004). The link between increased activity/flight and reproduction in insects deserves further study, perhaps with the use of tethered flight to force allocation to performance and stimulate trade-offs (Gu and Barker, 1995; Minter et al., 2018).

Reproductive investment: juvenile hormone and the HPG axis

Juvenile hormone signaling has also been compared with the hypothalamus–pituitary–gonadal (HPG) axis in vertebrates. In vertebrates, the hypothalamus releases gonadotropin-releasing hormone, which stimulates the anterior pituitary to release luteinizing hormone (and follicle-stimulating hormone), which stimulates the gonads to release testosterone and other sex steroids. Testosterone secretion is typically more pronounced in males, promoting growth, fertility and social behavior of males (Ketterson and Nolan, 1992), but also suppressing immune function (Folstad and Karter, 1992; Wingfield et al., 2001; Cox and John-Alder, 2007) and decreasing other traits that affect fitness (e.g. parental care). Testosterone may also increase oxidative stress and decrease resistance to oxidative damage (von Schantz et al., 1999), through either increased metabolic rate and subsequent increased ROS production (Finkel and Holbrook, 2000; but see Koch et al., 2021) or increased locomotor activity with subsequent high muscle activity that might increase ROS production (Finaud et al., 2006). Although testosterone has pro-oxidant effects in mammals, it also enhances antioxidant production via non-genomic actions in mammalian cardiomyocytes (Cruz-Topeta et al., 2020), but these effects are almost certainly tissue-specific and poorly known for other taxa. Nevertheless, testosterone is a textbook example of hormonal pleiotropy, regulating behavior and life-history traits associated with both survival and reproduction (Ketterson and Nolan, 1992; McGlothlin and Ketterson, 2008; Hau, 2007). Increased activity can suppress reproduction indirectly via reduction in fat stores and leptin secretion (Husak et al., 2016; Wang et al., 2019; see also below) or perhaps enhance male reproductive investment by increasing testosterone secretion as in human athletes (Vingren et al., 2010). This latter scenario may be restricted to cases where resources are unlimited, such as in humans, where muscle growth can occur despite the increased metabolic requirements of increased activity.

JHs are sesquiterpenoid lipid-like hormones that influence development and metamorphosis, as well as aspects of adult behavior and physiology such as diapause, sexual behavior and circadian rhythms. Neuropeptides from the insect brain regulate release of JH from the endocrine corpora allata posterior to the brain, including stimulatory allatotropins and inhibitory allatostatins (Stay and Woodhead, 1993). High levels of JH promote reproduction and competition in many insects, as well as reproduction in females (not always in males; Dumser, 1980). Although JH does not appear to affect parental care, it does modulate male aggression and, at least partially, the longevity–reproduction trade-off (Flatt and Kawecki, 2007) by suppressing the immune system and reducing survival (Tibbetts et al., 2020). Ecdysteroids and JH appear to work in conjunction to regulate insect metamorphosis, reproduction and survival, with ecdysteroids apparently playing a lesser role in the expression of phenotypic trade-offs (Tibbetts et al., 2020). Although high activity levels can increase JH (Min et al., 2004), this is not consistent across taxa and more studies are needed to determine how common this pattern is and what the phenotypic consequences are.

Energy storage: unpaired-2 and leptin

Animals must integrate information regarding nutrient status with other energetically costly processes, such as growth, activity, food intake and reproduction. In addition to the mechanisms discussed above, both insects and vertebrates have a mechanism to relay information about stored energy. In vertebrates, white adipose tissue secretes the hormone leptin in amounts proportional to the amount

Table 1. Summary of conserved and convergent mediators of performance–life-history trade-offs

Mediator	Summary of known trade-offs/links	What is next?
Conserved		
Muscle structure and myokines	Performance, immunity, energy storage and mitochondrial function	Physiological roles of known myokines Comparative studies of myokine function
ILS and mTOR	Performance, growth, maintenance, reproduction and longevity	Comparative studies of signal molecule functions as related to different kinds of environmental stimuli
Sirtuins, AMPK and dietary restriction	Performance, maintenance and longevity	Role of sirtuins in the interaction between performance and longevity
Mitochondria	Performance, mitochondrial structure and function; numerous other traits through ROS and antioxidant production; trade-offs among performance traits	Comparative studies of mitochondrial responses to activity, especially endotherms versus ectotherms Roles of ROS and antioxidants in other aspects of life history Role of mitochondrial variation in performance variation
Hypoxia-inducible factors	Trade-offs among performance traits, mitochondrial function, growth and longevity	Downstream impacts of upregulated/downregulated HIF on other traits in life-history context, especially in vertebrates Comparative studies of HIF function
Convergent		
Adipokinetic hormones, octopamine, catecholamines, glucocorticoids and glucagon	Energy regulation: performance, energy availability, immunity and reproduction	Specific roles of AKHs compared with glucocorticoids (e.g. preparative effects of AKH) Comparative studies of links between octopamine and life history axes
Juvenile hormones and thyroid hormones	Development: performance, development and reproduction	Comparative studies of how activity affects JH and what the consequences are Role of developmental JH secretion on current and future performance Role of TH in non-mammalian performance
Juvenile hormones and the HPG axis	Reproductive investment: performance and reproduction	Mechanistic links between activity, JH and reproduction Comparative studies of how increased activity affects testosterone secretion and reproduction
Unpaired-2 and leptin	Energy storage: performance, signal of energy availability, immunity	Further characterize phenotypic effects of unpaired expression and receptor distribution

We also suggest some avenues of future research that will help clarify the role of each mediator in a broader context, as well as the extent of conserved and convergent functions. AKH, adipokinetic hormone; HPG axis, hypothalamus–pituitary–gonad axis; JH, juvenile hormones; ROS, reactive oxygen species; TH, thyroid hormones.

of stored fats (Londraville et al., 2014). Leptin thus serves as a signal of available stored fat, and leptin receptors are found throughout the body to regulate reproduction via effects on the HPG axis (Baldelli et al., 2002; Childs et al., 2021), growth via thyroid hormones and IGF-1 (Li et al., 2011), and the immune system directly (Carlton et al., 2012; Naylor and Petri, 2016; Abella et al., 2017). In insects, the cytokine protein unpaired-2 is secreted by fat body cells under high fat diets, stimulating insulin-secreting cells in the brain to increase growth and nutrient storage and use (Rajan and Perrimon, 2012). The activation of the ILS pathway in turn increases JH secretion and promotes investment in reproduction (Mirth et al., 2019). Unpaired-2 is also secreted by muscle upon stimulation by FOXO, the former of which stimulates AKH secretion for lipid homeostasis (Zhao and Karpac, 2017). High-fat diets also stimulate *Drosophila* macrophages to secrete unpaired-3, which disrupts glucose homeostasis and reduces lifespan via activation of the JAK–STAT pathway (Woodcock et al., 2015). Unpaired-3 is also essential for male and female gametogenesis (Wang et al., 2014), though it is unclear how this link might cause adult phenotypic trade-offs. Despite similarities between unpaired-2 and leptin, there are some differences that require further exploration from a life-history perspective. For example, chronically high activity in vertebrates without increases in food intake decreases stored fat and, in turn, leptin levels in the body (Ishigaki et al., 2005), causing phenotypic trade-offs with reproduction (indirectly via HPG axis suppression) and immunity (Wang et al., 2019). It is unclear how unpaired cytokines fit into performance–life-history trade-offs, but it is most likely via the ILS pathway.

What comes next?

We highlight several mechanisms that hold promise for understanding trade-offs among whole-organism performance traits and other aspects of the integrated phenotype, but we also reveal shortcomings that hamper progress in this area (see Table 1). Primary among them is the lack of a proper comparative perspective on many of the processes of interest. The shared mechanisms that link life-history traits may be conserved across animals, but we only understand the details of many from studies of humans, laboratory rodents, *Drosophila* and a few other species. Comparative studies are desperately needed for us to understand how the multivariate phenotype, and the mechanisms that govern it, evolves.

A second shortcoming is how performance itself is measured. Although specific types of performance are more easily assayed in certain taxa than others, there is considerable inconsistency across different fields in how whole-organism performance is measured. Performance researchers have historically concentrated on measuring maximum performance using standardized protocols (Losos et al., 2002). Although measuring maximum performance is open to criticism for several reasons, the standardization produces performance outcomes that are comparable across a range of disparate taxa. Additionally, researchers whose primary interest is not in understanding variation in performance tend to use general assays of locomotor activity that are arguably more ‘behavior’ than true performance, or specific performance measures such as climbing that, while possibly ecologically relevant to the organism in question, are not measured in a standardized way. Yet another gambit is to consider the ‘performance’ of an organism in a more general sense by measuring one or more gross measures of overall physiological

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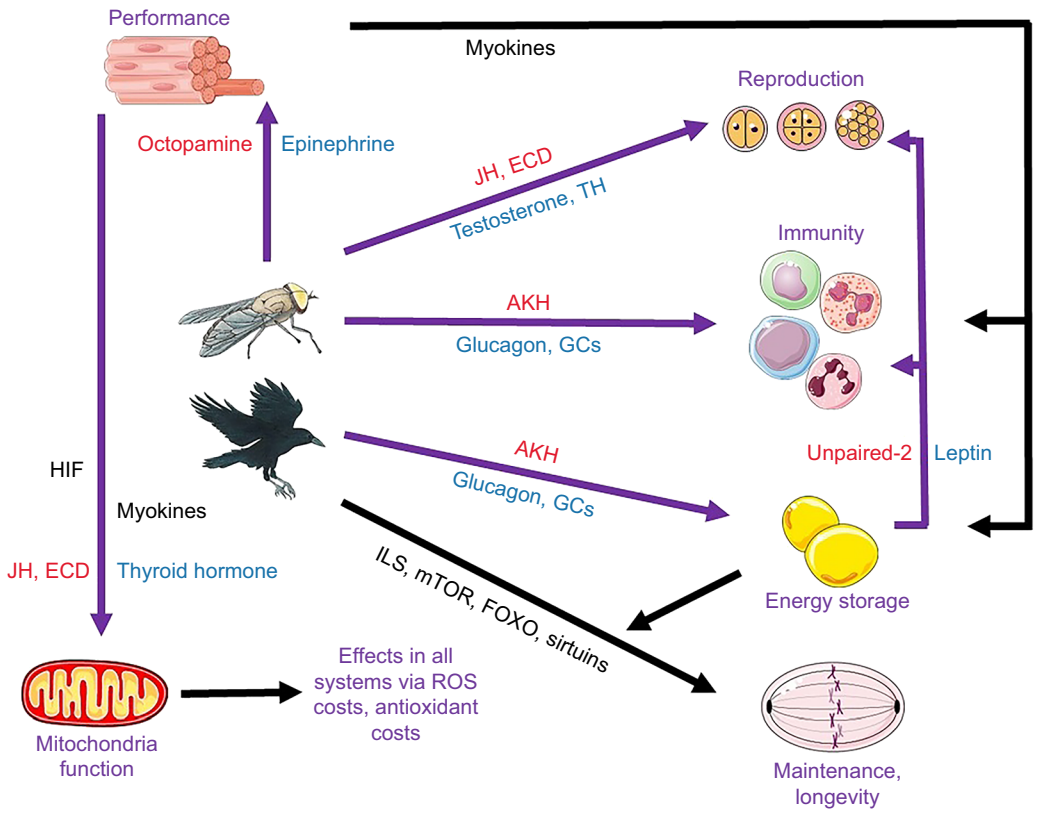

Fig. 2. Performance–life-history trade-offs are likely ubiquitous and regulated by conserved and convergent mediators. Chronically increased aerobic activity results in more muscle contractions and increased oxygen demand, as well as a necessity to mobilize energy and suppress other phenotypic traits. Some pathways are conserved across metazoans (black text and arrows), whereas others convergently mediate functions (purple arrows) in arthropods (red) and vertebrates (blue). For brevity, we have not included all possible links, only the major ones. Increased aerobic activity will enhance performance, survival, maintenance and longevity, but at a potential cost to somatic growth, reproduction and immunity. Mitochondrial changes will likely have widespread effects in many systems (not shown). Although in this scenario we start with increased activity and investment in performance, one could instead start with higher immune activation or reproductive output and predict other phenotypic effects. ROS will also be generated at many steps, but predicting effects is complicated as explained in Fig. 1. The extent to which each of these pathways is activated, as well as the direction and magnitude of resulting trade-offs, is likely species-specific and dependent on their life history and species-specific adaptations. We recognize that many of these links are still theoretical, and future studies are needed for validation. ADK, adipokinetic hormones; ECD, ecdysteroids; FOXO, forkhead box proteins; HIF, hypoxia-inducible factors; ILS, insulin/insulin-like signaling; JH, juvenile hormones; mTOR, mechanistic target of rapamycin; ROS, reactive oxygen species; TH, thyroid hormones. Fly and bird drawings by Margaret Duerwachter; remaining images modified from Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/.

function, such as metabolic rate. Such measures, though undeniably relevant to energetic trade-offs, tend to be proximate neither to performance nor to fitness in many taxa (Arnold et al., 2021). The past four decades of performance research have been conducted under the auspices of an important conceptual framework called the ecomorphological paradigm, which specifically argues that selection acts more strongly on performance than on the morphological and physiological underpinnings of performance. The apparent simplicity of this paradigm masks complexity in the relationships between morphology and performance, and the subsequent relationships between performance and fitness. This complexity has important implications for how researchers should design studies that incorporate performance. Researchers interested in measuring the mechanisms influencing performance variation should measure ecologically relevant performance traits themselves, which are characterized by standardized protocols with confounding variables controlled and a rich comparative literature for context. Collaborations among disciplines will be crucial to address these issues.

The type of performance measured also matters, particularly when considering links between certain performance traits and other life-history traits. For example, in a comparative study of 25 species of phrynosomatid lizards, Husak and Lailvaux (2017) found both positive and negative relationships between several life-history traits and endurance, but none between life history and sprint speed. The physiological differences underlying aerobic and anaerobic performance capacities in particular could therefore drive different sets of trade-offs in organisms that rely extensively on one or the other, because the mechanisms and pathways linking them are not the same; yet time and again we find cases where researchers either do not consider the physiological underpinnings of the performance traits they measure, or conduct non-standard performance measurements that incorporate both aerobic and anaerobic aspects, further confusing mechanisms and potential trade-offs. We urge researchers to pay close attention to the extensive literature on performance physiology, and to choose their performance measurements judiciously.

Perhaps the greatest future research opportunities lie in testing for the various mechanisms discussed above within the context of life history as a whole. Whole-organism performance traits occupy a unique position in that performance exerts fitness effects on both survival (Husak and Lailvaux, 2019) and reproduction (Husak et al., 2006). It could be that the ‘decision’ to invest in performance is species-specific, depending on how a given organism uses its performance abilities to accrue fitness; therefore, performance

trade-offs could fall on either side of the reproduction/survival divide (simplistic as that may be). Fig. 2 shows one possible scenario of increased aerobic performance in a population (van Dijk and Matson, 2016; Wang and Husak, 2020), and what the resultant trade-offs might be. However, we note that elevated anaerobic performance, such as burst performance associated with escape or pursuit, would be expected to drive different trade-offs because of the differences in the underlying mechanisms. Furthermore, despite the clear convergence in mechanisms between vertebrates and invertebrates, the specific actions of convergent pathways, though generally similar, are not identical. Consequently, although we might predict largely similar sets of trade-offs under similar conditions in each, the details of those trade-offs might differ, perhaps even implicating additional or disparate traits to comparable net fitness effects. The lack of relevant data is an enormous impediment to our understanding of convergence in the details of specific performance–life-history trade-offs, and increased attention to the convergent mechanisms we have highlighted will be valuable for understanding what trade-offs to expect in different contexts.

Finally, flexibility in how performance contributes to fitness might make it difficult to discern general patterns regarding how such traits respond to environmental effects such as dietary restriction relative to other components of the integrated organismal phenotype. This is especially true in laboratory settings, where performance and its advantages are not realistic. For example, animals in cages that are not moving freely will invest less in locomotor performance compared with free-living animals. A testable hypothesis is that performance is more relevant to the survival–longevity life-history axis, as opposed to the reproduction axis, although again this might vary depending on the species in question and the nature of performance (e.g. aerobic or anaerobic) that is most relevant to them. Further work testing for links between performance and key aspects of life history within different contexts and species holds enormous potential for improving our understanding not only of whole-organism performance, but of life-history strategies as well. Finally, we have focused on proximate mechanisms that produce trade-offs in response to environmental stimuli, but similar general principles should apply at the evolutionary scale (e.g. Marden et al., 2013). Variation in performance and other life-history traits should be linked to differences in relevant portions of the genome or epigenome.

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References
Abella, V., Scotece, M., Conde, J., Pino, J., Gonzalez-Gay, M. A., Gómez-Reino, J. J., Mera, A., Lago, F., Gómez, R. and Guallilo, O. (2017). Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nat. Rev. Rheumatol.* **13**, 100-109. doi:10.1038/nrrheum.2016.209

Ables, E. T. and Drummon-Barbosa, D. (2010). The steroid hormone ecdysone functions with intrinsic chromatin remodeling factors to control female germline stem cells in *Drosophila*. *Cell Stem Cell* **7**, 581-592. doi:10.1016/j.stem.2010.10.001

Adamo, S. A. (2017). The stress response and immune system share, borrow, and reconfigure their physiological network elements: evidence from insects. *Horm. Behav.* **88**, 25-30. doi:10.1016/j.yhbeh.2016.10.003

Altizer, S., Bertel, R. and Han, B. A. (2011). Animal migration and infectious disease risk. *Science* **331**, 296-302. doi:10.1126/science.1194694

Ameln, H., Gustafsson, T., Sundberg, C. J., Okamoto, K., Jansson, E., Poellinger, L. and Makino, Y. (2005). Physiological activation of hypoxia inducible factor-1 in human skeletal muscle. *FASEB J.* **19**, 1009. doi:10.1096/fj.04-2304fje

Arnold, S. J. (1983). Morphology, performance, and fitness. *Am. Zool.* **23**, 347-361. doi:10.1093/icb/23.2.347

Arnold, P. A., Delean, S., Cassey, P. and White, C. R. (2021). Meta-analysis reveals that resting metabolic rate is not consistently related to fitness and performance in animals. *J. Comp. Physiol. B* **191**, 1097–1110. doi:10.1007/s00360-021-01358-w

Baldelli, R., Dieguez, C. and Casanueva, F. F. (2002). The role of leptin in reproduction: experimental and clinical aspects. *Ann. Med.* **34**, 5-18. doi:10.1080/07853902317338599

Beattie, J., Al-Khafaji, H., Noer, P. R., Alkharobi, H. E., Alhodhodi, A., Meade, J., El-Gendy, R. and Oxvig, C. (2018). Insulin-like growth factor-binding protein action in bone tissue: a key role for pregnancy- associated plasma protein-A. *Front Endocrinol* **9**, 31. doi:10.3389/fendo.2018.00510

Beatty, A. E. and Schwartz, A. M. (2020). Gene expression of the IGF hormones and IGF binding proteins across time and space in a model reptiles. *Physiol. Genomics* **52**, 423-434. doi:10.1152/physiolgenomics.00059.2020

Bishop, D. J., Botella, J., Genders, A. J., Lee, M. J., Saner, N. J., Kuang, J., Yan, X. and Granata, C. (2019). High-intensity exercise and mitochondrial biogenesis: current controversies and future research directions. *Physiology* **34**, 56-70. doi:10.1152/physiol.00038.2018

Bloise, F. F., Cordeiro, A. and Ortiga-Carvalho, T. M. (2018). Role of thyroid hormone in skeletal muscle physiology. *J. Endocrinol.* **236**, R57-R68. doi:10.1530/JOE-16-0611

Bocco, B., Louzada, R. A. N., Silvestre, D. H. S., Santos, M. C. S., Anne-Palmer, E., Rangel, I. F., Abdalla, S., Ferreira, A. C., Ribeiro, M. O., Gereben, B. et al. (2016). Thyroid hormone activation by type2 deiodinase mediates exercise-induced peroxisome proliferator-activated receptor-gamma coactivator-1 alpha expression in skeletal muscle. *J. Physiol. Lond.* **594**, 5255-5269. doi:10.1113/JP272440

Braendle, C., Heyland, A., Flatt, T. (2011). Integrating mechanistic and evolutionary analysis of life history variation. In *Mechanisms of Life History Evolution: The Genetics and Physiology of Life History Traits and Trade-Offs* (ed. T. Flatt and A. Heyland), pp. 3-10. Oxford University Press.

Bubak, A. N., Grace, J. L., Watt, M. J., Renner, K. J. and Swallow, J. G. (2014). Neurochemistry as a bridge between morphology and behavior: perspectives on aggression in insects. *Curr. Zool.* **60**, 778-790. doi:10.1093/czoolo/60.6.778

Carlton, E. D., Demas, G. E. and French, S. S. (2012). Leptin, a neuroendocrine mediator or immune responses, inflammation, and sickness responses. *Horm. Behav.* **62**, 272-279. doi:10.1016/j.yhbeh.2012.04.010

Carter, C. S., Ramsey, M. M., Ingram, R. L., Cashion, A. B., Cefalu, W. T., Wang, Z. Q. and Sonntag, W. E. (2002). Models of growth hormone and IGF-1 deficiency: applications to studies of aging processes and life-span determination. *J. Gerontol. A Biol. Sci. Med. Sci.* **57**, B177-B188. doi:10.1093/gerona/57.5.B177

Casasa, S. and Moczek, A. P. (2018). Insulin signaling's role in mediating tissue-specific nutritional plasticity and robustness in the horn-polyphenic beetle *Onthophagus taurus*. *Proc. R. Soc. B Biol. Sci.* **285**, 20181631. doi:10.1098/rspb.2018.1631

Chapman, J. W., Reynolds, D. R. and Wilson, K. (2015). Long-range seasonal migration in insects: mechanisms, evolutionary drivers and ecological consequences. *Ecol. Lett.* **18**, 287-302. doi:10.1111/ele.12407

Childs, G. V., Odle, A. K., MacNicol, M. C. and MacNicol, A. M. (2021). The importance of leptin to reproduction. *Endocrinology* **162**, bqaa204. doi:10.1210/endocr/bqaa204

Clemmons, D. R. (2018). Role of IGF-binding proteins in regulating IGF responses to changes in metabolism. *J. Mol. Endocrinol.* **61**, T139-T169. doi:10.1530/JME-18-0016

Condon, C. and Lailvaux, S. P. (2016). Losing reduces maximum bite performance in house cricket contests. *Funct. Ecol.* **30**, 1660-1664. doi:10.1111/1365-2435.12654

Constantini, D., Lindecke, O., Pëtersons, G. and Voigt, C. C. (2019). Migratory flight imposes oxidative stress in bats. *Curr. Zool.* **65**, 147-153. doi:10.1093/cz/zoy039

Contreras-Garduño, J., Córdoba-Aguilar, A., Lanz-Mendoza, H. and Rivera, A. C. (2009). Territorial behaviour and immunity are mediated by juvenile hormone: the physiological basis of honest signalling? *Funct. Ecol.* **23**, 157-163. doi:10.1111/j.1365-2435.2008.01485.x

Cox, R. M. and John-Alder, H. B. (2007). Increased mite parasitism as a cost of testosterone in male striped plateau lizards *Sceloporus virgatus*. *Funct. Ecol.* **21**, 327-334. doi:10.1111/j.1365-2435.2007.01251.x

Cruz-Topeta, D., Dominici, P. and Stokes, K. Y. (2020). Uncovering sex=specific mechanisms of action of testosterone and redox balance. *Redox Biol.* **31**, 101490. doi:10.1016/j.redox.2020.101490

Dantzer, B. and Swanson, E. M. (2012). Mediation of vertebrate life histories via insulin-like growth factor-1. *Biol. Rev. Camb. Philos. Soc.* **87**, 414-429. doi:10.1111/j.1469-185X.2011.00204.x

de Lange, P., Lanni, A., Beneduce, L., Moreno, M., Lombardi, A., Silvestri, E. and Goglia, F. (2001). Uncoupling protein-3 is a molecular determinant for the regulation of resting metabolic rate by thyroid hormone. *Endocrinology* **142**, 3414-3420. doi:10.1210/endo.142.8.8303

Dell, G., Ward, A., Shokrai, A., Madej, A. and Engstrom, W. (1999). Regulation of the IGF system by glucocortidoids. *Zool. Sci.* **16**, 377-385.
Demas, G. E., Adamo, S. A. and French, S. S. (2011). Neuroendocrine-immune crosstalk in vertebrates and invertebrates: implications for host defence. *Funct. Ecol.* **25**, 29-39. doi:10.1111/j.1365-2435.2010.01738.x
Demontis, F., Piccirillo, R., Goldberg, A. L. and Perrimon, N. (2013). The influence of skeletal muscle on systemic aging and lifespan. *Aging Cell* **12**, 943-949. doi:10.1111/acel.12126
Dingle, H. and Winchell, R. (1997). Juvenile hormone as a mediator of plasticity in insect life histories. *Arch. Insect Biochem. Physiol.* **35**, 359-373. doi:10.1002/(SICI)1520-6327(1997)35:4<359::AID-ARCH2>3.0.CO;2-N
Dumser, J. B. (1980). The regulation of spermatogenesis in insects. *Annu. Rev. Entomol.* **25**, 314-369. doi:10.1146/annurev.en.25.010180.002013
Emlen, D. J., Warren, I. A., Johns, A., Dworkin, I. and Lavine, L. C. (2012). A mechanism of extreme growth and reliable signaling in sexually selected ornaments and weapons. *Science* **337**, 860-864. doi:10.1126/science.1224286
Fernandez-Marcos, P. J. and Auwerx, J. (2011). Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis. *Am. J. Clin. Nutr.* **93**, 884S-890S. doi:10.3945/ajcn.110.001917
Finaud, J., Lac, G. and Filaire, E. (2006). Oxidative stress - relationship with exercise and training. *Sports Med.* **36**, 327-358. doi:10.2165/00007256-200636040-00004
Finch, C. E. and Rose, M. R. (1995). Hormones and the physiological architecture of life history evolution. *Q. Rev. Biol.* **70**, 1-52. doi:10.1086/418864
Finkel, T. and Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of aging. *Nature* **408**, 239-247. doi:10.1038/35041687
Fishman, R. H. B., Feigenbaum, J. J., Yanai, J. and Klawans, H. L. (1983). The relative importance of dopamine and norepinephrine in mediating locomotor activity. *Prog. Neurobiol.* **20**, 55-88. doi:10.1016/0301-0082(83)90010-2
Flatt, T. and Kawecki, T. J. (2007). Juvenile hormone as a regulator of the trade-off between reproduction and life span in *Drosophila melanogaster*. *Evolution* **61**, 1980-1991. doi:10.1111/j.1558-5646.2007.00151.x
Flatt, T., Moroz, L. L., Tatar, M. and Heyland, A. (2006). Comparing thyroid and insect hormone signalling. *Integr. Comp. Biol.* **46**, 777-794. doi:10.1093/icb/icl034
Flatt, T., Tu, M. P. and Tatar, M. (2005). Hormonal pleiotropy and the juvenile hormone regulation of *Drosophila* development and life history. *BioEssays* **27**, 999-1010. doi:10.1002/bies.20290
Folstad, I. and Karter, A. J. (1992). Parasites, bright males, and the immunocompetence handicap. *Am. Nat.* **139**, 603-622. doi:10.1086/285346
Friesen, C. R., Wilson, M., Rollings, N., Sudkya, J., Giraudeau, M., Whittington, C. M. and Olsson, M. (2021). Exercise training has morph-specific effects on telomere, body condition and growth dynamics in a color-polymorphic lizard. *J. Exp. Biol.* **224**, jeb242164. doi:10.1242/jeb.242164
Gangloff, E. J., Schwartz, T. S., Klabacka, R., Huebschman, N., Liu, A. and Bronikowski, A. M. (2020). Mitochondria as central characters in a complex narrative: linking genomics, energetics, and pace-of-life in natural populations of garter snakes. *Exp. Gerontol.* **137**, 110967. doi:10.1016/j.exger.2020.110967
Gatten, R. E. and Clark, R. M. (1989). Locomotor performance of hydrated and dehydrated frogs - recovery following exhaustive exercise. *Copeia* **1989**, 451-455. doi:10.2307/1445442
Ghalambor, C. K., Walker, J. A. and Reznick, D. N. (2003). Multi-trait selection, adaptation, and constraints on the evolution of burst swimming performance. *Integr. Comp. Biol.* **43**, 431-438. doi:10.1093/icb/43.3.431
Glinka, A. V., Kleiman, A. M. and Wyatt, G. R. (1995). Roles of juvenile hormone, a brain factor and adipokinetic hormone in regulation of vitellogenin biosynthesis in *Locusta migratoria*. *Biochem. Mol. Biol. Int.* **35**, 323-328.
Goossens, S., Wybouw, N., Van Leeuwen, T. and Bonte, D. (2020). The physiology of movement. *Mov. Ecol.* **8**, 5. doi:10.1186/s40462-020-0192-2
Gormally, B. M. G. and Romero, L. M. (2020). What are you actually measuring? A review of techniques that integrate the stress response on distinct time-scales. *Funct. Ecol.* **34**, 2030-2044. doi:10.1111/1365-2435.13648
Gu, H. and Barker, J. S. F. (1995). Genetic and phenotypic variation for flight ability in the cactophilic *Drosophila* species, *D. aldrichi* and *D. buzzatii*. *Entomol. Exp. Appl.* **76**, 25-35. doi:10.1111/j.1570-7458.1995.tb01943.x
Habegger, K., Heppner, K., Geary, N., Bertness, T. J., DiMarchi, R. and Tschöp, M. R. (2010). The metabolic actions of glucagon revisited. *Nat. Rev. Endocrinol.* **6**, 689-697. doi:10.1038/nrendo.2010.187
Hau, M. (2007). Regulation of male traits by testosterone: implications for the evolution of vertebrate life histories. *BioEssays* **29**, 133-144. doi:10.1002/bies.20524
Hau, M., Ricklefs, R. E., Wikelski, M., Lee, K. A. and Brawn, J. D. (2010). Corticosterone, testosterone and life-history strategies of birds. *Proc. R. Soc. B Biol. Sci.* **277**, 3203-3212. doi:10.1098/rspb.2010.0673
Heine, K. B. and Hood, W. R. (2020). Mitochondrial behaviour, morphology, and animal performance. *Biol. Rev. Camb. Philos. Soc.* **95**, 730-737. doi:10.1111/brv.12584
Hood, D. A. (2009). Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle. *Appl. Physiol. Nutr. Metab.* **34**, 465-472. doi:10.1139/H09-045
Hoppeler, H. and Vogt, M. (2001). Hypoxia training for sea-level performance - Training high - living low. In *Hypoxia: From Genes to the Bedside: Advances in Experimental Medicine and Biology*, Vol. 502 (ed. R. C. Roach, P. D. Wagner and P. H. Hackett), pp. 61-73. New York: Kluwer Academic/Plenum Publ.
Hoyer, S. C., Eckart, A., Herrel, A., Zars, T., Fischer, S., Hardie, S. L. and Heisenberg, M. (2008). Octopamine in male aggression of *Drosophila*. *Curr. Biol.* **18**, 159-167. doi:10.1016/j.cub.2007.12.052
Hudson, S. B., Virgin, E. E., Brodie, E. D. and French, S. S. (2021). Recovery from discrete wound severities in side-blotched lizards (*Uta stansburiana*): implications for energy budget, locomotor performance, and oxidative stress. *J. Comp. Physiol. B* **191**, 531-543. doi:10.1007/s00360-021-01347-z
Husak, J. F. and Fox, S. F. (2008). Sexual selection on locomotor performance. *Evol. Ecol. Res.* **10**, 213-228.
Husak, J. F., Ferguson, H. A. and Lovern, M. B. (2016). Trade-offs among locomotor performance, reproduction and immunity in lizards. *Funct. Ecol.* **30**, 1665-1674. doi:10.1111/1365-2435.12653
Husak, J. F. and Lailvaux, S. P. (2014). An evolutionary perspective on conflict and compensation in physiological and functional traits. *Curr. Zool.* **60**, 755-767. doi:10.1093/czoolo/60.6.755
Husak, J. F. and Lailvaux, S. P. (2017). How do we measure the cost of whole-organism performance traits? *Integr. Comp. Biol.* **57**, 333-343. doi:10.1093/icb/icx048
Husak, J. F. and Lailvaux, S. P. (2019). Experimentally enhanced performance decreases survival in nature. *Biol. Lett.* **15**, 20190160. doi:10.1098/rsbl.2019.0160
Husak, J. F., Fox, S. F., Lovern, M. B. and Van Den Bussche, R. A. (2006). Faster lizards sire more offspring: Sexual selection on whole-animal performance. *Evolution* **60**, 2122-2130. doi:10.1111/j.0014-3820.2006.tb01849.x
Husak, J. F., Rohlf, C. M. and Lailvaux, S. P. (2021). Immune activation affects whole-organism performance in male but not female green anole lizards (*Anolis carolinensis*). *J. Comp. Physiol. B* **191**, 895-905. doi:10.1007/s00360-021-01370-0
Husak, J. F. and Swallow, J. G. (2011). Compensatory traits and the evolution of male ornaments. *Behaviour* **148**, 1-29. doi:10.1163/000579510X541265
Ishigaki, T., Koyama, K., Tsujita, J., Tanaka, N., Hori, S. and Oku, Y. (2005). Plasma leptin levels of elite endurance runners after heavy endurance training. *J. Physiol. Anthropol. Appl. Hum. Sci.* **24**, 573-578. doi:10.2114/jpa.24.573
Johnson, C. G. (1969). *Migration and Dispersal of Insects by Flight*. London: Methuen.
Julian, C. G. and Moore, L. G. (2019). Human genetic adaptation to high-altitude: evidence from the Andes. *Genes* **10**, 150. doi:10.3390/genes10020150
Jung, S. and Kim, K. (2014). Exercise-induced PGC-1α transcriptional factors in skeletal muscle. *Integr. Med. Res.* **3**, 155-160. doi:10.1016/j.imr.2014.09.004
Kaelin, W. G. and Ratcliffe, P. J. (2008). Oxugen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol. Cell* **30**, 393-402. doi:10.1016/j.molcel.2008.04.009
Ketterson, E. D. and Nolan, V. (1992). Hormones and life histories - an integrative approach. *Am. Nat.* **140**, S33-S62. doi:10.1086/285396
Khoo, E. Y. H., Wallis, J., Tsintzas, K., Macdonald, I. A. and Mansell, P. (2010). Effects of exenatide on circulating glucose, insulin, glucagon, cortisol and catecholamines in healthy volunteers during exercise. *Diabetologia* **53**, 139-143. doi:10.1007/s00125-009-1579-1
Koch, R. E., Buchanon, K. L., Casagrande, S., Crino, O., Dowling, D. K., Hill, G. E., Hood, W. R., McKenzie, E., Mariette, M. M., Noble, D. W. A. et al. (2021). Integrating mitochondrial aerobic metabolism into ecology and evolution. *Trends Ecol. Evol.* **36**, 321-332. doi:10.1016/j.tree.2020.12.006
Kodrík, D. (2008). Adipokinetic hormone functions that are not associated with insect flight. *Physiol. Entomol.* **33**, 171-180. doi:10.1111/j.1365-3032.2008.00625.x
Kodrik, D. and Goldsworthy, G. J. (1995). Inhibition of RNA synthesis by adipokinetic hormones and brain factor(s) in adult fat body of *Locusta migratoria*. *J. Insect Physiol.* **4**, 127-133. doi:10.1016/0022-1910(94)00096-Y
Kodrík, D., Socha, R. and Zemek, R. (2002). Topical application of Pya-AKH stimulates lipid mobilization and locomotion in the flightless bug, *Pyrrhocoris apterus* (L.) (Heteroptera). *Physiol. Entomol.* **27**, 15-20. doi:10.1046/j.1365-3032.2002.00261.x
Lailvaux, S. P., Breuker, C. J. and Van Damme, R. (2017). Water stress affects development time but not takeoff performance in the butterfly *Pararge aegeria*. *Physiol. Biochem. Zool.* **90**, 54-62. doi:10.1086/689995
Lailvaux, S. P. and Husak, J. F. (2014). The life-history of whole-organism performance. *Q. Rev. Biol.* **89**, 285-318. doi:10.1086/678567
Lailvaux, S. P. and Husak, J. F. (2017). Predicting life-history trade-offs with whole-organism performance. *Integr. Comp. Biol.* **57**, 325-332. doi:10.1093/icb/icx073
Lailvaux, S. P. and Irschick, D. J. (2006). A functional perspective on sexual selection: insights and future prospects. *Anim. Behav.* **72**, 263-273. doi:10.1016/j.anbehav.2006.02.003
Lang, C. H., Vary, T. C. and Frost, R. A. (2003). Acute in vivo elevation of insulin-like growth factor (IGF) binding protein-1 decreases plasma free IGF-I and muscle protein synthesis. *Endocrinology* **144**, 3922-3933. doi:10.1210/en.2002-0192
Leal, L. G., Lopes, M. A. and Batista, M. L. (2018). Physical exercise-induced myokines and muscle-adipose crosstalk: a review of current knowledge and the

implictions for health and metabolic diseases. *Front. Physiol.* **9**, 1307. doi:10.3389/fphys.2018.01307
Lee, K. A. (2006). Linking immune defenses and life history at the levels of the individual and the species. *Integr. Comp. Biol.* **46**, 1000-1015. doi:10.1093/icb/icl049
Lee, J. H. and Jun, H.-S. (2019). Role of myokines in regulating skeletal muscle mass and function. *Front. Physiol.* **10**, 42. doi:10.3389/fphys.2019.00042
Li, R., Hu, Y., Xia, D., Grossmann, R. and Zhao, R. (2011). Leptin stimulates hepatic activation of thyroid hormones and promotes early posthatch growth in the chicken. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* **160**, 200-206. doi:10.1016/j.cbpa.2011.06.001
Liang, H. and Ward, W. F. (2006). PGC-1alpha: a key regulator of energy metabolism. *Adv. Physiol. Educ.* **30**, 145-151. doi:10.1152/advan.00052.2006
Liao, S., Amcoff, M. and Nässel, D. R. (2021). Impact of high-fat diet on lifespan, metabolism, fecundity and behavioral senescence in *Drosophila*. *Insect Biochem. Mol. Biol.* **133**, 103495. doi:10.1016/j.ibmb.2020.103495
Lira, V. A., Benton, C. R., Yan, Z. and Bonen, A. (2010). PGC-1 alpha regulation by exercise training and its influences on muscle function and insulin sensitivity. *Am. J. Physiol. Endocrinol. Metab.* **299**, E145-E161. doi:10.1152/ajpendo.00755.2009
Londraville, R. L., Macotela, Y., Duff, R. J., Easterling, M. R., Liu, Q. and Crespi, E. J. (2014). Comparative endocrinology of leptin: assessing function in a phylogenetic context. *Gen. Comp. Endocrinol.* **203**, 146-157. doi:10.1016/j.ygcen.2014.02.002
Lorenz, M. W. (2003). Adipokinetic hormone inhibits the formation of energy stores and egg production in the cricket *Gryllus bimaculatus*. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **136**, 197-206. doi:10.1016/S1096-4959(03)00227-6
Lorenz, M. W. and Gäde, G. (2009). Hormonal regulation of energy metabolism in insects as a driving force for performance. *Integr. Comp. Biol.* **49**, 380-392. doi:10.1093/icb/icp019
Losos, J. B., Creer, D. A. and Schulte, II, J. (2002). Cautionary comments on the measurement of maximum locomotor capabilities. *J. Zool.* **258**, 57-61. doi:10.1017/S0952836902001206
Mair, W. and Dillin, A. (2008). Aging and survival: The genetics of life span extension by dietary restriction. *Annu. Rev. Biochem.* **77**, 727-754. doi:10.1146/annurev.biochem.77.061206.171059
Malamud, J. G., Mizisin, A. P. and Josephson, R. K. (1988). The effects of octopmaine on contraction kinetics and power output of a locust flight muscle. *J. Comp. Physiol. A Sens. Neural Behav. Physiol.* **162**, 827-835. doi:10.1007/BF00610971
Marden, J. H., Fescemyer, H. W., Schilder, R. J., Doerfler, W. R., Vera, J. C. and Wheat, C. W. (2013). Genetic variation in HIF signaling underlies quantitative variation in physiological and life-history traits within lowland butterfly populations. *Evolution* **67**, 1105-1115. doi:10.1111/evo.12004
Marden, J. H., Langford, E. A., Robertson, M. A. and Fescemyer, H. W. (2021). Alleles in metabolic and oxygen-sensing genes are associated with antagonistic pleiotropic effects on life history traits and population fitness in an ecological model insect. *Evolution* **75**, 116-129. doi:10.1111/evo.14095
Marks, J. R., Beatty, A. E., Schwartz, T. S., Sorlin, M. and Lailvaux, S. P. (2021). Expression of insulin-like growth factors depends on both mass and resource availability in female green anoles (*Anolis carolinensis*). *J. Exp. Biol.* **224**, jeb242665. doi:10.1242/jeb.242665
Martin, J. R., Ernst, R. and Heisenberg, M. (1998). Mushroom bodies suppress locomotor activity in *Drosophila melanogaster*. *Learn. Mem.* **5**, 179-191. doi:10.1101/lm.5.1.179
Maxwell, P. H. (2005). Hypoxia-inducible factor as a physiological regulator. *Exp. Physiol.* **90**, 791-797. doi:10.1113/expphysiol.2005.030924
McCay, C. M. and Maynard, L. (1935). The effect of retarded growth upon the length of life and ultimate size. *J. Nutr.* **10**, 63-79. doi:10.1093/jn/10.1.63
McEwan, B. S. and Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Horm. Behav.* **43**, 2-15. doi:10.1016/S0018-506X(02)00024-7
McGlothlin, J. W. and Ketterson, E. D. (2008). Hormone-mediated suites as adaptations and evolutionary constraints. *Philos. Trans. R. Soc. B Biol. Sci.* **363**, 1611-1620. doi:10.1098/rstb.2007.0002
Metcalfe, C. J. E. and Graham, A. L. (2018). Schedule and magnitude of reproductive investment under immune trade-offs explains sex differences in immunity. *Nat. Commun.* **9**, 4391. doi:10.1038/s41467-018-06793-y
Min, K. J., Jones, N., Borst, D. W. and Rankin, M. A. (2004). Increased juvenile hormone levels after long-duration flight in the grasshopper, *Melanoplus sanguinipes*. *J. Insect Physiol.* **50**, 531-537. doi:10.1016/j.jinsphys.2004.03.009
Minter, M., Pearson, A., Lim, K. A. S., Wilson, K., Chapman, J. W. and Jones, C. M. (2018). The tethered flight technique as a tool for studying insect life-history strategies association with migration in insects. *Ecol. Entomol.* **43**, 297-411. doi:10.1111/een.12521
Mirth, C. K., Alves, A. N. and Piper, M. D. W. (2019). Turning food into eggs: insights from nutritional biology and developmental physiology of *Drosophila*. *Curr. Opin. Insect. Sci.* **31**, 49-57. doi:10.1016/j.cois.2018.08.006
Monaghan, P., Metcalfe, N. B. and Torres, R. (2009). Oxidative stress as a mediator of life history trade-offs: mechanisms, measurements and interpretations. *Ecol. Lett.* **12**, 75-92. doi:10.1111/j.1461-0248.2008.01258.x
Moore, F. R. and Gatten, R. E. (1989). Locomotor performance of hydrate, dehydrated, and osmotically stressed anuran amphibians. *Herpetologica* **45**, 101-110.
Myint, P. K., Ito, A., Appiah, M. G., Obeng, G., Darkwah, S., Kawamoto, E., Gaowa, A., Park, E. J. and Shimaoka, M. (2021). Irisin supports integrin-mediated cell adhesion of lymphocytes. *Biochem. Biophys. Rep.* **26**, 100977. doi:10.1016/j.bbrep.2021.100977
Naylor, C. and Petri, W. A. (2016). Leptin regulation of immune responses. *Trends Mol. Med.* **22**, 88-98. doi:10.1016/j.molmed.2015.12.001
Palazon, A., Goldrath, A. W., Nizer, V. and Johnson, R. S. (2014). HIF transcription factors, inflammation, and immunity. *Immunity* **41**, 518-528. doi:10.1016/j.immuni.2014.09.008
Parik, S., Tewary, S., Ayyub, C. and Kolthur-Seetharam, U. (2018). Loss of mitochondrial SIRT4 shortens lifespan and leads to a decline in physical activity. *J. Biosci.* **43**, 243-247. doi:10.1007/s12038-018-9754-5
Pedersen, B. K. (2011). Muscles and their myokines. *J. Exp. Biol.* **214**, 337-346. doi:10.1242/jeb.048074
Pedersen, B. K. (2013). Muscle as a secretory organ. *Compr. Physiol.* **3**, 1337-1362. doi:10.1002/cphy.c120033
Pedersen, B. K., Åkerström, T. C. A., Nielsen, A. R. and Fischer, C. P. (2007). Role of myokines in exercise performance and metabolism. *J. Appl. Physiol.* **103**, 1093-1098. doi:10.1152/japplphysiol.00080.2007
Pedersen, B. K. and Hoffman-Goetz, L. (2000). Exercise and the immune system: regulation, integration, and adaptation. *Physiol. Rev.* **80**, 1055-1081. doi:10.1152/physrev.2000.80.3.1055
Peterson, K. J., Cotton, J. A., Gehling, J. G. and Pisani, D. (2008). The Ediacaran emergence of bilaterians: congruence between the genetic and the geological fossil records. *Philos. Trans. R. Soc. B* **363**, 1435-1443. doi:10.1098/rstb.2007.2233
Piccirillo, R. (2019). Induced myokines with therapeutic potential for muscle wasting. *Front. Physiol.* **10**, 287. doi:10.3389/fphys.2019.00287
Pifferi, F., Del-Pan, A., Languille, S. and Aujard, F. (2013). Effects of resveratrol on daily rhythms of locomotor activity and body temperature in young and aged grey mouse lemurs. *Oxid. Med. Cell. Longev.* **2013**, 187301. doi:10.1155/2013/187301
Pisani, D., Poling, L. L., Lyons-Weiler, M. and Hedges, S. B. (2004). The colonization of land by animals: molecular phylogeny and divergence times among arthropods. *BMC Biol.* **2**, 1. doi:10.1186/1741-7007-2-1
Pontzer, H., Raichlen, D. A., Wood, B. M., Thompson, M. E., Racette, S. B., Mabulla, A. Z. P. and Marlowe, F. W. (2015). Energy expenditure and activity among Hadza hunter-gatherers. *Am. J. Hum. Biol.* **27**, 626-637. doi:10.1002/ajhb.22711
Rai, M. and Demontis, F. (2016). Systemic nutrient and stress signaling via myokines and myometabolites. *Annu. Rev. Physiol.* **78**, 85-107. doi:10.1146/annurev-physiol-021115-105305
Rajan, A. and Perrimon, N. (2012). *Drosophila* cytokine unpaired 2 regulates physiological homeostasis by remotely controlling insulin secretion. *Cell* **151**, 123-137. doi:10.1016/j.cell.2012.08.019
Rankin, M. A., McAnelly, M. L. and Bodenhamer, J. E. (1986). The oogenesis-flight syndrome revisited. In *Insect Flight: Dispersal and Migration* (ed. W. Danthanarayana), pp. 27-48. Berlin, Heidelberg: Springer.
Regan, J. C., Froy, H., Walling, C. A., Moatt, J. P. and Nussey, D. H. (2020). Dietary restriction and insulin-like signaling pathways as adaptive plasticity: a synthesis and re-evaluation. *Funct. Ecol.* **34**, 107-128. doi:10.1111/1365-2435.13418
Ricklefs, R. E. and Wikelski, M. (2002). The physiology/life-history nexus. *Trends Ecol. Evol.* **17**, 462-468. doi:10.1016/S0169-5347(02)02578-8
Rius-Pérez, S., Torres-Cuevas, I., Millán, I., Ortega, A. L. and Pérez, S. (2020). PGC-1α, inflammation, and oxidative stress: an integrative view in metabolism. *Oxid. Med. Cell. Longev.* **2020**, 1452696. doi:10.1155/2020/1452696
Roeder, T. (2020). The control of metabolic traits by octopamine and tyramine in invertebrates. *J. Exp. Biol.* **223**, jeb194282. doi:10.1242/jeb.194282
Rogowitz, G. L., Cortes-Rivera, M. and Nieves-Puigdoller, K. (1999). Water loss, cutaneous resistance, and effects of dehydration on locomotion of *Eleutherodactylus* frogs. *J. Comp. Physiol. B Biochem. Syst. Environ. Physiol.* **169**, 179-186. doi:10.1007/s003600050209
Roy, S., Saha, T. T., Zou, Z. and Raikhel, A. S. (2018). Regulatory pathways controlling female insect reproduction. *Annu. Rev. Entomol.* **63**, 489-511. doi:10.1146/annurev-ento-020117-043258
Sapolsky, R. M., Romero, L. M. and Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* **21**, 55-89.
Sauve, A. A., Wolberger, C., Schramm, V. L. and Boeke, J. D. (2006). The biochemistry of sirtuins. *Annu. Rev. Biochem.* **75**, 435-465. doi:10.1146/annurev.biochem.74.082803.133500
Schaeffer, P. J., Conley, K. E. and Lindstedt, S. L. (1996). Structural correlates of speed and endurance in skeletal muscle: the rattlesnake tailshaker muscle. *J. Exp. Biol.* **199**, 351-358. doi:10.1242/jeb.199.2.351

Scheele, C., Nielsen, S. and Pedersen, B. K. (2009). ROS and myokines promote muscle adaptation to exercise. *Trends Endocrinol. Metab.* **20**, 95-99. doi:10.1016/j.tem.2008.12.002
Schnyder, S. and Handschin, C. (2015). Skeletal muscle as an endocrine organ: PGC-1α, myokines, and exercise. *Bone* **80**, 115-125. doi:10.1016/j.bone.2015.02.008
Schofield, C. J. and Ratcliffe, P. J. (2004). Oxygen sensing by HIF hydroxylases. *Nat. Rev. Mol. Cell Biol.* **5**, 343-354. doi:10.1038/nrm1366
Schwartz, T. S. and Bronikowski, A. M. (2016). Evolution and function of the insulin and insulin-like signaling network in ectothermic reptiles: some answers and more questions. *Integr. Comp. Biol.* **56**, 171-184. doi:10.1093/icb/icw046
Seebacher, F., Guderley, H., Elsey, R. M. and Trosclair, P. L. (2003). Seasonal acclimatisation of muscle metabolic enzymes in a reptile (*Alligator mississippiensis*). *J. Exp. Biol.* **206**, 1193-1200. doi:10.1242/jeb.00223
Semenza, G. L. (1998). Hypoxia-inducible factor 1: a master regulator of O_2 homeostasis. *Curr. Opin Genet. Dev.* **8**, 588-594. doi:10.1016/S0959-437X(98)80016-6
Shpigler, H. Y., Herb, B., Drnevich, J., Band, M., Robinson, G. E. and Bloch, G. (2020). Juvenile hormone regulates brain-reproduction tradeoff in bumble bees but not in honey bees. *Horm. Behav.* **126**, 104844. doi:10.1016/j.yhbeh.2020.104844
Silva, J. F., Ocarino, N. M. and Serakides, R. (2018). Thyroid hormones and female reproduction. *Biol. Reprod.* **99**, 907-921.
Speakman, J. R. and Mitchell, S. E. (2011). Caloric restriction. *Mol. Asp. Med.* **32**, 159-221. doi:10.1016/j.mam.2011.07.001
Speakman, J. R., Blount, J. D., Bronikowski, A. M., Buffenstein, R., Isaksson, C., Kirkwood, T. B. L., Monaghan, P., Ozanne, S. E., Beaulieu, M., Briga, M. et al. (2015). Oxidative stress and life histories: unresolved issues and current needs. *Ecol. Evol.* **5**, S745-S757. doi:10.1002/ece3.1790
Staats, S., Wagner, A., Kowalewski, B., Rieck, F. T., Soukup, S. T., Kulling, S. E. and Rimbach, G. (2018). Dietary resveratrol does not affect life span, body composition, stress response, and longevity-related gene expression in *Drosophila melanogaster*. *Int. J. Mol. Sci.* **19**, 223. doi:10.3390/ijms19010223
Stay, B. and Woodhead, A. P. (1993). Neuropeptide regulators of insect corpora allata. *Am. Zool.* **33**, 357-364. doi:10.1093/icb/33.3.357
Steiner, J. L., Murphy, A., MClellan, J. L., Carmichael, M. D. and Davis, J. M. (2011). Exercise training increases mitochondrial biogenesis in the brain. *J. Appl. Physiol.* **11**, 1066-1071. doi:10.1152/japplphysiol.00343.2011
Stevenson, P. A., Dyakonova, V., Rillich, J. and Schildberger, K. (2005). Octopamine and experience-dependent modulation of aggression in crickets. *J. Neurosci.* **25**, 1431-1441. doi:10.1523/JNEUROSCI.4258-04.2005
Swanson, E. M. and Dantzer, B. (2014). Insulin-like growth factor-1 is associated with life-history variation across Mammalia. *Proc. R. Soc. B Biol. Sci.* **281**, 7. doi:10.1098/rspb.2013.2458
Takeda, N., O'Dea, E. L., Doedens, A., Kim, J. W., Weidemann, A., Stockmann, C., Asagiri, M., Simon, M. C., Hoffman, A. and Johnson, R. S. (2010). Differential activation and antagonistic function of HIF-alpha isoforms in macrophages are essential for NO homeostasis. *Genes Dev.* **24**, 491-501. doi:10.1101/gad.1881410
Tank, A. W. and Wong, D. L. (2015). Peripheral and central effects of circulating catecholamines. *Compr. Physiol.* **5**, 1-15.
Tibbetts, E. A., Laub, E. C., Mathiron, A. G. E. and Goubalt, M. (2020). The challenge hypothesis in insects. *Horm. Behav.* **123**, 104533. doi:10.1016/j.yhbeh.2019.05.002
Uryu, O., Ameku, T. and Niwa, R. (2015). Recent progress in understanding the role of ecdysteroids in adult insects: germline development and circadian clock in the fruit fly *Drosophila melanogaster*. *Zool. Lett.* **1**, 32. doi:10.1186/s40851-015-0031-2
Valenzano, D. R., Terzibasi, E., Genade, T., Cattaneo, A., Domenici, L. and Cellerino, A. (2006). Resveratrol prolongs lifespan and retards the onset of age-related markers in a short-lived vertebrate. *Curr. Biol.* **16**, 296-300. doi:10.1016/j.cub.2005.12.038
van Dijk, J. G. B. and Matson, K. D. (2016). Ecological immunology through the lens of exercise immunology: new perspective on the links between physical activity and immune function and disease susceptibility in wild animals. *Integr. Comp. Biol.* **56**, 1-14. doi:10.1093/icb/icw073
Vingren, J. L., Kraemer, W. J., Ratamess, N. A., Anderson, J. M., Volek, J. S. and Maresh, C. M. (2010). Testosterone physiology in resistance exercise and training. *Sports Med.* **40**, 1037-1053. doi:10.2165/11536910-000000000-00000
von Schantz, T., Bensch, S., Grahn, M., Hasselquist, D. and Wittzell, H. (1999). Good genes, oxidative stress, and condition-dependent sexual signals. *Proc. R. Soc. B* **266**, 1-12. doi:10.1098/rspb.1999.0597
Walker, D. W., Hájek, P., Knoepfle, D., Conelison, S., Attardi, G. and Benzer, S. (2006). Hypersensitivity to oxygen and shotened lifespan in a *Drosophila* mitochondrial complex II mutant. *Proc. Natl Acad. Sci. USA* **103**, 16382-16387. doi:10.1073/pnas.0607918103
Wang, A. Z. and Husak, J. F. (2020). Endurance and sprint training affect immune function differently in green anole lizards (*Anolis carolinensis*). *J. Exp. Biol.* **223**, jeb232132. doi:10.1242/jeb.232132
Wang, A. Z., Husak, J. F. and Lovern, M. (2019). Leptin ameliorates the immunity, but not reproduction, trade-off with endurance in lizards. *J. Comp. Physiol. B Biochem. Syst. Envir. Physiol.* **189**, 261-269. doi:10.1007/s00360-019-01202-2
Wang, L., Sexton, T. R., Venard, C., Giedt, M., Guo, Q., Chen, Q. and Harrison, D. A. (2014). Pleiotropy of the *Drosophila* JAK pathway cytokine Unpaired 3 in developement and aging. *Dev. Biol.* **395**, 218-231. doi:10.1016/j.ydbio.2014.09.015
Waterson, M. J., Chung, B. Y., Harvanek, Z. M., Ostojic, I., Alcedo, J. and Pletcher, S. D. (2014). Water sensor ppk28 modulates *Drosophila* lifespan and physiology though AKH signaling. *Proc. Natl Acad. Sci. USA* **111**, 8137-8142. doi:10.1073/pnas.1315461111
Wenger, R. H. (2002). Cellular adaptation to hypoxia: O_2-sensing protein hydroxylases, hypoxia-inducible transcription factors, and O_2-regulated gene expression. *FASEB J.* **16**, 1151-1162. doi:10.1096/fj.01-0944rev
Wingfield, J. C. (2018). Environmental endocrinology: insifhts into the diversity of regulatory mechanisms in life cycles. *Integr. Comp. Biol.* **58**, 790-799. doi:10.1093/icb/icy081
Wingfield, J. C., Lynn, S. E. and Soma, K. K. (2001). Avoiding the 'costs' of testosterone: ecological bases of hormone–behavior interactions. *Brain Behav. Evol.* **57**, 239-251. doi:10.1159/000047243
Wittman, T. N., Robinson, C. D., McGlothlin, J. W. and Cox, R. M. (2021). Hormonal pleiotropy structures genetic covariance. *Evol. Lett.* **5**, 397-407. doi:10.1002/evl3.240
Wong, B. W., Kuchnio, A., Bruning, U. and Carmeliet, P. (2013). Emerging novel functions of the oxygen-sensing prolyl hydroxylase domain enzymes. *Trends BiochemSci* **38**, 3-11. doi:10.1016/j.tibs.2012.10.004
Woodcock, K. J., Kierdorf, K., Pouchelon, C. A., Vivancos, V., Dionne, M. S. and Geissmann, F. (2015). Macrophage-derived upd3 cytocine causes impaired glucose homeostasis and reduced lifespan in *Drosophila* fed a lipid-rich diet. *Immunity* **42**, 133-144. doi:10.1016/j.immuni.2014.12.023
Yang, S., Loro, E., Wada, S., Kim, B., Tseng, W. J., Li, K., Khurana, T. S. and Arany, Z. (2020). Functional effects of muscle PGC-1alpha in aged animals. *Skeletal Muscle* **10**, 14. doi:10.1186/s13395-020-00231-8
Zamora-Camacho, F. J., Reguera, S., Rubino-Hispan, M. V. and Moreno-Rueda, G. (2015). Eliciting an immune response reduces sprint speed in a lizard. *Behav. Ecol.* **26**, 115-120. doi:10.1093/beheco/aru170
Zera, A. J. and Denno, R. F. (1997). Physiology and ecology of dispersal polymorphism in insects. *Annu. Rev. Entomol.* **42**, 207-231. doi:10.1146/annurev.ento.42.1.207
Zera, A. J. and Harshman, L. G. (2001). The physiology of life-history trade-offs in animals. *Annu. Rev. Ecol. Syst.* **32**, 95-126. doi:10.1146/annurev.ecolsys.32.081501.114006
Zhang, Y. and Wong, H. S. (2021). Are mitochondria the main contributor of reactive oxygen species in cells? *J. Exp. Biol.* **224**, jeb221606. doi:10.1242/jeb.221606
Zhao, X. and Karpac, J. (2017). Muscle directs diurnal energy homeostasis through a myokine-dependent hormone module in *Drosophila*. *Curr. Biol.* **27**, 1941-1955. doi:10.1016/j.cub.2017.06.004