Endocrine flexibility can facilitate or constrain the ability to cope with global change.

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ABSTRACT

Global climate change has increased average environmental temperatures world-wide, simultaneously intensifying temperature variability and extremes. Growing numbers of studies have documented phenological, behavioral, and morphological responses to climate change in wild populations. As systemic signals, hormones can contribute to orchestrating many of these phenotypic changes. Yet little is known about whether mechanisms like hormonal flexibility (reversible changes in hormone concentrations) facilitate or limit the ability of individuals, populations, and species to cope with a changing climate. In this perspective, we discuss different mechanisms by which hormonal flexibility, primarily in glucocorticoids, could promote versus hinder evolutionary adaptation to changing temperature regimes. We focus on temperature because it is a key gradient influenced by climate change, easy to quantify, and links to hormones are well established. We argue that reaction norm studies that connect individual responses to population-level and species-wide patterns will be critical for making progress in this field. We also develop a case study on urban heat islands, where several key questions regarding hormonal flexibility and adaptation to climate change can be addressed. Understanding the mechanisms that allow animals to cope when conditions become more challenging will help in predicting which populations are vulnerable to ongoing climate change.

Keywords: physiological flexibility, global climate change, within-individual reaction norms, coping ability

Introduction.

Global climate change has resulted in increased exposure to both higher yearly average temperatures and to greater temperature variability for most wild animals [1,2]. A growing number of studies have documented the effects of changing temperature regimes on morphology [3,4], behavior [5,6], species ranges [7], and population stability [8]. These population-wide responses occur through a combination of evolutionary responses to selection and developmental plasticity induced, in part, by experiencing a warmer and more variable climate [3,4,9,10]. Understanding these patterns is crucial to predicting the effects of climate change, because evidence has mounted that in many cases populations that are unable to keep pace with climate change are more vulnerable [11] and that particular behaviors, life history strategies, or morphologies predispose some species or populations to increased or decreased capacity to cope with a warming world [12]. However, despite strong support for a set of 'universal responses' to climate change that parallel known eco-geographical gradients [7,13], less is known about general patterns of variation in hormonal systems as a consequence of climate change.

Hormonal response systems are critically important to coping with changing temperature regimes over short and long-time scales [14] and – in some cases – hormones may actually underpin the observed morphological and behavioral responses to climate change. A great deal of the insight about population responses to climate change has come from the availability of long-term museum collections [3], continuously studied populations [7,15], genomic comparisons [16], and community science databases that record occurrence and phenology [6]. Unfortunately, most physiological traits are not preserved in traditional specimens or reported by community scientists and few resources exist to evaluate whether there have been similar long-term changes in these response systems. Recent studies have begun to shed light on the macroevolutionary patterns of hormone levels in relation to climate [e.g., 17], but collecting these data is challenging and it is even more difficult to measure endocrine flexibility because cross-sectional studies or measurements under a single set of conditions may not capture critical variation in flexibility [18–20].

Because projections suggest that climate change will result in a higher frequency of extreme temperature and weather conditions with increased severity and longer duration [21,22], the ability to flexibly adjust to variable or extreme temperatures may be a key predictor of resilience. Even when considering morphology and phenology, recent papers have identified a gap between our understanding of the large-scale and long-term effects of climate change, inferred from records like museum specimens and community science databases, and the actual, individual-level processes through which animals interact with their environment [23,24]. While the most obvious effect of climate change is an increase in long-term average temperature, individual animals do not directly experience long term averages and the ability to cope with temperature extremes might be a key predictor of resilience [25]. Moreover, even modest changes in temperature that do not approach critical thermal limits can have major indirect effects on fitness-related behaviors like the timing of breeding and migration or provisioning and incubation behavior, which may in turn be regulated by endocrine flexibility [11].

For example, at a population level, great tits (*Parus major*) breeding in Wytham Woods have advanced their breeding phenology consistently since the 1960s [15]; however, the change in breeding phenology is spatially variable and this variability appears to be driven by differences in the timing of food resources, such that the optimal timing of breeding differs between territories [23]. Thus, individual flexibility in timing of breeding is a critical determinant of breeding success or failure. Flexibility in this population may facilitate adaptation by matching breeding timing with food resources [15], but it can also exacerbate climate change impacts by increasing exposure to bad weather [24]. In a different population of great tits, glucocorticoid flexibility to spring temperature differs between individuals, suggesting that endocrine flexibility might be a key mechanism underpinning the ability to cope with changing climates [26]. Interaction with the environment at this immediate scale forms the basis of much work in environmental endocrinology over the past 50 years, yet flexibility has not been well integrated into the framework of individual- and population-level consequences of shifting temperature regimes.

In this paper, we explore the importance of flexibility in hormones and, therefore, in the physiological or behavioral traits that they mediate as a key driver of the ability to cope with changing temperatures at different time scales and hierarchical levels (individuals, populations, species). We focus primarily on birds and glucocorticoid hormones, because these examples are best studied, but the framework we develop should apply to other taxa and endocrine systems. We highlight responses to temperature variation because changes in temperature are the most easily observed and pervasive measures of climate change but note that endocrine flexibility is likely also relevant for understanding responses to other indirect effects of climate change, such as changing food availability, mismatched photoperiodic cues, and community composition. In some cases, endocrine flexibility may allow animals to cope with increased temperature extremes and variability over the short term even when the environment is not optimal for a particular species [14]. In this scenario, endocrine flexibility buffers against the negative consequences of climate change and may allow populations to persist long enough for evolutionary processes to result in changes to population behavior and morphology as described above [i.e., the Baldwin effect, genetic accommodation, and genetic assimilation, 27,28]. In other cases, a lack of endocrine flexibility among individuals may mean that populations do not have enough phenotypic and genetic standing variation to respond evolutionarily to selection pressures from climate change or flexibility might result in increased exposure to unfavorable conditions or costs from climate change [24,29].

A number of recent review papers have described the application of a reaction norm approach to individual endocrine flexibility [18,30,31] and the role hormones play in coping with temperature [14,32]. Thus, we review these ideas only briefly here. Instead, we focus on building an explicitly hierarchical approach (i.e., from individuals to species) within an evolutionary framework to studying endocrine flexibility in the context of changing temperature regimes. This framework results in testable predictions and suggestions for expanded empirical study that will broaden the scope of current approaches to studying endocrine flexibility. We first discuss key aspects of flexibility in endocrine systems and how these traits might facilitate or constrain adaptation to changing climates with an emphasis on integrating from individual to population level approaches. Using this framework, we next suggest a potential case study for future work focused on the role of endocrine flexibility in coping with variable temperature gradients associated with urbanization and the heat island effect. Finally, we discuss challenges and opportunities for studying endocrine flexibility in a changing world.

Endocrine systems involved in coping with temperature

We define endocrine flexibility as reversible changes in endocrine response systems [30,33,34]. Endocrine flexibility might occur through changes in various components of endocrine systems, such as receptor density in different tissues or production and clearance of hormones. In most cases, only circulating hormone concentrations are measured and we refer to these measures as indicating hormonal flexibility, which is a subset of endocrine flexibility. In general, we expect circulating hormone levels to be more flexible than receptors, but relatively little is known about flexibility in receptors because they cannot be measured repeatedly in the same individuals. Undoubtedly, temperature exposure can also generate irreversible developmental plasticity in these same endocrine systems that may persist throughout the lifetime and contribute to the subsequent ability to cope with temperature challenges [14,35]. However, in the interest of focus, we mostly discuss reversible flexibility during adulthood. We also note that other mechanisms, such as neural regulation of temperature control and metabolism also play a major role in responding to temperature changes but are not discussed here [36]. Flexibility in several endocrine systems is likely critical to enabling wild animals to cope with the rapid changes in temperature that are typical of natural populations.

The hypothalamic-pituitary-adrenal (HPA) axis has both direct and indirect effects on the response to variation in temperature. These effects can include behavioral changes to avoid more extreme thermal challenges as well as changes to critical behaviors, such as incubation and provisioning, within the thermoneutral zone. Thermoregulatory responses to cold and heat can sometimes be energetically expensive (although the metabolic costs of high temperatures may be more variable than those for low temperatures). Glucocorticoid hormones, which are produced by the HPA axis, mediate phenotypes in a variety of ways that influence the amount of energy available for behavioral changes or thermoregulation [reviewed by 14,32]. Although mean global temperature changes so far are too small to generate major challenges for endothermic thermoregulation, the increased frequency of extreme weather events resulting from climate change may push animals outside of their thermoneutral zone more often. Glucocorticoids promote movement and food seeking behavior [37–41]. They also mobilize glucose and replenish energy reserves, particularly in fasted animals [42,43]. Glucocorticoids can also alter the timing of and investment in expensive life history stages [44,45] affecting both the energy available for thermoregulation and the presence of thermoregulatory needs specific to life stages (e.g., breeding). At least in some cases, these effects can come through glucocorticoid-mediated changes in the activity of the hypothalamic-pituitary-gonadal (HPG) axis.

The hypothalamic-pituitary-thyroid (HPT) axis is also a major mediator of thermoregulation, yet much less is known about the presence or functional consequences of individual variation in flexibility of the HPT axis. Temperature influences the production of the thyroid hormone thyroxine (T4) by the HPT axis, and the rate at which it is converted to triiodothyronine (T3; the bioactive form) in the tissues [46,47]. Within the thermoneutral zone, thyroid hormones affect temperature by influencing metabolic rates and respiration [14,47]. Furthermore, glucocorticoids are known to interact with the HPT axis, with corticotropin-releasing hormone (CRH) secreted from the hypothalamus stimulating thyroid hormone release in non-mammalian vertebrates [48]. Glucocorticoids can increase T3 availability by regulating the gene expression of two diodinase enzymes, while thyroid hormones can suppress glucocorticoid release via negative feedback on the pituitary and hypothalamus [48]. Both endocrine systems also influence the development of thermoregulation in avian species [14]. In this way, glucocorticoid flexibility can impact thermoregulatory traits indirectly by influencing patterns of thyroid hormone release.

Measuring flexibility and sources of variation in flexibility.

Studying how and why individuals differ in these hormonal responses to environmental factors may help to predict the likelihood that individuals and populations can cope with changing climate [Figure 1, 14,30,32,49]. In recent years, within-individual reaction norm modeling has emerged as the primary statistical tool to quantify flexibility because of its distinct advantages over simpler approaches. First, it has the power to partition individual phenotypic variation into its main components, allowing accurate quantification of how much variation in a trait is explained by flexibility (see below). Second, when pedigree data are available, the approach can be used to partition variation into genetic, environmental, and gene by environment components. Finally, the approach can be extended to explicitly model multi-level samples that reflect the hierarchical nature of variation in traits moving from individuals, to among-individual variation and, ultimately, to populations and species within a single coherent framework [18,30,31,but see, 50].

Reviewing the full reaction norm approach, as well as its challenges, is beyond the scope of this paper [for a detailed review see, 18,51]. But it is important to note here that at the most basic level individual differences in hormone responses to a gradient, such as temperature, can be present in three trait components, represented by among-individual variation in: i) average hormone concentrations along a gradient (i.e., the 'elevation' or 'intercept' of a linear reaction norm); ii) the degree of hormonal change to that gradient (i.e., the 'slope' of a linear reaction norm, which we refer to as hormone flexibility); and iii) the covariation between average concentration and flexibility [18,51]. While individual differences in average hormone concentrations and in the degree of hormonal change indicates 'standing phenotypic variation' that (if heritable) selection could act on, any covariation between these two traits indicates that they are linked in their response to environmental variation. Such a linkage could either limit or facilitate evolutionary change in these traits, and raises interesting questions about the origin of that linkage (e.g., genetic, developmental, environmental). For simplicity, we focus on linear reaction norms, but note that these relationships can include threshold effects or other non-linear patterns

[52] and that many additional layers of complexity can be added to the simple examples we develop, such as considering among-individual differences in both expressed and optimal flexibility [30].

A small but growing number of studies have demonstrated among-individual variation in endocrine flexibility in experimental lab conditions [e.g., 53–55]. Recently, for the first time, individual differences in hormonal flexibility to temperature variation were demonstrated in free-living birds [26]; in this case, individuals differed in both average glucocorticoids (elevation) and flexibility (slope), but there was a negative covariation between the two traits for baseline corticosterone regulation [26]. Moving up to the species level, one recent paper also used a reaction norm approach to demonstrate that some components of glucocorticoid flexibility differ between species and are associated with the thermal environment that species live in [56]. Thus, evidence is accumulating that individuals and species differ in hormonal flexibility in ways that could be important for coping with temperature, but relatively little is known at this point about the ultimate versus proximate sources of this variation. Understanding the source of differences in endocrine flexibility is critical for predicting its importance in coping with climate change because it will determine how rapidly evolution can shape changes in flexibility.

Developmental plasticity likely plays a role in generating observed patterns of variation in endocrine flexibility. Although developmental temperature can significantly alter the subsequent function of both the HPA and HPT axes [35,57], few studies have addressed whether developmental temperature affects the subsequent flexibility of endocrine responses. Some insight comes from work in poultry: in chickens, embryonic exposure to heat produces chicks that mount a weaker corticosterone response to a subsequent heat challenge [58]. Exposure to acute cold shortly after hatching also causes chicks to later mount a shorter corticosterone response to a cold challenge [have stronger negative feedback, 59]. Several studies in wild birds also show that thermal challenges early in development can affect the strength of the corticosterone response to a standardized stressor later in the juvenile period [60,61], and even into adulthood [62]. If these individuals also have a greater glucocorticoid response to thermal challenges then their thermogenic capacity could also be more flexible. Through this route, individual differences in developmental environments could generate variation in thermoregulatory capacity.

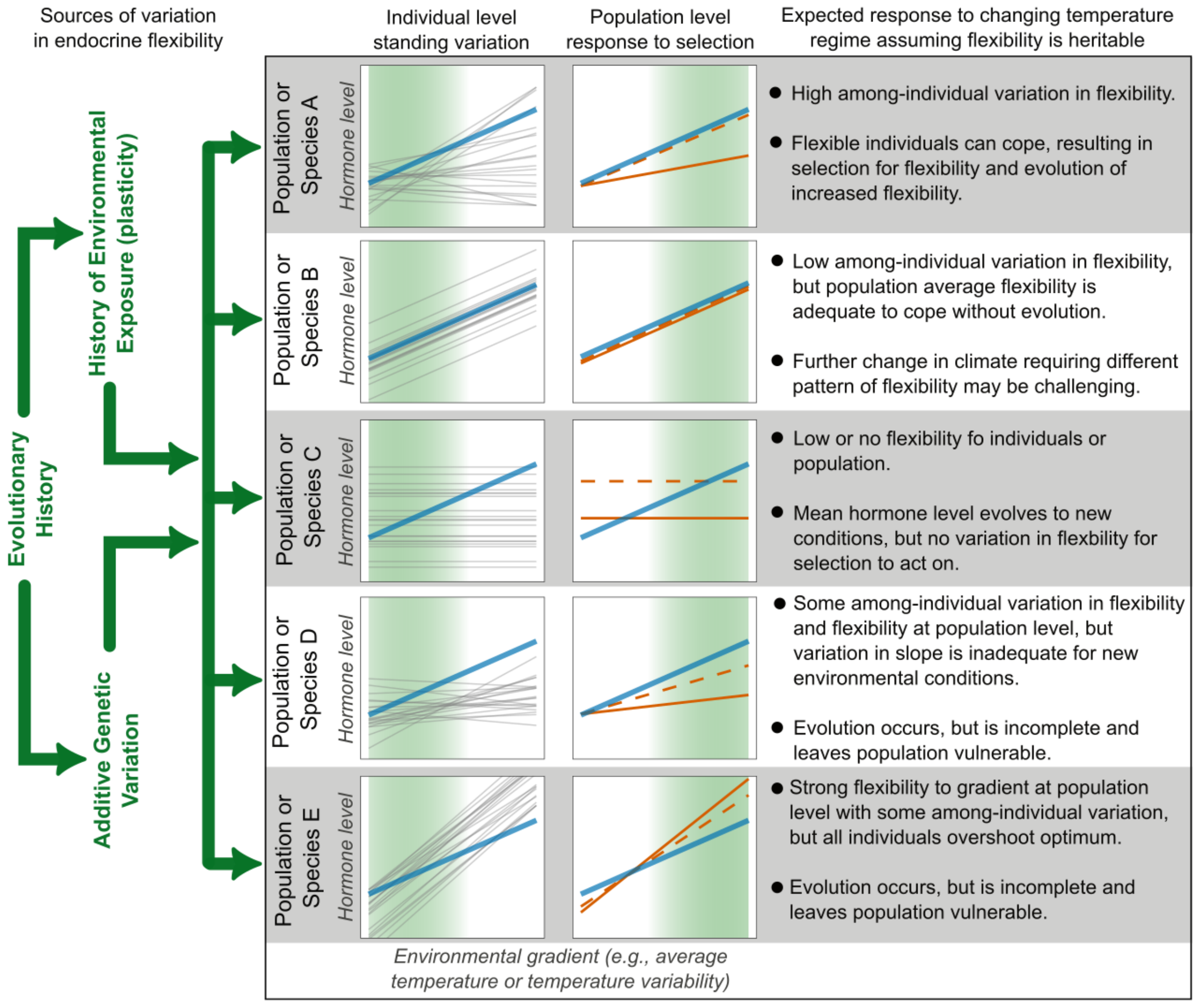
Individuals and populations might also differ in endocrine flexibility as a result of differences in additive genetic variation. In some cases, this variation may be critical for endocrine flexibility to effectively buffer populations against climate change because it would make it possible for flexibility to evolve in response to climate induced selection. To our knowledge, only one study has measured heritability of endocrine flexibility to an environmental gradient, which demonstrated moderate heritability [63]. Several recent studies do demonstrate heritability under natural conditions of various aspects of hormone regulation, including the acute stress-induced increase in glucocorticoids, which can be considered a type of rapid endocrine flexibility [64–66]. It is likely that observed variation in endocrine flexibility arises from a combination of developmental environment and additive genetic variation, both of which may be influenced by a species' evolutionary history

(Figure 1, sources of variation in endocrine flexibility). Disentangling these sources of variation in the context of climate change is particularly challenging, because changing temperature regimes can simultaneously result in altered selection pressures leading to evolution and in systematic differences in developmental environments that trigger plasticity [9]. This important distinction has recently been explored for climate-induced changes in phenology [6,67] and body size [3,9,10], but has not been systematically explored in endocrine flexibility. Better understanding and characterizing variation in endocrine flexibility is a first step in determining when it acts as a facilitator or constraint on coping with climate for both individuals and species.

Endocrine flexibility as a facilitator of coping with changing temperatures.

In general, flexibility is expected to be beneficial if relevant cues are reliable in predicting future environmental conditions and the time lag of response is fast enough to reduce the time spent being phenotypically mismatched with the environment [68]. Animals can assess current environmental temperature directly with little cost [although current temperatures may not predict future temperature and future temperature may become even less predictable as environments become more variable due to climate change, 24,25]. Hormone concentrations can also change rapidly in response to these conditions. For example, circulating glucocorticoid concentrations change within a few minutes of perception of a stimulus [69,70], including changes in temperature [reviewed in 39].

For flexibility to be favored, fitness benefits must outweigh any costs. At present, the costs of endocrine flexibility, including those of different degrees of flexibility, are still poorly understood. Steroid hormones like glucocorticoids are considered to be cheap to produce [71,72], but the phenotypic effects of endocrine flexibility may be energetically expensive in some cases, since many changes in behavior (e.g., moving to a more favorable microclimate) and physiological traits (e.g., increased heat production or dissipation) necessitate at least transient increases in metabolic rate [see 18,30]. However, these responses could be crucial in buffering deleterious effects of thermal challenges, thus improving fitness outcomes. Even behaviors that may not directly increase energetic costs, such as moving to the shade, may have opportunity costs because they trade-off with other behaviors, such as providing parental care [73]. Hence, the cost to benefit ratio of endocrine flexibility with regard to fitness will be important to determine experimentally.



- High among-individual variation in flexibility.
- Flexible individuals can cope, resulting in selection for flexibility and evolution of increased flexibility.

- Low among-individual variation in flexibility, but population average flexibility is adequate to cope without evolution.
- Further change in climate requiring different pattern of flexibility may be challenging.

- Low or no flexibility fo individuals or population.
- Mean hormone level evolves to new conditions, but no variation in flexbility for selection to act on.

- Some among-individual variation in flexibility and flexibility at population level, but variation in slope is inadequate for new environmental conditions.
- Evolution occurs, but is incomplete and leaves population vulnerable.

- Strong flexibility to gradient at population level with some among-individual variation, but all individuals overshoot optimum.
- Evolution occurs, but is incomplete and leaves population vulnerable.

Figure 1. Illustration of possible patterns of endocrine flexibility. The first column describes sources of variation in endocrine flexibility. Observed patterns of variation in flexibility result from a combination of additive genetic effects and the proximate history of environmental exposure, both of which are ultimately shaped by a species evolutionary history. Five hypothetical scenarios (A-E) are described with different patterns of flexibility at the among-individual and population level. For the purposes of this illustration, populations can be considered different populations of one species or different species. For each population, the first plot illustrates among-individual variation in endocrine flexibility. Faded gray lines are individual reaction norms, the thick blue line is the optimal reaction norm (i.e., optimal flexibility), and the shaded green region indicates the typical range of environmental conditions experienced by the population (e.g., average temperature or amount of temperature variability). The second plot for each population displays average population level flexibility before and after selection imposed by a new set of environmental conditions. The optimal response across all conditions (blue line) is unchanged, but the shaded green box indicates an altered distribution of environmental conditions resulting from climate change. The solid orange line is the population average flexibility before selection (i.e., the average of individuals from the first plot), and the dashed orange line is the expected population response to selection assuming that flexibility is heritable. The last column summarizes the variation at each level and the expected response of flexibility to altered selection from changing temperatures. We note that this is not an exhaustive set of patterns of variation.

There is ample evidence both that thermal flexibility occurs in hormones and that hormones in turn support physiological, behavioral, and morphological traits that likely promote thermoregulation, evading unfavorable conditions, or temperature related changes in behaviors that influence fitness. For example, glucocorticoids mediate changes in behavior, such as foraging, locomotion, and parental care in individuals [38]; although studies showing covariation of flexibility for glucocorticoids and flexibility in behavior at the individual level are rare [but see 74]. Behavioral thermoregulation involves moving to the shade, forgoing foraging [73], reducing chick provisioning in high heat [75,76] or moving to different places [77], among others. Thus, individuals or populations exhibiting greater endocrine flexibility may cope better with climate change because their flexibility produces stronger, and perhaps better attuned behavioral responses, allowing these individuals to increase their fitness relative to less flexible conspecifics [Figure 1, population A, 14,32,78] and allowing these populations or species to persist better than less flexible ones (Figure 1, population A or B). In this way, endocrine flexibility may effectively buffer populations from adverse effects of climate change for some time, until evolution can take place [67,79,80].

The pleiotropic effects of hormones may also help individuals – and thus populations – cope with climate change, because they simultaneously mediate flexibility in several traits [e.g., endocrine ‘phenotypic integration’; reviewed by e.g., 18,81–85]. Such hormonal linkages can either result in positive or in negative covariation (e.g., trade-offs). If the (genetic) linkage between traits matches prevailing selection pressures, it could accelerate the rate of evolution [86]. For example, this might occur if hormonal flexibility induced appropriate coordinated changes in an individual’s behavioral response to temperature changes and physiology. We note, however, that non-adaptive or environmentally-induced linkages can also exist [82]. Studies on hormonal pleiotropy have been primarily conducted at the population level [87,88] and we do not know whether an individual with strong endocrine flexibility in response to environmental temperature also shows strong flexibility in other traits [discussed in 18]. In general, if an environment is fairly predictable or constant, phenotypic integration can be adaptive because past selection pressures have promoted favorable simultaneous flexibility in different traits [82].

Endocrine flexibility as a constraint on coping with changing temperatures.

In contrast to the patterns described above, endocrine flexibility – or the lack thereof – might sometimes act as a constraint that prevents individuals or species from successfully coping with climate change. For example, in highly variable and unpredictable environments (which will become more common with climate change), phenotypic integration can limit the ability of individuals to cope and for populations to rapidly evolve due to trait covariation [82–84]. We note, however, that even strong trait covariation might be overcome by strong and consistent selection over time [84,89].

Alternatively, individuals or populations may simply have no or little variation in hormonal flexibility, perhaps because of past selection pressures when inhabiting more thermally stable environments (Figure 1, population C). Thus, even if individuals differed from one another in average hormone concentrations (i.e., standing variation in the elevation of the reaction norm), the population would not exhibit sufficient standing variation in flexibility for an evolutionary response. This is a cornerstone of the ‘mountain passes are higher in the tropics’ hypothesis [90], which suggested that the thermally stable conditions in lowland tropical habitats selected for low physiological plasticity [which is supported for ectotherms 91,92 but less so for endotherms, especially birds ,93]. We also note that even if endocrine flexibility was large, and standing variation in the population was generally high, endocrine flexibility could hinder or delay evolutionary changes by hiding (genetic) among-individual variation from the actions of selection until conditions are so extreme that maladaptive changes occur [i.e., the Bogert effect, 94, although stress-induced plasticity can also increase phenotypic variation, thereby speeding up evolution, 95,96]. Furthermore, if only a few individuals in a population are capable of modulating their hormonal profiles within the optimal range, this might result in a population unable to respond quickly enough to sudden temperature increases.

Even if endocrine flexibility itself helps individuals cope with changing temperatures or delays fitness loss (see above), the lack of sufficient phenotypic and genetic standing variation in endocrine flexibility may limit the ability of individuals to respond appropriately and the ability of populations to persist. For instance, individual variation in hormonal flexibility may exist, but the range of individual variation may not be sufficient to achieve an optimal response to changed environmental conditions (Figure 1, population D). Similarly, flexibility in response to novel environmental conditions that have rarely been experienced in a species’ evolutionary history might result in overcompensation past a new optimal response, resulting in negative consequences for both individuals and populations (Figure 1, population E). For example, in response to extreme environmental temperatures, some individuals may increase glucocorticoid concentrations into the stress-induced range, prioritizing their own survival at the cost of reproductive attempts and, consequently, their reproductive fitness [discussed by 32].

Finally, individuals may exhibit flexible responses to changing temperatures without differing from each other in their flexibility [Figure 1, population B, 54,97,98]. This lack of among-individual variation in flexibility might not represent an issue so long as the population response matches the optimal response required to overcome changes in temperature. However, if this was not the case or if the changing climate required a type of flexibility beyond that expressed by individuals there may be too little variation for selection to act and for evolution to occur. At the population level, opposing selection pressures at different times of year or fluctuating selection across time or space [e.g., for populations in different habitats, 12,99] might limit or even decrease the benefits of hormonal flexibility. For example, in populations with long-distance dispersal or migration, if selection in one habitat type disfavors endocrine flexibility, or the cues that induce flexibility are not available, individuals and populations might be limited in their ability to cope with variable temperatures in the other habitat [100].

Endocrine flexibility as an unimportant trait in coping with changing temperatures.

A final possibility is that endocrine flexibility, when present, may play little role in either facilitating or constraining the ability to cope with temperature change. In cases where flexibility is linked with other hormonal traits that are more important in a given environment (e.g., average hormone concentrations, the strength of negative feedback) then apparent relationships between flexibility and coping ability might be spurious. Reaction norm linkages for hormonal traits measured in different environmental conditions (e.g., baseline corticosterone at different temperatures) have only been tested in a handful of studies [reviewed by 18,51], but studies done both in the lab [54] and the wild [26] support such covariation for glucocorticoids. For example, wild great tits with either high or low average corticosterone concentrations changed glucocorticoid concentrations more with temperature compared to individuals with average corticosterone [26]. This is important since it implies that even if flexibility *per se* was not beneficial, temperature change induced selection on average hormone concentrations would also favor endocrine flexibility.

Hormones integrate and respond to external and internal stimuli. Hence, endocrine flexibility is likely to occur across different environmental gradients. We are not aware of field studies that have tested whether individuals show similar endocrine flexibility to different environmental gradients, but this pattern has been shown in captivity [53]. Yet, individuals from different populations show flexibility in glucocorticoid concentrations along gradients of food availability [55], conspecific density [101], and environmental temperature [26]. When endocrine flexibility is present in the same individual across different environmental gradients, it might be that selection did not shape this flexibility to facilitate coping with changing temperatures, but instead promoted individual hormonal responses to another ecological factor. In the context of climate change, a wide variety of factors, such as the reliability of photoperiodic cues, availability of food resources, and community composition are likely to change as a direct or indirect consequence of temperature changes. Thus, apparent selection on endocrine flexibility may be attributable to these indirect effects rather than to the ability to cope with temperature changes.

Urban heat islands: a case study where endocrine flexibility may be critical and tractable

Generating convincing empirical evidence for the importance of endocrine flexibility as either a facilitator or constraint on coping with climate at both the individual and population level will be a major challenge. A complete case study should be able to demonstrate consistent among-individual or population differences in endocrine flexibility [e.g., 26], disentangle sources of variation in flexibility, connect among-individual variation to fitness, link environmental change to population or species level differences in selection, and use this information to make predictions about species level differences in vulnerability to predicted changes in environmental exposure under climate change scenarios (Figure 1). Each of these questions can be addressed in a wide variety of contexts, but one particular case that might offer both a promising system for taking an integrative approach and the possibility for tractable study and replication involves studying endocrine flexibility along urban gradients.

Urban expansion is a global phenomenon happening at relevant timescales to many populations and species with naturally-replicated sites. After twenty years of urban ecology and evolutionary endocrinology studies, we now have a robust literature looking for signatures of urban tolerance [102]. As there is no generalizable trend in endocrine response to urbanization [103,104], endocrine flexibility may be a more promising predictor to explore in the context of responses to urbanization. Individuals, populations, and species vary in their ability to thrive in cities and endocrine traits likely facilitate this ability. The focus of urban endocrinology in the past has been on means [i.e., do mean concentrations of a hormone differ across an urban gradient, 104]. Very few studies have focused on variation in endocrine flexibility as a predictor of individual or species responses to urban challenges [105,106].

A typical way of categorizing "urbanness" of cities in urban ecology uses aerial or satellite imagery to quantify the amount of green space in an area. However, cities occupy three dimensional space, and this factor is often overlooked but can be critical, as it can be a close proxy for human density or how "steeply" a city is built [107]. Importantly, building height is associated with higher temperatures and contributes significantly to urban heat island effects [108]. For endocrinologists interested in a reaction norm approach, this characteristic of cities is ideal for investigating flexibility at the population level. We can imagine different cities with different "steepness" (Figure 2) and corresponding differences in abiotic conditions, such as temperature. We acknowledge that urbanization also impacts other variables, such as predator prevalence and human disturbance, which may or may not correlate with ambient temperature. To fully understand endocrine response to urbanization, various reaction norms may be needed for multiple environmental variables (e.g., temperature, predation risk, pollutant exposure, etc). In this perspective we focus on the urban heat island effect, a phenomenon in which cities, especially city centers, are several degrees hotter than surrounding habitats [109]. This heat island effect will be much stronger for city A than for city B (Figure 2), creating a steeper gradient of ambient air temperatures for its inhabitants. We note that we have two cities illustrated for simplistic purposes, but in order to distinguish the effects of city and temperature, multiple cities and temperature profiles will be required as other factors within a city could also cause changes in hormone profiles. Hence, replication with other cities or translocation experiments between cities are needed, but are often lacking in the field of urban ecology.

Correspondingly, one can predict that due to this difference in steepness of environmental temperature differences, endocrine reaction norms (or selection on reaction norm components) might also differ for animals that inhabit this space. For example, assuming similar space use, in a city with a steeper temperature gradient or more variable temperature regimes, individuals may need to flexibly adjust their endocrine profiles to match increasing environmental variation (Figure 2A; see sections above on facilitation and constraints). It is also possible that individuals are more mobile across urban environments to avoid being exposed to high temperatures at certain times of the day. If this is the case, and moving to a different part of the city is metabolically demanding, then increased endocrine flexibility could help to support this behavior. Conversely, for cities that are more homogeneous in human densities or steepness, ambient temperatures are more constant across the city, and we predict less endocrine flexibility (Figure 2B). We note, however, that in homogeneous cities the temperature range throughout the day might pose thermal challenges for individuals that also require hormone flexibility. These predictions could be tested at different spatial and temporal scales depending on the organism of study. For example, it is likely that the steepness of both the temperature gradient and the hormone response are affected by a species' average home range size (i.e., species in which individuals have larger average home ranges may experience more variation in temperatures) and the space use of individuals within each species. Furthermore, these predictions could be tested longitudinally as cities expand and comparatively for different species inhabiting the same cities. For example, researchers could investigate whether pioneering phenotypes are better able to inhabit a newly established city versus an aged city [110,111].

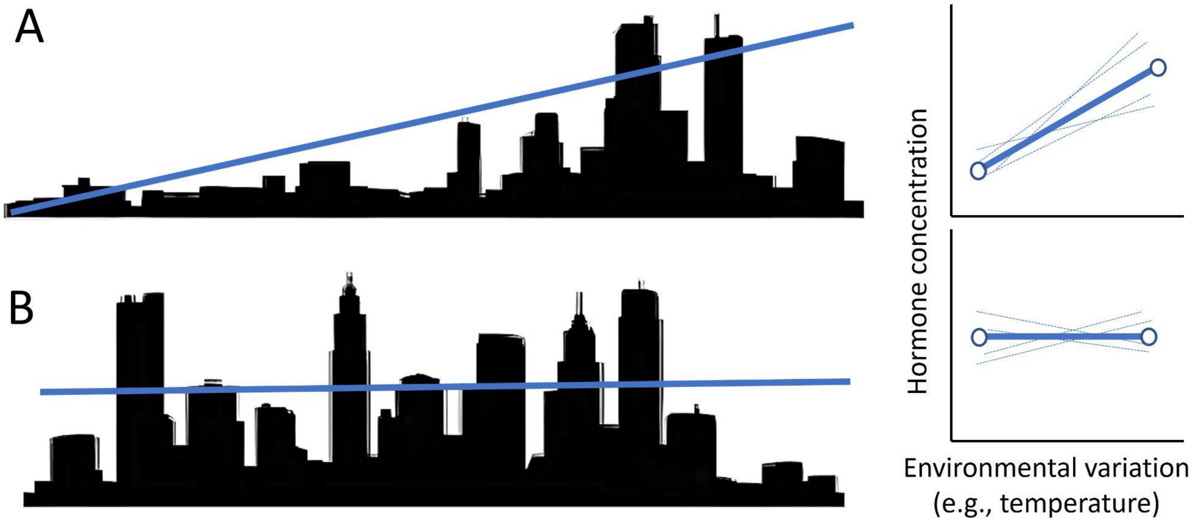


Figure 2. Hypothetical cities (A and B) and corresponding predicted reaction norms (thick solid line: population level, thin lines: individual level). The steepness of the city may impact optimal phenotypic responses. Individuals that live in cities with a steeper slope may exhibit steeper reaction norms than individuals that live in cities characterized by continuous urban sprawl, which may exhibit flattened reaction norms. Individuals are assumed to have home ranges that span the illustrated scale. We assume that temperature variations and means co-vary in A and B but they may not covary in some cities.

Future directions and open questions

We are poised at an exciting time when research in eco-evolutionary dynamics has begun to make great strides in illuminating the role of endocrine flexibility in the response to climate change. Predicting how animals will respond to global change is an issue at the forefront of biological sciences. However, there are research gaps that will necessitate novel data sets at different temporal and organizational scales to provide substantive answers. Currently, while we have a few examples of individual and species differences in endocrine reaction norms [26,56], we know very little about whether these differences can be attributed to flexibility or evolution, or about the degree to which the same selection pressures result in the evolution of similar patterns of endocrine flexibility [i.e., parallelism, 112]. We also do not yet have convincing evidence that variation in endocrine flexibility is causally linked to fitness measures, such as lifetime reproductive success or survival [18]. Hence, estimating reaction norms for both endocrine and fitness-related traits in free-living individuals, combined with experimental studies where ecological conditions are modified or animals are translocated to address causality, will be essential in future studies [80]. As with research at the individual level, recent work has only begun to explore patterns of macro-evolutionary variation in endocrine evolution [17] or endocrine flexibility [56] and there has been little effort yet to explicitly link questions targeted at the individual, population, and species level, but relationships and processes at these levels might differ drastically or interact with each other [Figure 1, 113].

In a series of influential papers published over a hundred years ago, Baldwin proposed that non-heritable plasticity resulting from novel environmental inputs, which makes an organism more fit in its current environment, can eventually facilitate evolution and the genetic accommodation or assimilation of the novel phenotype [28,114]. While there is no definitive demonstration of this effect for endocrine flexibility, we know that global climate change is producing novel temperature regimes for many species and that endocrine systems have evolved as a mechanism to allow animals to adjust their phenotype to the environment [17,115]. Because the Baldwin effect can connect initial phenotypic retention of adaptive changes and eventual genetic determination, it may be critical for adaptation to climate change [27]. Analyses that combine longitudinal data on environmental change with data on developmental plasticity and the genetic basis of endocrine responses could provide important insights into whether the Baldwin effect is shaping variation in endocrine flexibility.

Because of the labor intensive nature of field and laboratory work required to study endocrine flexibility, the questions that we raise here are not amenable to the kinds of ‘big data’ approaches that have been so useful for understanding other aspects of animal responses to climate change [6,10,116]. Field-based observation and capture will remain a central focus of endocrine flexibility and recent studies have demonstrated that these approaches can be successful despite the data hungry nature of reaction norm models [26]; in the future, it may be possible to repeatedly measure plasma hormone levels with bio-loggers, which would be a breakthrough for studies of endocrine flexibility. At present, excellent models for study design and necessary sample sizes can be borrowed from the behavioral reaction norm literature [52,117] and several recent papers detail particular considerations for physiological traits like hormones [18,19,51].

Given these challenges, progress will require a combination of traditional field based approaches, consideration of different experimental design and sampling schemes [19], and collaboration between empiricists and theoreticians to generate novel hypotheses, confirm empirical findings, and guide empirical work towards collecting critical missing data. For example, experimental treatments that combine samples from multiple individuals can describe group level differences in hormonal reaction norms that circumvent the limitations of repeated sampling within individuals [30,118]. Similarly, comparative studies of populations or species can provide evidence for factors shaping endocrine flexibility [56] as they have for other trait responses to changing temperature [10]. The hierarchical framework that we develop demonstrates how these different lines of evidence can be combined to produce a more nuanced understanding of the importance of endocrine flexibility. In addition to more diverse empirical approaches, a recent increase in modeling interest in endocrine flexibility also demonstrates the promise of this approach [119–121]. For example, optimality models show that the evolution and magnitude of the stress response depends on the temporal autocorrelation (predictability over time) of a punctuated stressor [e.g., a predator that occasionally comes into contact with an organism and increases its mortality, 120]. Other models have explored the predictability of environmental cues, speed of plastic responses, and environmental variability [33,119,122].

Despite the logistical difficulties of studying endocrine flexibility, it may play a fundamental role in facilitating – or constraining – the ability to respond to rapidly changing climates. While we focus primarily on temperature, global climate change is also altering a variety of biotic and abiotic gradients [123] and endocrine flexibility likely plays a role in responding to each of these. The field stands at an exciting crossroads, and there are many opportunities to establish connections between endocrine flexibility and the approaches and techniques employed in recent studies of behavioral, phenological, or morphological responses to climate change [6,10,12,100,124]. Whether similar eco-geographic patterns exist for endocrine flexibility, and whether those patterns are changing predictably with climate change is an open question. The statistical, empirical, theoretical, and conceptual tools and frameworks are available to determine if endocrine flexibility is a central organizer and shared mechanism contributing to observed morphological and behavioral patterns. Similar approaches in the field of thermal physiology have demonstrated that physiological performance traits, such as temperature tolerance, often act as both a motor – facilitating evolution and adaptation – and a brake – constraining and limiting adaptive evolution [91,125–129]. We suggest a similar role for endocrine flexibility as an organizing mechanism that can either facilitate or constrain the response to climate change in different situations or for different species.

Data accessibility

This article has no additional data.

Competing interests

The authors declare no competing interests.

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Author contribution

All authors contributed to the conceptualization of the paper and wrote the original drafts of some sections. CCT edited and combined sections into the original complete draft. All authors contributed to reviewing and editing the final submission.

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