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Climate change and its effects on body size and shape: the role of endocrine mechanisms

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In many organisms, rapidly changing environmental conditions are inducing dramatic shifts in diverse phenotypic traits with consequences for fitness and population viability. However, the mechanisms that underlie these responses remain poorly understood. Endocrine signalling systems often influence suites of traits and are sensitive to changes in environmental conditions; they are thus ideal candidates for uncovering both plastic and evolved consequences of climate change. Here, we use body size and shape, a set of integrated traits predicted to shift in response to rising temperatures with effects on fitness, and insulin-like growth factor-1 as a case study to explore these ideas. We review what is known about changes in body size and shape in response to rising temperatures and then illustrate why endocrine signalling systems are likely to be critical in mediating these effects. Lastly, we discuss research approaches that will advance understanding of the processes that underlie rapid responses to climate change and the role endocrine systems will have. Knowledge of the mechanisms involved in phenotypic responses to climate change will be essential for predicting both the ecological and the long-term evolutionary consequences of a warming climate.

This article is part of the theme issue 'Endocrine responses to environmental variation: conceptual approaches and recent developments'.

1. Introduction

Climate change is altering habitats worldwide with unprecedented speed and the changes affect the evolution, distribution and viability of species [1–5]. Although climate change has been implicated as the cause of changes to diverse phenotypes, including range distributions, the timing of breeding, and life-history traits such as body size [4,6,7], the physiological mechanisms that underlie these phenotypic shifts remain poorly understood. Yet, there is a growing appreciation that this information will be essential for predicting how climate change will affect the evolution and long-term viability of organisms [8–12].

Endocrine signalling systems, characterized by centrally produced molecules that alter actions elsewhere in the body, are expected to play an important role in shaping complex phenotypes in response to rapidly changing environments because they allow coordinated changes across multiple traits [13–15], and they are often highly sensitive to changes in environmental conditions that are shifting as a result of climate change, such as temperature [16–21]. Body size is a general characteristic of all animals, with three key elements that make it an excellent test case to investigate how hormonal signalling systems mediate responses to climate change. First, body size has important fitness consequences [22–25] and integrates with an array of other

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life-history traits. Second, much is known about the endocrine mechanisms that influence the development of body size, though this knowledge comes mostly from model systems under controlled laboratory conditions [26–28]. Finally, both spatial and temporal patterns in body size suggest that it will be sensitive to changing climate, either via selection on existing genetic variation or through the effects of environmental cues on the developmental mechanisms (e.g. phenotypic plasticity). Here, we review what is known about how differences in body size and shape are influenced by endocrine mechanisms: the processes through which hormones act on the morphological, physiological and behavioural traits of an organism. We discuss how these mechanisms, which include changes in hormone concentrations as well as cellular- and tissue-level factors (e.g. hormone receptor densities, transcription factors, epigenetic modifications etc.) can produce complex actions. For illustrative purposes, we restrict much of our discussion to insulin-like growth factor-1 (IGF-1) given its highly conserved role in regulating growth in vertebrates [29,30], but we also highlight other hormonal systems that are likely to be important. We focus on birds and mammals because, as endotherms, which regulate their body temperature via internal metabolic processes, they face energetic constraints that differ from those of ectotherms when confronted with a warming climate [25,31]. We then use these groups as examples to illustrate why endocrine signalling systems are likely to be central players in shaping phenotypic responses to climate change in any organism. Lastly, we describe research approaches that can identify the endocrine mechanisms mediating responses to climate change and highlight important areas for future research. Understanding the mechanisms that allow organisms to respond to rapidly changing environmental conditions, including to what degree changes are due to microevolution or to phenotypic plasticity, will be essential for predicting the long-term consequences of climate change.

2. Body size and shape variation in the era of climate change

Body size is an emergent property of a suite of structural morphological traits [32], including but not limited to overall height and/or length, length of appendages and weight. Because it cannot be measured directly, body size is a latent trait that is statistically inferred from correlations among individual measures (box 1). Shape is a related concept that is characterized by independent variation in size of some subset of structural traits that are potentially correlated with each other (box 1). Because different body shapes lead to different traits being used to measure body size (e.g. snout–vent length in a lizard versus tarsus length in a bird), operationally body size and shape might best be defined relative to the organism and which elements of the phenotype can be measured, yet conceptually size and shape have broad relevance across diverse taxa. We refer most often to this general concept but will invoke more specific definitions when necessary.

Recent changes in climate seem to have contributed to changes in body size and shape across many endothermic taxa, but the direction of these changes is mixed [24,34]. Some studies suggest a pattern of overall shrinking body size. Over the last few decades, for example, adult male body mass has declined across 105 terrestrial bird species [39], bill surface area has increased in multiple Australian parrot species [40], and wing length has increased in 129 North and South American bird species [41]. Similar patterns have been detected in some mammals, such as a decline in body mass in white-throated woodrats (*Neotoma albigula*) [42] and Soay sheep (*Ovis aries*) [43], and an increase in masked shrew (*Sorex cinereus*) tail length [44]. Experimental manipulations of temperature have also revealed that warmer temperatures lead to elongated limbs and/or appendages in crocodiles and several mammals [20,45–48]. Other studies, by contrast, have produced different patterns. For example, while some Australian passerines have exhibited declining body size in recent decades, others have increased in size while still others remain the same size [24,49]. No unifying relationship between tarsus length and climate was detected in specimens from 11 common European bird species while wing length shrank in some [50], and no evidence of lengthening of appendages (neither bills nor legs) was detected in Australian whistlers and shrike-thrushes [51].

Changes involving a shrinking body size seem to parallel pre-existing patterns along temperature clines. Bergmann's Rule [52] describes the pattern of increasing size with latitude, and Allen's Rule [53] refers to the trend towards relatively shorter appendages with latitude. Many endotherms conform to these ecogeographic rules [54–58]. Both Bergmann and Allen proposed that the patterns they described were driven by temperature and the way heat can be dissipated by more surface area. That is, smaller body size and longer appendages are favoured in lower latitudes because they increase surface area to body volume ratios. Because many of the phenotypic changes over time fit the heat dissipation hypothesis, it is tempting to conclude that the changes to a warming climate are adaptive.

However, evidence for adaptive changes in body size or shape due to warming is quite weak [7,59]. Moreover, the selective forces shaping body size are likely to be complex. Increasing body size in any organism likely accrues both benefits and costs [22,60] and some ecological factors can impact both. Predation, for example, could favour larger body size if being larger allows individuals to better escape most predators [61], but conversely taking longer to develop to reach a larger size might expose vulnerable juveniles to predators for longer [62]. Growing fast may allow an organism to reach a larger size more quickly, but faster growth may come with its own costs, such as increased oxidative stress [60] and earlier or more rapid senescence [63]. Models [64] of how multiple selective factors might interact emphasize that if thermoregulatory benefits of larger size interact with other costs, such as exposure to predators, then straightforward predictions about how climate change will influence selection acting on existing body size variation may be difficult to make (figure 1). Moreover, the effects of climate change may extend beyond changes in ambient temperature and influence other factors such as food supply, disease prevalence, competition or predation [65], and these could alter selection on body size or shape. Finally, if environmental factors also act as cues affecting the plasticity of body size, then it is possible for climate change to produce maladaptive body sizes. For example, body size changes in both Soay sheep [43] and tree swallows [66] appear to be driven more by plastic effects of environments that oppose apparent selection for larger body size.

Box 1. Statistical approaches to the biology of integrated traits

Body size is the iconic example of a concept about an organism that cannot be measured directly but is inferred from an array of traits that can. Height or length, width, weight or appendage length are measurable and because they often are correlated, they allow us to infer an underlying attribute we can call body size. The measurable attributes are integrated via some developmental mechanism and become surrogates of the underlying concept of body size [33]. Like most individual traits, this integration arises through the influence of both genetic and environmental variation. Exactly how climate change might affect such integration (e.g. might it favour changes in shape rather than size? [34]) is thus a compelling issue, and there are implications on both short (developmental) and long (evolutionary) timescales. Because the statistical tool used can constrain the biology being revealed, we suggest it is vitally important that researchers match the statistical tool to their question. We illustrate some of the issues here.

Principal component analysis (PCA) is the common method of distilling multiple measures into underlying factors used for a variety of trait metrics, from behavioural responses (e.g. aggression, [35]) to body size [36]. A variety of adjustments to using PCA for integrated traits have been suggested, and for many applications this tool is quite useful. However, we note two limitations. First, PCA averages relationships over all the data used and produces standardized scores, thus making hierarchical structure in datasets (e.g. comparing differences in correlation structures among families or populations as well as within) harder to explore. Second, there is no direct way to explore hypotheses about potential causal relationships among variables, such as assessing an environmental cause of a change in integration. Both are important elements of investigating the developmental or evolutionary processes influencing integrated phenotypes under climate change.

Structural equation models (SEMs) [37,38] provide a better fit for questions about the development or evolution of integrated traits under climate change. SEMs can combine factor analysis and path analysis in multilevel data, since they can incorporate hierarchical structure in the data, and direct and indirect causal relationships (path analysis), and can reveal correlations among components at multiple levels. Figure A illustrates a simplified case of relevance to hormonal control of body size attributes during an example developmental process when attributes are measured at two time points. At the first age, body size as a latent variable is inferred from the correlations among three measurable traits, each of which has some uncorrelated residual variation. Hormone 1 predicts the magnitude of the latent variable, and so has an indirect effect on all three traits via this variable (i.e. body size). At a later age (age 2), complexities emerge along with two potential physiological explanations. Body size is still a latent variable extracted from the correlations among all three traits but shows no influence of either hormone expressed at this time. Also, now traits 1 and 2 have additional correlation structure (indicated by *r*) independent from the common effect of body size (shape distinct from size). Two possible pathways for hormonal effects are shown: with the solid black lines, hormone 1 now correlates with the linked residuals of traits 1 and 2, suggesting that trait 3 has become refractory to its effects; alternatively, with the dotted line, hormone 2 is acting solely on trait 3, producing variation in that trait independent from the other two. SEM analysis of these hypotheses could provide values for all the arrows shown, and thus allow more insights on the underlying biology of integrated traits. For an excellent example focusing on genetic variance in integrated traits associated with body size, see Araya-Ajoy *et al*. [33].

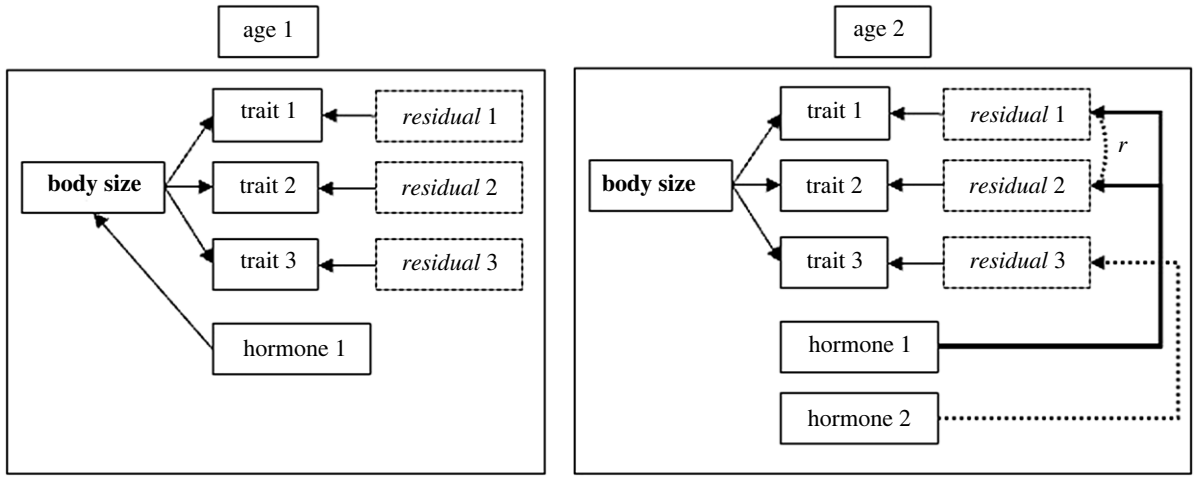

Figure A. Schematic of a hypothesized set of measured and inferred (latent) variables across two ages in a developmental timeline that could be assessed using structural equation modelling. Traits (1–3) are measurable aspects of the morphological phenotype, and hormones 1 and 2 are physiological measures. Body size is a latent variable inferred from the correlation structure among traits 1–3. 'residual' refers to variation in each trait that is uncorrelated with other traits or the latent variable.

To predict the effects of climate change on body size and shape, there are thus several compelling questions that need to be better addressed, including: (1) What is the relative importance of genes and environment in driving these observed changes in body size or shape? (2) What elements of the signalling systems harbour phenotypic variation that selection can act on and genetic variation that can evolve? (3) If changes are maladaptive, and are

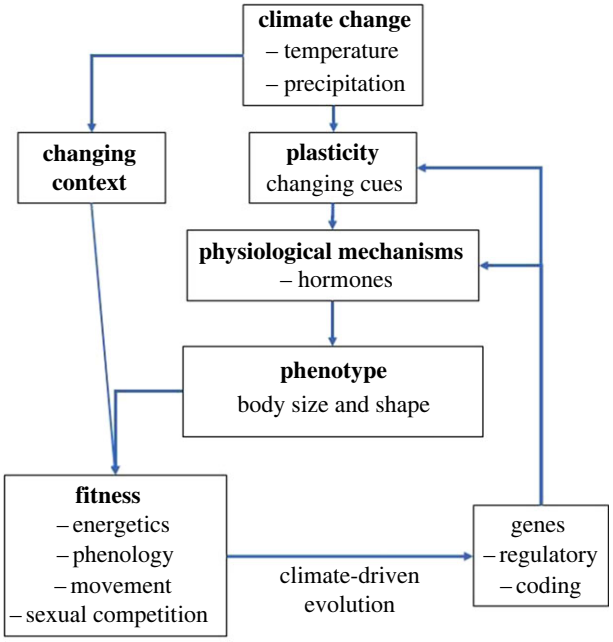

Figure 1. Framework of how climate change may influence body size through hormonal pathways. Climate change alters the environmental cues that can feed into existing mechanisms of plasticity (including an array of physiological hormone signalling systems) which may impact body size in ecological time. Climate change also potentially alters the environmental context for how body size or shape impacts fitness and, coupled with any standing genetic variation in the mechanisms underlying body size or shape, can lead to climate-driven evolution of those mechanisms and hence of body size. (Online version in colour.)

occurring despite opposing selection pressures, how might evolution switch from traits being integrated to varying independently?

Many types of information will be necessary to converge on clear answers to these questions (figure 1), but a central player relevant to all these questions is the physiological mechanism(s) underlying body size and shape variation. Structural characters that comprise body size and shape are integrated traits, and their variation is heavily influenced by physiological signalling systems, such as endocrine signals, that coordinate their expression. How might such mechanisms contribute to the response to climate change? Here, we review some salient features of systems underlying variation in structural characters relevant to body size and shape. We then outline an integrated study design that may best produce what we need to know to answer questions about the impact of climate change on structural characters.

3. Endocrine mechanisms and climate change

Endocrine mechanisms are conserved signalling systems that transduce information throughout the body to influence suites of behavioural, physiological and morphological traits, and coordinate key biological processes, including development, metabolism, the ability to cope with stressors, and reproduction. However, the actions of endocrine mechanisms can be complex and difficult to predict because changes in hormone levels and receptor densities can be mediated by genetics, plasticity or both [13,67] and these differentially affect opportunities for and responses to selection [68]. Moreover, there are multiple places in the complex control of hormonal pathways where genetic variation could exist and so respond to selection, but the extent of variation may vary, thereby putting constraints on some kinds of potential changes [69–71]. Endocrine mechanisms also have the capacity to impact an individual trait or influence suites of related traits, causing their phenotypic outcomes to be diverse [13,71].

Body size is a polygenic trait, and several hormones are known to regulate variation in body size, including (but not limited to) members of the growth axis (IGF-1, IGF-2 and growth hormone), thyroid hormones and glucocorticoids (figure 2). We focus our discussion on hormones in the IGF signalling pathway as this is a highly conserved pathway that is expected to play a critical role in pre- and post-natal growth in vertebrates [29,30]. However, we emphasize here that growth is a complex process and we expect that several physiological networks interact [72] to influence body size and shape, and we provide some details for thyroid hormones and glucocorticoids in box 2.

(a) Insulin-like growth factor signalling pathway

One endocrine mechanism likely to play an important role in regulating variation in body size and shape is the insulin-like growth factor (IGF) signalling pathway [91]. In response to endogenous and environmental cues (figure 2, number 1), the hypothalamus releases growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHIH) (also called somatostatin) (figure 2, number 2), which regulates the secretion of growth hormone (GH) from the anterior pituitary (figure 2, number 3). GH secretion then stimulates the liver to produce insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) (figure 2, number 4), which travels through the blood bound to binding proteins and binds to receptors in skeletal muscle and bone (figure 2, number 5) to induce somatic growth through both autocrine and paracrine actions and exerts negative feedback on GHRH and GH production [92–94]. IGF-1 and IGF-2 in concert with GH help to regulate linear growth (figure 2, number 6), principally through their actions on chondrocytes at growth plates, which are cartilaginous layers in most bones where chondrocytes proliferate, enlarge and secrete extracellular matrix components. Each of these processes contributes to the generation of new cartilage, the growth of new bone and an increase in size [95–97]. IGF-1 promotes bone growth by protecting chondrocytes from apoptosis through multiple pathways [98] and promoting chondrocyte proliferation [99]. GH promotes new bone growth by stimulating increased circulating levels of IGF-1 and local IGF-1 production at the growth plate and may also directly stimulate resting chondrocytes to transition to the proliferative state [88]. IGF-1 may also enhance body size through its effects on protein synthesis and muscle hypertrophy [100]. Binding of IGF-1 to its receptor in skeletal muscle stimulates the phosphatidylinositol-3 kinase/Akt pathway and subsequent increases in gene expression in signalling pathways necessary for protein synthesis, including the mammalian target of rapamycin (mTOR) pathway [101].

IGF-2 has been much less studied than IGF-1 but is expressed pre- and postnatally across amniotes, often at higher levels of expression than IGF-1 [102], and can stimulate growth and metabolism [103]. We might anticipate that changes in circulating hormone levels in the insulin/insulin-like signalling network would promote changes in total

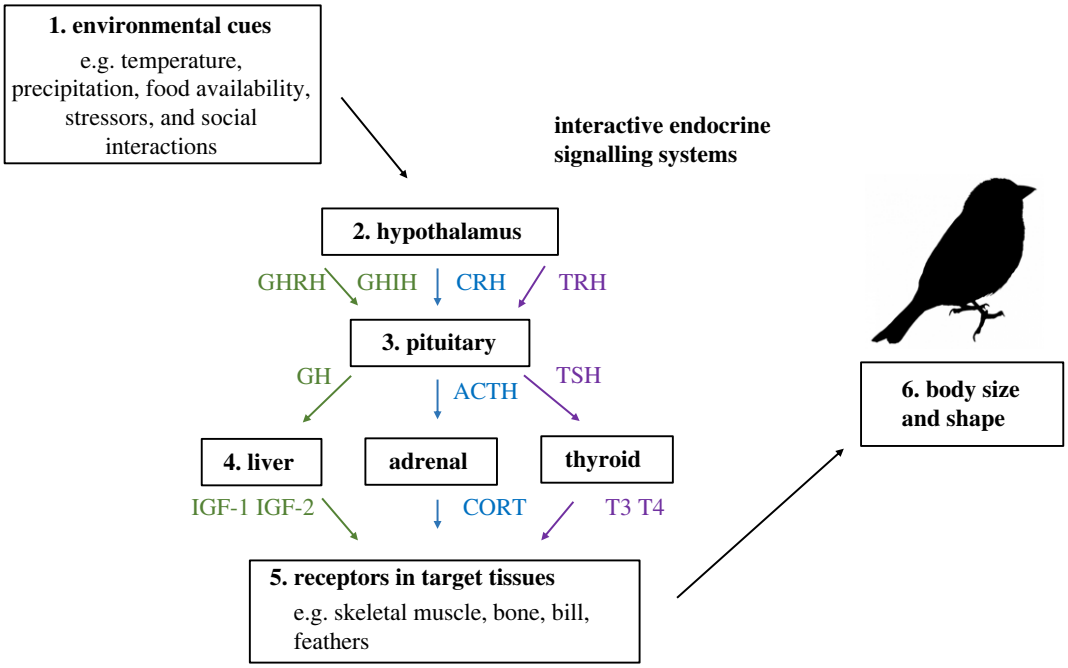

Figure 2. Three interactive endocrine pathways that are likely to be important in regulating shifts in body size and shape in response to climate change, including the growth axis (in green and described in §3a), the stress hormone axis (in blue and described in box 2) and the thyroid hormone axis (in purple and described in box 2). (Online version in colour.)

Box 2. Other hormone signalling systems with effects on body size or shape

Thyroid hormones

Thyroid hormones, regulated by the hypothalamus–pituitary–thyroid axis (HPT), and their receptors can influence the growth, differentiation, development, temperature acclimation, metabolism and tissue maturation of vertebrates [73,74]. Triiodothyronine (T_3) and thyroxine (T_4) both affect growth and development, but T_3 is more biologically active, and T_4 may be converted to T_3 at the bone plate by thyroid hormone deiodinase 2 [75]. Hypothyroid animals have decreased proliferative and hypertrophic zones in the growth plates, as a result of reduced chondrocyte proliferation and hypertrophy [76]. Thyroid hormones also have synergistic or permissive effects with GH and IGF-1 to promote bone formation [77].

Thyroid hormone secretion is also influenced by environmental conditions, including temperature, and are key regulators of thermogenesis [78]. Thermoreceptors trigger the activation of the HPT axis to induce the release of thyroid hormones in response to cold exposure, which ultimately increases heat production and respiration [78]. Through these mechanisms, thyroid hormones allow reversible phenotypic plasticity in response to temperature variation over timescales of days to weeks (reviewed in [78]). For example, wood ducks (*Aix sponsa*) incubated at warmer temperatures hatched earlier, had higher levels of circulating T_3 and elevated $T_3 : T_4$ ratios at hatching, and had higher body condition compared with those incubated at cooler temperatures [17], suggesting that temperature may accelerate development through thyroid hormones. In adult animals, exposure to elevated temperatures leads to an increase in T_4 and a decrease in T_3 levels. As T_3 is a primary mediator of heat production, T_4 is less readily converted to T_3 peripherally by deiodinases after heat exposure [79]. Similar processes occur, sometimes with long-term changes in thermotolerance, after exposure to heat challenge during early development [80]. Extensive research in the poultry industry aimed at improving heat tolerance of poultry in production facilities has tested various heat conditioning regimes during incubation to improve lifelong heat tolerance [79]. Post-hatch thermotolerance is most improved by thermal priming during the period of embryogenesis that encompasses the development of the HPT and the hypothalamic–pituitary–adrenal axis (HPA) [81,82], and this is associated with decreased plasma levels of T_3 [81–84].

Glucocorticoids

Glucocorticoids, such as cortisol and corticosterone, are regulated by the HPA axis [85] and can slow growth at bone growth plates through direct and indirect effects [86]. Chondrocytes in the growth plate have glucocorticoid receptors, allowing direct effects [87]. *In vitro* studies support the idea that glucocorticoids slow chondrocyte proliferation [88]. Some of the effects of glucocorticoids on bone growth may be mediated through indirect effects on local IGF-1 production and growth hormone (GH) receptor expression. These effects are complex and dependent on the dose and duration of exposure [88].

Glucocorticoids are also responsive to thermal conditions in vertebrates. Baseline and acute stress-induced glucocorticoid levels are generally positively correlated with changes in temperature, although the strength of these relationships varies across taxa [89]. Furthermore, as suggested by the poultry studies cited above, the HPA axis interacts closely with the HPT axis, at least in non-mammalian vertebrates, and thus may contribute to thermal sensitivity and thermoregulation (reviewed in [78]). In just one mechanistic linkage, the hypothalamic hormone corticotropin releasing hormone (CRH) stimulates the release of hormones in both the HPA and HPT axes (adrenocorticotropin releasing hormone (ACTH) and thyroid stimulating hormone (TSH), respectively; [90]) by acting through separate receptors.

body size in accordance with Bergmann's rule, whereas local actions of the IGFs and GH at the growth plate might instead promote changes in appendage length in accordance with Allen's Rule. Changes in receptor expression, binding proteins and heat shock proteins might also allow more local modification of growth plate activity.

Changes in body size and shape mediated by endocrine mechanisms could be due to a mix of microevolution and phenotypic plasticity, but the relative importance of these processes or how they might integrate is not well understood and this information will be necessary for predicting evolutionary outcomes. Some of the variation in the regulation of the insulin-like signalling pathway is genetic and can respond to selection, although the caveat is that most of our understanding of the genetic variation in this pathway is derived from artificial selection studies on body size in a few model organisms. One of the best-known examples is that among domestic dogs; all small breeds have a single nucleotide polymorphism in IGF-1 [28]. Second, in poultry, selection to increase growth rates has altered GH receptor levels with consequences for the secretion of IGF-1 [28]. Finally, variation in human height and growth, which have been more thoroughly studied, are determined not just by the GH/IGF-1 axis but by several other hormones (box 2), by genes, and by local regulation at the growth plate [104]. Thus, the regulation of body size and shape is likely to be complex and not regulated exclusively by a single endocrine axis. The complexity in the regulation of the insulin-like signalling pathway extends to encompass responsiveness to a range of environmental cues, including temperature, nutrient availability and stress, which likely plays an important role in allowing organisms to respond plastically to changing environmental conditions [29,95,105–107]. For example, in addition to nutrient availability, IGF-1 levels are also very sensitive to temperature. A meta-analysis involving experimentally warmed bird eggs and nestlings revealed that 61% of studies detected a decrease in size related to higher temperatures during development, and suggested changes in IGF-1 signalling resulting from developmental plasticity as a potential mechanism [108]. Interestingly, the effects of temperature can vary depending on both the intensity and duration of exposure. For example, acute exposure to elevated temperatures tends to increase IGF-1 levels and growth and/or feeding rates [16,109], and chronic exposure to elevated temperatures can have opposing effects [108]. Because changes in temperature can also modify metabolic rates and/or resource availability, it will be important to separate the direct effects of temperature acting on the endocrine mechanisms from indirect effects mediated through changes in resource availability [110].

(b) Endocrine mechanisms can affect evolutionary responses to climate change

Identifying the relative contributions of genetics and plasticity to phenotypic changes in response to climate change is necessary to determine evolutionary consequences. Whether plasticity in endocrine mechanisms is sufficient to help organisms cope with climate change will partially depend on the scope and magnitude of climate change. In the case of temperature fluctuations or increased weather variability, plastic responses could be preferred because individuals would be able to adjust to new conditions over shorter timescales (i.e. [111]). By contrast, if the new environment is too different compared with the original habitats, plasticity may be insufficient to promote the physiological changes necessary to keep up [112]. Microevolutionary changes in hormone levels could be most advantageous under novel environmental conditions that are directional and predictable, such as persistent increases in ambient temperature. However, more variable conditions, possible under climate change [113], could slow the rate of evolution because the responses to selection may no longer be relevant or adaptive in the rapidly changing environment [5]. Thus, it will be essential for future studies to determine the degree to which observed changes in body size and shape and endocrine signalling are due to microevolutionary processes versus phenotypic plasticity to predict evolutionary outcomes.

Another aspect of endocrine mechanisms that is likely to have important evolutionary consequences is that changes in circulating hormones often influence multiple traits because many tissues and cell types have receptors for and thus respond to increases or decreases in the signal, resulting in integrated changes in suites of traits [13,114]. When multiple traits are responsive to the same hormonal signal, changes in hormone levels can facilitate rapid integrated responses across suites of traits [14,69,115]. The extent to which traits are linked via hormonal mechanisms can therefore strongly influence the ability for those traits to respond to selection and, thus, be adaptive in novel environmental conditions. Under some circumstances, physiological integration could allow organisms to adaptively respond to rapidly changing environmental conditions. In the case of body size, this might allow coordinated increases in size across diverse tissues. However, under other conditions, physiological integration could constrain the independent evolution of these integrated traits. As described above, although Bergmann's Rule generally predicts that rising temperatures will favour smaller size, Allen's Rule predicts that these effects will vary across tissues and that retaining larger appendages will allow greater heat dissipation. Thus, to what extent and at what rate is it possible for organisms to decrease in overall size, while simultaneously increasing the size of certain appendages (e.g. bill size or wing or leg length)?

Mechanistic details may determine the answer to these questions. Traits responsive to the same hormone can become less integrated through a variety of mechanisms, including changes in receptor densities, epigenetic modifications, evolution of tissue-specific transcription factors, gene duplication, and crosstalk with other signalling systems, and each of these might allow traits to evolve more independently of one another (commonly referred to as phenotypic independence). For example, elegant experimental work on brown anoles (*Anolis sagrei*) has demonstrated a central role for hormones in the insulin-like signalling network in the integration of body size traits [69], which may have implications for the way that organisms will be able to adjust their body sizes in response to climate change. Brown anole males and females begin life at the same size [69]. Over ontogeny, males gradually grow to become two to three times heavier than females [116]. This sexual dimorphism is triggered by testosterone, which acts on the liver and other tissues to increase the expression of genes in the GH/IGF axis, mTOR network and insulin-like signalling network. Testosterone also increases the expression of hormone receptors and binding proteins in these networks, demonstrating that

multiple mechanisms may contribute to modification of sensitivity to the hormone signal [69]. In this case, testosterone is acting as an epigenetic modifier to alter the transcriptional activities of metabolic genes and magnify sexual dimorphism across ontogeny in this species of anole [69,117]. In the context of climate change, this example illustrates the potential for other hormones or epigenetic modifiers to interact with the GH/IGF axis and exert coordinated effects on body size through the integration of hormonal mechanisms. Because the GH/IGF axis coordinates a high degree of hormonal pleiotropy and the effects that it exerts on body size are often (though not always) difficult to reverse, we might predict that selection should favour changes in the sensitivity of particular tissues to hormones in the axis, rather than changes in hormone levels themselves [71].

In addition to changes in overall body size, there is also evidence that changes in the sensitivity of specific tissues to ligands in the insulin/IGF pathway can result in dramatic changes in organismal shape. For example, in male rhinoceros beetles (*Trypoxylus dichotomus*) horn size is highly variable and more sensitive to changes in insulin/IGF signalling than other body tissues (e.g. wing and genitalia) [118]. Consequently, experimentally increasing insulin/IGF signalling greatly increases the size of horns, but not these other tissues [118]. Another recent example of this can be found in black-bellied seedcrackers (*Pyrenestes ostrinus*), birds that exhibit three discrete bill size morphs (small, large and mega) maintained by disruptive selection for feeding specialization that appear to be driven by differences in IGF-1 signalling [119]. The small and large morphs differ in bill size but not body size and these differences are associated with a single locus (TGU1A) which includes IGF-1 [119]. By contrast, the transition to the mega morphs, which are larger than the other two morphs in both bill size and body size, appears to involve changes across a more extensive region of the same chromosome [119]. Recent research also suggests that aspects of IGF-1 and IGF-2 signalling contribute to variation in bill size and shape in Darwin's finches [120]. Taken together these results are consistent with the idea that the tissue sensitivity of appendages can be modified to alter the coupling of overall body size from appendages and potentially increase the ability of organisms to conform to both Bergmann's and Allen's rules. In birds, bill size and shape are often strongly associated with differences in feeding ecology and this trait may be less integrated with body size than other appendages.

Phenotypic integration is expected to influence not only the evolution of different morphological traits, but also an organism's life-history strategy [121]. For example, in addition to effects on growth and body size, correlational and experimental studies have also demonstrated that IGF-1 influences longevity and may underlie the commonly observed life-history trade-off between growth rate and lifespan [29,97,122,123]. For example, in female mice, IGF-1 receptor knockouts lived 33% longer than controls [124]. In addition, longer-lived inbred mouse strains have lower IGF-1 levels than shorter-lived inbred strains [125]. Further, smaller dog breeds characterized by lower IGF-1 signalling also have greater longevity [26]. Recent comparative studies in mammals and birds also reported that species with higher IGF-1 have a 'faster pace of life' characterized by more rapid growth, higher reproductive output and reduced lifespans [121,126]. These studies suggest that, within and among species, hormones and life-history traits can evolve in unison and changes in hormone levels, such as IGF-1 can result in coordinated changes in suites of traits, including body size [121]. Thus, to predict how organisms will respond to rapidly changing environmental conditions it will also be essential to know more about how these endocrine mechanisms are influencing these integrated phenotypic responses.

4. Future directions using integrated approaches

It is abundantly clear that the impacts of climate change in both ecological and evolutionary time will be a major focus of interest for some time. Body size and shape specifically offer new opportunities to tackle unanswered questions about the biology of rapid change [59]. Definitive answers to these questions as applied to body size [7] and shape [34] are lacking. Many researchers call for more studies, but it is worth asking what kind of studies might provide key insights. It is clear to us that details of the underlying physiological mechanisms influencing complex traits like body size and shape and integrating them with life-history characters will be an important area of future research. There are multiple ways of incorporating physiology more fully, including in theory (box 3).

Merilä & Hendry [59] review a variety of specific approaches for addressing questions about how complex traits might respond to climate change. We will not repeat details here but will instead make the case that using an integrative design that combines some of these approaches with measures of endocrine mechanisms may be particularly useful for avoiding some of the pitfalls they present. We suggest the following ideal study design (figure 3): (1) measuring multivariate phenotypes to be analysed with appropriate multivariate statistics (box 1), (2) employing new statistical methods of measuring selection, especially with richer assessments of the environment, (3) using study organisms that exist along environmental clines and, if possible, having replicated longitudinal studies along the cline, (4) replicating experiments such as translocations across times, and (5) most importantly, measuring the underlying endocrine mechanisms as part of these approaches. We appreciate that some of these approaches simply may not be possible in some systems and emphasize that additional studies in each of these areas will yield important insights. We briefly explore each of these components in more detail below.

(a) Multivariate morphological and endocrine phenotypes

First, fully answering questions about the impact of rapid change on phenotypes will benefit from more expansive measurements of phenotypes. Body size and shape are excellent examples of complex phenotypes that are not easily measured and a focus on single measures is limiting. Body mass, for example, is a commonly used metric for size, but large within-individual variance causes several problems, notably with measures of selection and reducing power in detecting genetic change. Moreover, given the many selective forces acting on body size, body shape might respond more quickly to climate change and so may be the more common response [34], but key questions about the potential constraints due to phenotypic integration cannot be addressed

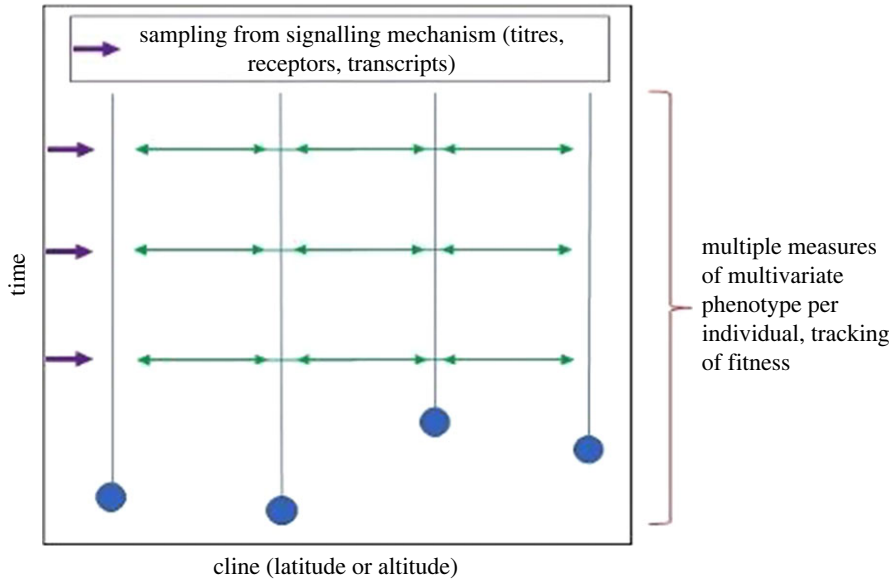

Figure 3. Schematic of an idealized study system in which long-term data collection (*y*-axis) is combined with replicate populations (blue circles) located along a cline (*x*-axis), with studies perhaps initiated at different times. Data are collected on multiple phenotypic measures through an individual's development at each location and in each cohort. Translocation experiments across locations occur periodically over time, with sampling of phenotype and of selected elements of the signalling mechanism (hormone titres, receptor densities or transcript levels) hypothesized to underlie phenotypic integration of both experimental and control individuals. The perfect system would also allow pedigree construction at each site and tracking of lifetime fitness. (Online version in colour.)

Box 3. Modelling approaches incorporating mechanisms

Responses of complex phenotypes to climate change are not easy to predict, especially if details of the physiological mechanisms are included. Mathematical modelling is another tool currently underutilized in developing a robust set of predictions about the impacts of climate change on complex phenotypes and the trickle-on effects on populations. Mathematical modelling can guide empirical work and suggest which mechanistic pathways might be most relevant. We introduce several avenues in which models have potential [127]. For researchers interested in testing which alternative proximate mechanism might be most likely to mediate relationships between climate change and growth, dynamical models of biochemical pathways, which are based on differential equations, can provide mechanistic insight. For example, sensitivity analyses were combined with ordinary differential equation models of the gut–bone axis to better understand the role of butyrate on regulatory T-cells in the gut–bone axis [128], but this approach could be modified to test endocrine mechanisms contributing to other aspects of the bone growth axis.

A key issue is the extent of pleiotropy in hormone systems and whether that constrains or facilitates phenotypic responses to selection. For example, one might ask how the strength of selection imposed by climate change affects correlated traits, such as different metrics of body size or how opposing selection pressures between sexes or age classes might affect the evolution of body size mediated by endocrine mechanisms [127]. Dantzer & Swanson [129] used a quantitative genetic model of a single hormone that impacted a performance trait and a life-history trait. They manipulated the genetic correlation between the hormone and the life-history trait and the selection gradient on the life-history trait and assessed the response to selection.

To integrate the population-level consequences of any effects of climate change on body size, one could use individual-based simulation models (IBMs; [127]). Although IBMs do not require estimates of survival and reproduction from the population being studied, they can incorporate data from pedigreed populations, reciprocal transplant or common garden experiments to generate testable predictions. IBMs have been applied to test how stressors and the response to stressors impact population sizes [130]. IBMs have the potential to explore the population consequences of changes in body size, while including correlated effects on survival and reproduction.

Finally, well-informed models of local adaptation and population connectivity can be used to project a species vulnerability to climate change [131]. For example, a combination of population genomics and environmental data allowed Bay *et al*. [132] to identify regions of the yellow warbler (*Setophaga petechia*) genome linked to climate, leading to predictions about which populations required the greatest genetic change to keep up with climate change. These populations had already suffered the largest declines. These predictive models identified populations at risk and provided hypotheses for the underlying reasons for the higher risk. Wider use of mathematical tools is likely to be additionally insightful.

with single measures of the phenotype. Finally, measuring traits throughout development may help illuminate the timing and impact of plastic responses to changing environments. Such multivariate and longitudinal measures will be particularly effective given that appropriate multivariate statistical tools are available (box 1) that can capture correlated or uncorrelated multivariate responses existing at multiple levels (times during development within individuals, among individuals within populations, and among populations) with potential causal pathways.

Importantly, the most compelling element of an integrated study design will be to layer on the sampling of endocrine signalling systems that produce integrated phenotypes such as body size and shape. As discussed above, the insulin-like signalling pathway is an excellent example, though body size and shape are complex traits that are likely influenced by multiple pathways (box 2); such pathways are central to the issues of genetic versus environmental influence, to adaptive responses, and to how independence might arise from integrated systems. Given that endocrine systems are dynamic traits that often respond plastically to environmental cues, it will be important to measure hormones at multiple time points under different environmental conditions and to use reaction norm approaches [127,133–135]. The timescale over which to collect samples to measure endocrine traits will depend on several factors, including: (1) the phenotype of interest, (2) the duration of exposure to elevated or reduced temperatures, (3) the temperature intensity, and (4) the age of the individual (e.g. embryo, juvenile, adult). As examples, we might predict that endocrine mechanisms that mediate reversible effects on body size (e.g. muscle or body mass) would be more sensitive to short-term fluctuations in environmental conditions, whereas endocrine mechanisms that mediate irreversible effects on structural components of body size should only be sensitive to longer-term changes in environmental conditions. There is also an increasing appreciation that to gain richer insight into trait integration and independence it will be essential not only to measure hormone levels, but to also measure receptor densities in target tissues [67,114,136]. Lastly, given that body size and shape are likely highly polygenic traits, many endocrine pathways may be important in mediating these differences. Transcriptomics is one approach that is likely to be particularly powerful for identifying the endocrine mechanisms that contribute to clinal patterns of body size and shape; however, it will require careful consideration of the tissues to be sampled and the time of collection [137]. If done in concert with common garden and/or reciprocal transplant experiments, it would also be possible to determine the relative influence of microevolutionary processes and plasticity on these mechanisms.

(b) Selection

The evidence for body size changes being adaptive is rather poor [7,43,66], and while circumstantial evidence points strongly towards adaptive changes in shape [34], such evidence does not meet the more stringent criteria for adaptation [59]. Assessing adaptation requires good measures of selection. Traits like body mass have relatively low repeatability, which means estimates of selection on them are biased downward [138]. Multivariate techniques [139] or errors-in-variables approaches [140] can produce less biased measures of even nonlinear selection [138]. This will be further aided by careful measurement of key environmental variables, which can separate confounding effects of environment on traits and fitness [141], assist in interpreting whether any changes in phenotype have been or are likely to be driven by selection, and help identify the full scope of rapid environmental changes (e.g. [66]).

(c) Environmental clines and experimental approaches

The clinal patterns in suites of morphological, physiological and behavioural traits, thought to be important in temperature regulation, including body size and shape (e.g. Bergmann's and Allen's rules), provide opportunities to address many of the questions about climate change, especially if coupled with other approaches. Adaptations that contribute to variation along the cline may also be favoured over time as temperatures continue to rise (e.g. it may be possible to substitute geographical space for evolutionary time). Thus, understanding the mechanisms that underlie clinal patterns in body size and shape may be key for predicting how organisms will respond to rapidly changing environmental conditions and inform future vulnerability. This approach has been used to examine the mechanisms that contribute to thermal tolerance along latitudinal clines in diverse organisms [46,142–148] and similar approaches could be used to examine the endocrine mechanisms that contribute to clinal patterns in body size and shape. For example, a recent study examined transcriptomic data from mice collected at five sites along a latitudinal cline and identified 17 genes as being associated with the cline, two of which were associated with variation in body mass [149]. Researchers have also examined the genetic mechanisms that contribute to variation in bill size and shape along environmental gradients [150,151] and have found that the genetic architecture is likely to be complex and involve several signalling mechanisms (e.g. bone morphometric protein). Clines also offer the opportunity to experimentally confirm the relative importance of variation due to plasticity versus that due to genetic variation through common garden and transplant experiments.

Experimental approaches along environmental clines can be particularly useful for identifying the mechanisms involved in mediating responses to climate change. For example, house mice (*Mus musculus domesticus*) exhibit latitudinal variation in body size and shape consistent with Bergmann's and Allen's rules, where individuals from more northern populations are heavier and have shorter appendages (tails and ears) than those from more southern populations [46]. Lines from the ends of the distributions were reared in the same environmental conditions (common garden) for several generations. The latitudinal differences in both size and shape persisted, implicating genetic effects. In a complementary experiment, sibling groups were split and reared at one of two temperatures (5 versus 21°C). Offspring reared at the cooler temperature had shorter appendages (tails and ears), implicating some role of phenotypic plasticity. The researchers then used exomic, genomic and transcriptomic data to identify the underlying genetic mechanisms. Most candidate single nucleotide polymorphisms are likely involved in gene regulation [146], suggesting genetic variation in plasticity. However, this study did not examine the selection pressures driving these differences or whether they are changing over time in response to climate change. Measuring changes over time requires longitudinal sampling as part of long-term studies or using museum collections [152,153].

(d) Longitudinal studies and long-term populations

Long-term studies have generated much of what we know about climate change and phenotypic changes as they are able to measure change over time. Detailed pedigree information in long-term studies allows animal model analysis to assess evolutionary versus plastic changes (e.g. [43]) or,

in some cases, the evolution of plasticity [111]. Use of museum collections [152,153] can also expand the time frame for documenting changes. There is a strong need for more long-term studies, perhaps designed with climate change in mind. A drawback of long-term studies of climate-induced change is that each one is an N of 1 and usually results are correlations, with the usual drawbacks of potential confounding effects. Comparative analyses can help solve the sample size issues, but the number of long-term studies is sufficiently small that finer details of the processes affected by climate change might not be resolvable. Thus, more studies are needed.

With climate potentially changing over time, we suggest a compelling focus might be longitudinal studies replicated along a cline of temperature. This design provides additional opportunities to assess the roles of genes and environment, especially if three additional types of information can be gathered: (1) pedigrees for animal model analysis, (2) fitness measures to assess changes in selection within each population, and (3) replicated experiments, such as translocations [145,154,155]. For example, Cayuela *et al*. [148] used marked-recaptures of Columbia spotted frogs (*Rana luteiventris*) from multiple populations along a temperature cline over multiple years. Along the cline, faster growth, reduced longevity and faster senescence were associated with warmer temperatures. Sequencing data from a subsample of frogs among 31 breeding sites along the cline revealed 148 single nucleotide polymorphisms and 39 copy number variants associated with temperature. Some of these were in potentially relevant areas of the genome, suggesting possible functional roles in responding to temperature. The specific role of the variants in mechanisms underlying temperature responses (and which phenotypic attributes they influence) and whether climate change has contributed to selection on these genes within populations is not known yet, but the setting of this study illustrates the great potential of the design.

We emphasize that an ideal study, possible with careful planning and cooperation among multiple groups, would be to use clines, long-term studies along those clines, experiments exploiting the clinal structure, and repeated measures of phenotypes including the hormonal mechanisms underlying morphology (figure 3). It is an ambitious goal, but one that seems especially timely and worth the effort given the pace of climate change. However, we also acknowledge that some of the approaches described here may simply not be possible in some systems and emphasize that advances in any of these areas will be critical for our understanding of how organisms are responding to climate change.

5. Conclusion

Understanding organismal responses to rapid environmental change in both ecological and evolutionary time is extraordinarily important and increasingly urgent in the face of global climate change. Growing evidence from a wide array of organisms indicates that complex traits, such as body size, may be affected. In many organisms, including diverse bird species, body size has become smaller in response to rising temperatures, and this is often assumed to be an adaptive response to a warming world. At the same time, however, many bird populations are experiencing dramatic declines [156], and both patterns could be due to deteriorating environmental conditions during early life, with long-term consequences for body size and fitness. Thus, there is a growing appreciation that to be able to accurately predict how organisms will respond to climate change it will be essential to understand the underlying physiological mechanisms. Physiological mechanisms both are phenotypically plastic and harbour genetic variation, so can also evolve. Thus, exactly how those might work together and over what timescales will require integrative studies in terms of the geographical scales at which the research is conducted, the tools applied and the expertise of researchers.

Data accessibility. This article has no additional data.

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

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