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# HPA flexibility and *FKBP5*: promising physiological targets for conservation

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Hypothalamic–pituitary–adrenal axis (HPA) flexibility is an emerging concept recognizing that individuals that will cope best with stressors will probably be those using their hormones in the most adaptive way. The HPA flexibility concept considers glucocorticoids as molecules that convey information about the environment from the brain to the body so that the organismal phenotype comes to complement prevailing conditions. In this context, FKBP5 protein appears to set the extent to which circulating glucocorticoid concentrations can vary within and across stressors. Thus, *FKBP5* expression, and the HPA flexibility it causes, seem to represent an individual's ability to regulate its hormones to orchestrate organismal responses to stressors. As *FKBP5* expression can also be easily measured in blood, it could be a worthy target of conservation-oriented research attention. We first review the known and likely roles of HPA flexibility and FKBP5 in wildlife. We then describe putative genetic, environmental and epigenetic causes of variation in HPA flexibility and *FKBP5* expression among and within individuals. Finally, we hypothesize how HPA flexibility and *FKBP5* expression should affect organismal fitness and hence population viability in response to human-induced rapid environmental changes, particularly urbanization.

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

## 1. What is HPA flexibility?

Organisms must cope with variety of unpredictable challenges in both natural and human-modified environments. Critical to responding to these challenges appropriately is the ability of an individual to adjust its phenotype to current or impending conditions [1,2]. In vertebrates, one hormonal system is exceptionally important to such adjustments, the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis enables organisms to respond to many factors but especially stressors (i.e. unpredictable or uncontrollable stimuli in the external and internal environments that threaten homeostasis), primarily via glucocorticoids (GCs) [3,4]. Circulating GCs mediate homeostasis and stress responses via a two-tiered receptor system [3,5]. Moderate daily and seasonally rhythmic variations in concentrations (i.e. baseline variation) are associated with changes in energy metabolism and behavioural activity and regulated largely by mineralocorticoid receptors (MRs). By contrast, rapid (i.e. within minutes) and larger increases in concentrations (i.e. stress responses), usually coincident with exposure to stressors, are regulated by glucocorticoid receptors (GRs) [3–5]. Surges like these are quickly (within minutes to hours) followed by decreases to pre-stressor concentrations (i.e. via negative feedback of the hormones on central GRs), an equally critical change, as sustained elevations of GCs can diminish health and fitness.

Whereas much attention has been devoted to understanding variation in GC concentrations in wildlife, no existing framework has yet proposed how

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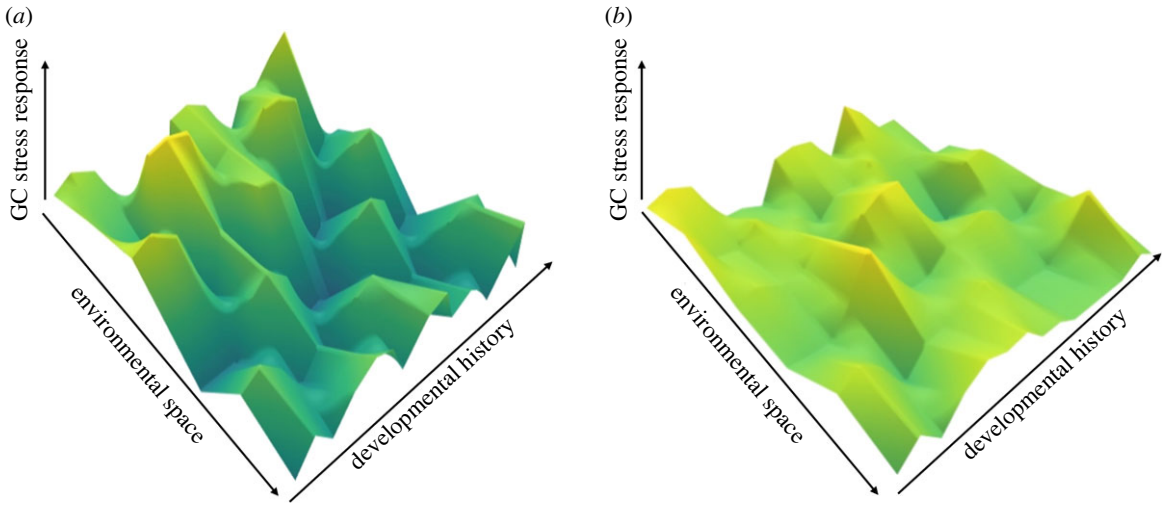


**Figure 1.** Examples of individuals with high (*a*) and low (*b*) HPA flexibility. The rugosity of the landscape depicts HPA flexibility, the variety of endocrine responses available to an organism over its life as a function of the prevailing environmental conditions, physiological state, and inherited factors (genotype and epigenetic effects). High HPA flexibility individuals should be better able to match their phenotypes to many more situations. By contrast, low HPA flexibility individuals should be less able to express an appropriate phenotype, at least in most contexts.

we might measure the trait central to the functional roles of glucocorticoids in the context of responses to stressors: the *ability of an individual to maintain and recover homeostasis*, what we and others have called endocrine or HPA flexibility. We know a lot about how glucocorticoids vary, but how this physiological variation *causes* variation in individual fitness is still obscure. Two ideas (i.e. allostasis and reactive scope) have generated a lot of research attention, but neither has yet resolved the roles of GCs in health nor conservation-related issues. Previously, we argued that these shortcomings derive from a lack of consideration of how GCs instantiate and convey *information* about stressors from the brain to the rest of the body [6,7]. Instead of trying to measure energy gains and losses and relating those changes to hormones (i.e. allostasis) or studying variation in mediator concentrations relative to presumably adaptive baselines, we could instead study hormones as difference-makers (i.e. the propensity of GCs to induce phenotypic change).

It is beyond the scope of this paper to detail the value of an information-based perspective for glucocorticoid regulation in the context of stress. However, our advocacy for HPA flexibility here is derived from this information-based mindset and is based on a few central tenets. First, our framework emphasizes that every organism will experience and need to resolve many kinds of stressors across its lifetime. Subsequently, one or a few concentration measures will be unlikely to capture the complex manner by which hormonal variation affects individual fitness. Sometimes one or a few plasma GC concentration measures predict variation in fitness, but examples are rare [8]. What we probably need to measure is the *ability* of an individual animal to regulate its hormones, in other words, HPA flexibility. Second, stressors vary in magnitude and type [6], so the relative fitness costs and benefits of GCs in stress responses will depend on the life-history stage, physiological state, and prior experience of an individual. The fittest individuals should be those that can most appropriately use their hormones to adjust the phenotype when the need arises, not those with high or low concentrations at various points in time. Third, circulating hormones are but one facet of how the phenotype is altered endocrinologically [1,9]. Salient information about stressors cannot just reside in hormone concentrations; substantial information must also reside in receptors, metabolic enzymes, and other factors that determine the outcomes of glucocorticoid responses to stressors [10]. In this light, then, the body and brain should change together over the lifetime [7]; tissues should learn from experience (i.e. GC exposure) in such a way that historical information about the adversity of the environment is encoded into HPA axis regulatory components [6]. GCs are thus best understood as info-chemicals [11], factors that help individuals construct their phenotypes and conform to the environment as best they can. How individuals *regulate* GCs across stressors, then, represents their different propensities to instantiate information in their genomes and their cells [12]. It is this propensity that we call HPA flexibility.

For years, related ideas have been percolating in eco-evolutionary endocrinology [2,6,7,13–15] (and other papers in this theme issue). Most researchers, like us, have defined HPA flexibility as the *capacity of an individual to modify its HPA axis in response to stressors across multiple contexts* or something similar. Labs have measured HPA flexibility differently, but the consensus is that because GCs can only have phenotypic effects *after* they bind receptors and/or those hormone–receptor complexes bind genome-response elements [3,6], a few concentration measurements will be insufficient to describe HPA flexibility [9]. In figure 1, we depict two extremes of HPA flexibility that one might find in a natural population of vertebrates. Each landscape in each panel depicts HPA flexibility for an individual, the variety of GC responses to stressors possible for that individual over the course of its life. We expect that the rugosity of each landscape is set by its genetic and epigenetic makeup in the context of environmental conditions at any point in time (see below). One organism (figure 1*a*) has high HPA flexibility, a GC regulatory capacity suitable to many types of stress responses, whereas another organism (figure 1*b*) does not. Functionally, high HPA flexibility individuals should be able to achieve the most appropriate phenotype for the greatest diversity of environmental conditions; in having the most rugged GC landscapes (figure 1*a*), they should be able to recruit more adaptive endocrine response given the type and magnitude of the stressor in the context

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of the current environment but also previous experience. Low HPA flexibility individuals, by contrast, should be able to realize fewer HPA phenotypes, limiting their ability to match their organismal phenotype to the environment (figure 1*b*). Such inflexibility could be wholly genetic, but it could also be environmentally induced, driven by stressors experienced during development. Nevertheless, as for GCs, fitness benefits of HPA flexibility are likely to be context-dependent. High HPA flexibility may not be advantageous in all environmental contexts because of the costs associated with high level of flexibility (e.g. information costs, search times for the optimal response in a complex landscape). Indeed, as GCs are pleiotropic hormones affecting multiple aspects of individuals' physiology and behaviour, in some environmental contexts it may better to be less flexible to avoid inappropriate responses. Thus, high HPA flexibility could be disadvantageous when living in a benign environment.

Below (§§4c,d), we discuss the promise of an HPA flexibility-based framework for understanding how individuals and hence populations of wild vertebrates will cope with human-induced rapid environmental change (HIREC) [16]. We first summarize how one could effectively measure endocrine flexibility (EF) in any vertebrate species. We then discuss the role of *FKBP5*, the gene encoding FK506 binding protein 51, as a promising and much more simply measured proxy for HPA flexibility [17]. We close by proposing hypotheses and a research plan to capitalize on HPA flexibility and especially *FKBP5* to mitigate effects of anthropogenic change. We predict that high HPA flexibility taxa are more apt to exploit and adjust to human-modified conditions, especially cities.

## 2. Measuring HPA flexibility

There is as yet no consensus approach to measure HPA flexibility [2,18], but the most popular methods involve descriptions of hormonal reaction norms. Typically, GC reaction norms are measured as the slopes of the relationships between hormone concentrations and environmental context for an individual animal [19–21]. While this approach has been insightful [22], we are sceptical of its suitability to describe HPA flexibility. GC concentrations measured prior to (i.e. baseline), during (i.e. post-stressor), and after (i.e. negative feedback) exposure to stressors will probably have co-evolved in such a way that they should be studied as a unit, a single physiological response. The current practice of estimating reaction norms for baseline, post-stressor, and post negative feedback concentrations, separately, unjustifiably analyses these measurements independently [7]. Individuals would be unlikely to have evolved to release excessive GCs into circulation if they lacked the ability to engage a robust negative feedback response [23–25]. HPA flexibility described as concentration reaction norms therefore does focus on the trait on which natural selection has acted, the *ability to regulate* the hormone [26]. As above, HPA flexibility is most sensibly understood as a landscape of GC responses available to an individual at any given time, a kind of endocrine hypervolume (i.e. the rugosity of the landscape in figure 1). Reaction norms for concentrations across temperature, social context or some other environmental gradient might resemble HPA flexibility as in figure 1, but this assumption must be substantiated empirically.

We recently proposed a fairly simple method to describe HPA flexibility, the square root of the mean squared differences (RMSSD) of sequential glucocorticoid stress responses measured in one animal [27]. Our rationale was that the more distinct sequential stress responses (and resolutions thereof) were in an individual across contexts, the higher HPA flexibility that individual must have. To test this idea, we first quantified RMSSD, developed initially to describe heart rate flexibility, using the mean glucocorticoid concentration across four stress responses of house sparrows (*Passer domesticus*); each stress response was described according to convention (i.e. baseline, post-stressor and after negative feedback activation concentrations for each individual) in stress responses measured a week apart [17]. We found that birds varied quite extensively in HPA flexibility; some had very high values (RMSSD = 24) whereas others were comparatively inflexible (RMSSD = 4). More importantly with respect to the presumed adaptiveness of HPA flexibility, birds with high RMSSD values were also more *behaviourally* flexible than birds with low RMSSD values [17]. More sophisticated and perhaps more accurate forms of descriptors of stress responses could have been used (e.g. area under the concentration curve, AUC) as well as more powerful statistical efforts (i.e. double-hierarchical general linear models, DHGLMs) [28], but for our purposes, the simplistic approach was effective. Individuals varied quite a bit in HPA flexibility, and HPA flexibility was related in the expected direction to a presumably adaptive behaviour.

## 3. *FKBP5*: a simple-to-describe proxy of HPA flexibility

Accurately quantifying HPA flexibility as RMSSD will always require several, repeated hormone measurements in the same individuals in different contexts. For many wild species, especially from threatened populations, those of small body size, or those particularly difficult to maintain in captivity, such data will be hard to collect. Consequently, we advocate that, instead, *FKBP5*, a co-chaperone in the GR complex regulating GR function and activity [1], be the focus of study. Extensive biomedical research shows that central *FKBP5* expression in the few vertebrates studied so far increases within about 1 h in response to elevated GC concentrations. These elevated local levels then create an intracellular, ultrashort negative feedback loop, regulating GR affinity for GCs [29,30]. At organismal level then, the more *FKBP5* that an individual expresses, the more its GR resistance is increased, lowering negative feedback efficacy of GCs on brain regions, and hence compromising adaptive GC regulation [29,31]. In the context of figure 1, then, *FKBP5* probably sets the rugosity of the landscape, giving some individuals but not others a propensity to manifest diverse endocrine responses contingent on historical and current context.

To date, almost all data supporting this possibility have come from humans and laboratory rodents [29,31,32]. Nevertheless, there is no obvious reason that these relationships would not apply to most vertebrate wildlife. In domesticated mice, low *FKBP5* expression underlies an attenuated stress response and increased negative feedback efficacy associated with enhanced stress-coping behaviour (i.e. exploration) [33,34]. In the above study of house sparrows, HPA flexibility (measured as RMSSD) was inversely correlated to *FKBP5*

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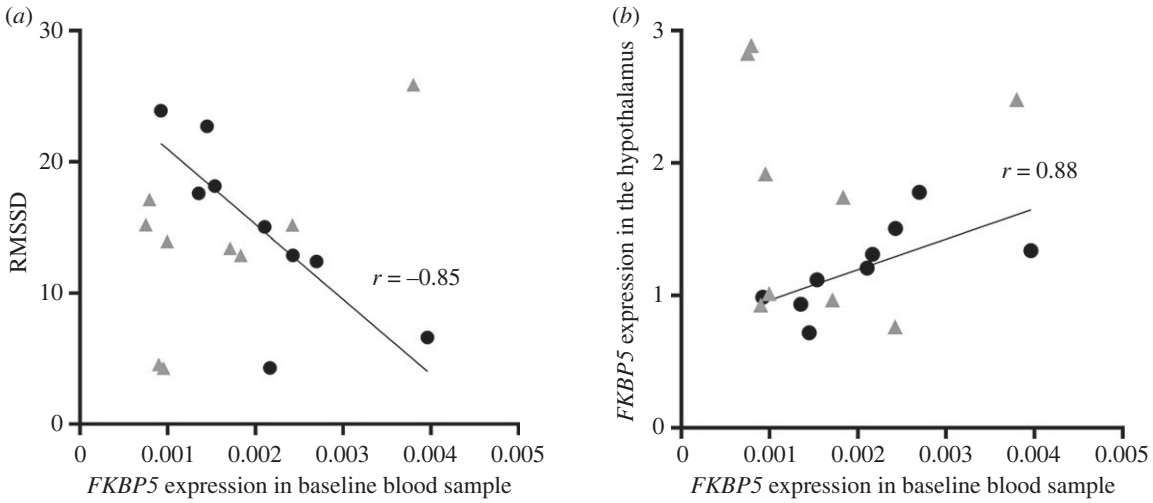


**Figure 2.** *FKBP5* expression as a biomarker of HPA flexibility in house sparrows (*Passer domesticus*). (*a*) Relationships between the square root of the mean squared differences of successive stress series (RMSSD) and *FKBP5* relative expression in baseline blood samples at capture in adult (black circle) and juvenile birds (grey triangle). (*b*) Relationship between *FKBP5* expression in the hypothalamus and the baseline blood samples at capture in adults (black circles) and juveniles (grey triangles). Regression lines were only calculated for adults. Reprinted with permission from [17].

expression in the hypothalamus [17]. In the same birds, low *FKBP5* expression in the hippocampus was also associated with higher level of exploration in a novel environment. Perhaps most promising to the utility of *FKBP5* in wildlife research, *FKBP5* expression in baseline blood samples from house sparrows was correlated with hypothalamic expression (figure 2). As this relationship also seems to exist in laboratory mice [31], scientists interested in studying HPA flexibility in threatened, small, or hard to keep captive wildlife might need only measure *FKBP5* in blood samples once. If such blood–brain relationships are confirmed in other species, they could become a very valuable marker of stress resilience in wildlife. It is possible that the level of *FKBP5* expression will not directly relate between blood and brain, but even in these cases, plasticity in *FKBP5* expression in response to external and internal factors might [9]. Indeed, in laboratory mice and house sparrows, *FKBP5* expression increased similarly in brain and peripheral tissues in response to experimental stressors and GC treatments [27,31,35,36]. As establishing this blood–brain correlation will not be possible in a threatened species, a closely related species of no or little conservation concern could be used as a proxy.

## 4. Causes of variation in endocrine flexibility and *FKBP5*

Differences in HPA flexibility may manifest through a variety of mechanisms besides *FKBP5*, including hormone levels, receptor abundance and affinity [37], or carrier proteins [38,39]. We expect *FKBP5* to be central to HPA flexibility, but much research lies ahead. If *FKBP5* largely determines HPA flexibility, it should be a major focus of natural selection [40]. It should therefore tend to be repeatable and heritable, and indeed, in house sparrows, *FKBP5* expression was repeatable ($R = 0.45 \pm 0.18$ [0.04–0.71], $p = 0.003$) in measurements in blood made weeks apart [17].

### (a) Among-individuals variation

Studies of *FKBP5* expression in wild animal populations are presently rare, but existing research in domesticated rodents and humans gives quite a lot of perspective about the causes and extent of individual variation. For instance, functional genetic polymorphisms for *FKBP5* (as well as MR and GR) exist in both humans and laboratory rodents, and partly explain variation among individuals in their sensitivity to GCs [41]. In humans, impaired GC receptor function also appears to underlie the development of many metabolic diseases [41,42] and psychiatric disorders [43]. *FKBP5* seems a key mechanism orchestrating these outcomes; upregulation of *FKBP5* results in stronger GR resistance, weaker HPA axis negative feedback, and sustained and high circulating GC concentrations [29,44,45]. A haplotype of *FKBP5*, characterized by high *FKBP5* expression in response to GR activation, has also been associated with differences in the risk of post-traumatic stress disorder [46–48], bipolar disorder [49,50] and high anxiety [34,51].

In many species, molecular epigenetic processes will probably also affect individual variation in HPA flexibility. DNA methylation, which largely occurs at CpG motifs in gene regulatory regions, allows the integration of environmental signals into the genome to affect subsequent gene expression [52]. These changes alter the accessibility of transcription factors to binding factors, including *FKBP5* [53], probably sculpting the chromatin such that its structure affects future endocrine responses. In the adaptive sense, this sculpting could better mould endocrine responses to prevailing and/or past conditions; in the maladaptive sense, the epigenetic marks could instead prevent the organismal phenotype from tracking salient environmental change [54]. As of now, we know little about how methylation and other marks on the DNA affect HPA flexibility, much less whether any are heritable [55]. Further, whereas there are many examples of enduring effects of early-life stressors on later-life GC regulation, whether these effects apply to HPA flexibility or involve *FKBP5* remain obscure. Early-life environmental conditions alter specific regulatory elements of HPA flexibility [56,57], and some such effects are epigenetically mediated [58,59]. Previous research in vertebrates also suggests that GR is a primary target for long-term epigenetic programming of the HPA axis. Epigenetic changes to GR can enduringly modify HPA axis regulation depending on the natal environments experienced by individuals

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[60–65]. Again, research investigating these patterns in wildlife are scarce, although recent work has reported comparable effects of early-life adversity on GR methylation and expression in both captive and free-living birds [66,67].

Given the function of *FKBP5* and the importance of its epigenetic regulation in biomedical contexts, molecular epigenetic factors are likely to be major drivers of within-individual variation in HPA flexibility in nature, too. In humans, DNA methylation of *FKBP5* affects individual risk of developing psychiatric disorders; exposure to adverse conditions during childhood, but not during adulthood, was associated with low methylation at specific CpG sites in the *FKBP5* gene in individuals with a certain genetic polymorphism (i.e. the risk T allele [68]). Long-lasting, lower methylation in *FKBP5* in response to adverse conditions during early life also seems to result from sustained GR activation in early life [29,69]. Based on these two studies, *FKBP5* methylation status could amplify or limit HPA flexibility depending on *actual* environmental adversity experienced by an individual [1]. Transgenerational effects of adverse conditions on DNA methylation of *FKBP5* have also been reported in humans [70] and rats [59]. In the latter study, rats with low *FKBP5* DNA methylation had high *FKBP5* expression and sustained HPA activation [59].

## (b) Within-individual variation

Within-individual variation in HPA flexibility and *FKBP5* expression could be extensive and driven by a variety of exogenous and endogenous environmental forces. Below, we outline four important contexts expected to affect HPA flexibility and *FKBP5* and make some predictions about both to motivate research efforts. We also recognize that by reviewing what is known or expected about within-individual variation in HPA flexibility, we emphasize that the landscapes in figure 1 could be in fact quite plastic [71,72]. If so, the study of these landscapes will be quite challenging (i.e. in terms of statistical power) [73]. Still, this complexity should not stop our investigations of them. We must instead apply creative methods (e.g. response-surface regression) to describing and understanding how landscape rugosity shapes and is shaped by experience [74].

### (i) Seasonal

Seasonal variation in HPA regulatory components is well known in wildlife and domesticated organisms, and seasonal differences in HPA flexibility and *FKBP5* expression are obviously expected. In free-living birds, multiple components of the HPA axis change over the year (i.e. membrane and cytosolic receptor levels, plasma GC levels, corticosteroid binding globulins; [75]). This variation has been linked to variation in behavioural and physiological responses of individuals to environmental challenges, consistent with expected functions of GCs for various seasonal [76] and daily [77] activities. One would expect HPA flexibility to be highest and *FKBP5* to be lowest in seasons were stressors are least predictable and/or most consequential for fitness.

### (ii) Resource availability

Very few studies have addressed how resource availability might affect HPA flexibility, although there is reason to expect that both food quantity and quality will be important. For instance, birds facing high foraging costs expressed less *GR* compared with birds facing low foraging costs; these patterns were also associated with changes in GC responses to a standardized stressor (i.e. higher baseline levels and weaker negative feedback response [67]). Consistently, too, food-restricted house sparrows increased baseline GC levels as their body masses decreased, but individuals differed in GC responses to food restriction [78]. In laboratory mice, after 24 h food deprivation, *FKBP5* expression was dramatically increased in many brain regions [79]. Altogether, higher foraging costs and/or lower food availability should lead to high *FKBP5* expression and low HPA flexibility.

### (iii) Social context

In both social and non-social taxa, the frequency and type of interactions with conspecifics can affect HPA axis activity [80]. Similar social conditions potentially also drive differences in HPA flexibility and *FKBP5* expression. To date, research in this area has almost exclusively focused on plasma GCs and responses to single stressors, yielding contrasting results [81–83]. To our knowledge, only one study has measured gene expression in a social stressor context, but GR was measured, not *FKBP5* [84]. In this study, social information from food-restricted individuals reduced GR expression in HPA tissues of red crossbills (*Loxia curvirostra*). These changes could reflect low GR sensitivity and potentially lower EF, but no specific data yet exist. One would expect that individuals with high HPA flexibility (and low *FKBP5*) would cope most effectively in novel social contexts. However, given the multitude of diverse costs and benefits of social interactions, the social roles of *FKBP5* and HPA flexibility could be quite complex.

### (iv) Age

GC secretion often increases with age, but it remains unknown whether these changes are indicative of adaptive HPA flexibility or simply senescence. In humans, older individuals tend to have weak negative feedback and high baseline GCs [85,86], the latter condition being associated with higher risk for many non-infectious diseases (e.g. diabetes, hypertension, cardiovascular diseases) as well as sleep deterioration and depression [85,87]. Interestingly, Blair *et al.* [88] showed that *FKBP5* expression and protein levels increased with age, which promoted the pathogenesis of Alzheimer's disease. Patients with Alzheimer's disease also had higher levels of *FKBP5* in the brain as compared with controls. Although further research is needed to confirm the consistency and generality of these patterns, the above evidence suggests that all increases in *FKBP5* might not reflect adaptive change. We do not know much about changes in GC secretion in aged wildlife. In birds, baseline and stress-induced GCs tend to decrease with age [89–93], but we know almost nothing about HPA axis regulation and flexibility in old individuals. Studies directed at age-related changes up to and around the time of reproductive maturation would be most likely to reveal adaptive, age-dependent variation in HPA flexibility and *FKBP5* in wildlife.

## (c) Eco-evolutionary implications of HPA flexibility

Although we presently know very little about HPA flexibility and *FKBP5* in wild animals, enough relevant literature exists to propose a promising research programme in the context of anthropogenic change. Whether GC regulation affects the

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ability of wildlife to cope well with anthropogenic change is still unclear [94–99], but a focus on HPA flexibility, instead of GC concentrations, reframes the scope of the problem in two hopefully productive ways. First, it shifts efforts to describe regulatory control of the hormones [6,7,18]. It is the ability to regulate GCs that should affect fitness [100]. Second, it views GCs as physiological sculptors [101,102], info-molecules that help the organism become what environmental signals convey that it should be [6,103–105], not simple proxies of stress. GCs are among the most pleiotropic molecules circulating in vertebrates [4,105–108], so traits that describe the propensity of individuals to regulate them are more apt to illuminate how particular taxa will endure or suffer from anthropogenic change [6,96,108,109].

Such a framework for understanding physiological responses to stressors in wildlife, based on HPA flexibility, resonates well with the 'morphology, performance, and fitness' paradigm so powerful in other subdisciplines of organismal biology [110]. We have previously focused on hormone concentrations, assuming them to be indicative of stress because it is comparatively easy to measure hormones, even in fur, feathers, faeces or scales. However, what we always needed to understand was the ability of an animal to use its hormones adaptively. In this light, we summarize below what is known and expected about HPA flexibility in animals occurring in cities, areas where HIREC is particularly concentrated [111]. We focus on birds because GCs in this taxon are so well studied and are also common exploiters and victims of HIREC [112]. However, our rationale likely applies to all vertebrates including fish, amphibians, and other aquatic species. Further, although we focus on urbanization, we expect that our ideas apply to other forms of HIREC, including climate-driven and more directly human-caused geographical range shifts, but also local forms of habitat degradation, including light, noise and toxicant pollution [113].

## (d) Life in the city

For well over a decade, extensive efforts have been made to understand urbanization and GCs in wildlife [114]. Whereas many studies have revealed differences in GC concentrations between urban and non-urban organisms (reviewed in [98]), strong support for GC dysregulation as a causative force driving conservation concerns in urban wildlife has been lacking [96]. Iglesias-Carrasco *et al.* [115], for instance, found no effects of urbanization on circulating GC concentrations among 27 avian species across 34 studies, even when accounting for many putative modifiers of urbanization effects (e.g. sex, season, life stage, taxon, size of the city, etc). By contrast, Injaian *et al.* [98] discovered that only one aspect of urbanization (i.e. noise pollution but not light pollution of an urbanization index) was related to GC concentrations in birds and reptiles. Even, noise pollution effects on GCs were revealed only after an urban adaptability score for species was included as a predictive factor in models. Because this latter project involved HormoneBase [116], a very large compilation of wildlife endocrine data, the absence of urbanization effects on GCs in this particular study suggests that either GCs truly play no role in adaptation or adjustment to cities or, more likely, efforts to discern how GCs enable or prevent populations from mitigating urban stressors will require more sophisticated approaches. A few studies have moved in this more sophisticated direction, focusing on specific *facets* of urbanization that might affect GCs. For example, chronic traffic noise was revealed to alter GC responses to physical restraint stressors in tree swallows (*Tachicyneta bicolor*) [117]. In another study, artificial (white) light at night exposure was found to change GC concentrations in wild great tits (*Parus major*) [118]. Although these studies and others imply that GC regulation probably affects successful coping (or not) with particular urban stressors, generalities are very few [119]. We propose that a shift to HPA flexibility (and/or *FKBP5*) will be useful and might even reveal some actionable, broad patterns.

Before we propose such a study plan, some simplifying assumptions are necessary. First, we agree with Deviche and colleagues [95] that attending better to the dimensions of cities apt to be acting as stressors to wildlife will augment progress. Not all cities will have the same stressors, just as not all urban stressors will have the same implications for GC regulation. Likewise, non-urban sites are not necessarily an appropriate foil for urban sites, as natural places are so heterogeneous that the type and extent of environmental variation in non-urban sites would make few non-urban sites appropriate comparators. We also agree with Injaian *et al.* [98] that the observations that some species thrive whereas others avoid or even suffer in cities [120] will be important to consider. Perhaps because some species evolved in environments resembling cities, or simply evolved to be generalists, a few taxa will do quite well in urban contexts. The roles of GCs in coping with urban conditions might be general, but outcomes could vary depending on the species studied, at least whether the species is an urban avoider or urban exploiter.

Finally, cities vary extensively on several continua (i.e. size, age, proximity to natural areas, greenspace, etc.), but some broad trends in stressors very likely exist. Compared with non-urban areas, for instance, urban ones will often be more stable because of deliberate, ongoing habitat modifications by humans [95,121]. From this perspective, *predictability* of stressors should be higher in most urban versus non-urban areas (figure 3*a*). The times and places that organisms are exposed to stressors, on both short (daily) and long (seasonal) time scales, should be more knowable than for non-urban areas. City-dwelling animals will not always have the capacity to mitigate such conditions, but some organisms might avoid some stress simply by learning when and where stressors are likely to occur. Relatedly, in cities, the evolutionary *novelty* of stressors will typically be higher (figure 3*a*). Adverse factors such as noise, light, endocrine-disrupting chemicals, and other stressors with which ancestral populations will have had little to no experience will abound in urban areas. Of course, these factors might be common in some non-urban areas, too, but on balance, the collective of novel stressors should be higher inside than outside cities [122]. Even novel *degrees* of natural stressors such as food availability (i.e. more low-quality but more predictable food [123]) and social conditions (i.e. higher conspecific densities over longer portions of the year) will differ between urban and non-urban places [124]. In cities, too, interactions among novel and natural stressors should be common [94], perhaps expanding combinatorially the scope of stressors that wildlife will encounter. From this perspective, diverse endocrine responses would presumably foster diverse organismal phenotypic responses. Cities should thus tend to contain individuals with high HPA

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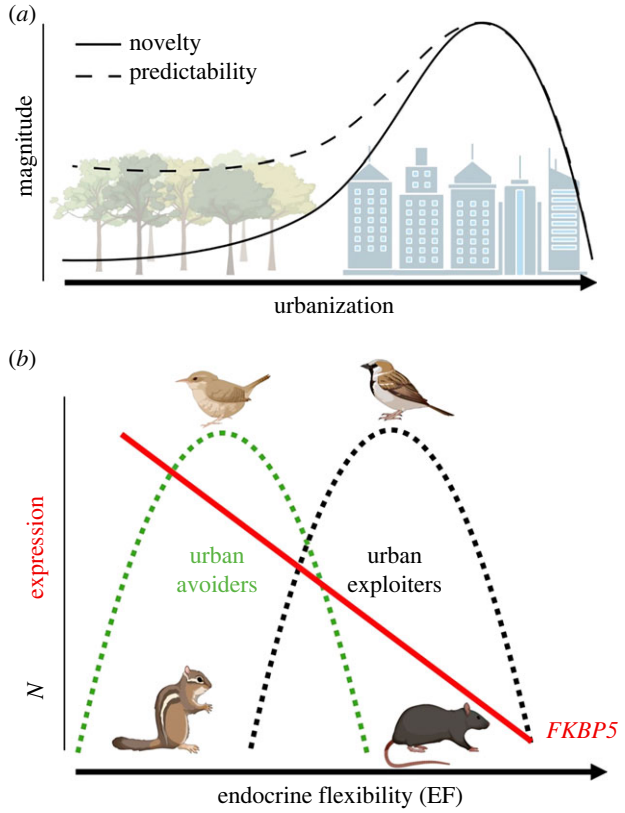


**Figure 3.** Stressors and organismal coping capacities for stressors along urban gradients. (*a*) Expected variation in stressor novelty and predictability along an urbanization gradient. Stressor novelty (in an evolutionary sense) should be higher in cities relative to surrounding natural areas. Stressor predictability, too, should be higher in cities given human amelioration of natural environmental change. However, even in non-urban areas, stressor predictability should not fall to zero but instead depend on local climate. (*b*) Predicted variation in HPA flexibility and *FKBP5* expression in city-dwelling organisms. Generally, individuals, populations or species with high HPA flexibility should fare best in cities, if the assumptions in (*a*) are valid. However, urban avoiders and exploiters should differ such that HPA flexibility should be low and *FKBP5* high in avoiders compared with exploiters. Created with Biorender.com.

flexibility and low *FKBP5*. On the other hand, if stressor predictability is more consequential than stressor novelty, fewer forms of GC responses (i.e. lower HPA flexibility) could instead be favoured in cities. These possibilities as yet await testing, but all things considered, we presently expect that high HPA flexibility and low *FKBP5* will largely be favoured in cities, even if stressors are relatively predictable there (figure 3*b*).

These propositions are offered solely as a reasonable starting place for investigation, and any productive future research will attempt to consider, empirically, stressor gradients in cities and organismal and endocrine responses to them. All such studies will also benefit by recognizing that species vary in how they cope with cities demographically; some species endure city conditions well (tolerators), others do not (avoiders), and still others seemingly thrive in their presence (i.e. preferers, exploiters and adapters) [120,125,126]. In figure 3*b*, we intermingle our expectations about urban stressors in figure 3*a* with known variation in ecological responses of species to anthropogenic effects. We favour the urban *tolerance* framework of Callaghan and colleagues [120] because it is a continuous form of responsiveness to city conditions and derived from more than 100 million observations of 338 avian species. Among that subset of birds, 75% of species had negative urban tolerance and 25% had positive tolerance, categories the authors named urban *avoiders* and *exploiters*, respectively [120]. The take-home message from that work is: most species do not fare well in cities, but quite a few do. We expect that HPA flexibility differs between these two categories of animals, with the highest forms of HPA flexibility and the lowest levels of *FKBP5* expression found in the exploiters (figure 3*b*). Of course, we should also moderate the above predictions with a few caveats. Some urban exploiters can also thrive outside cities, and those populations might have appreciably lower HPA flexibility than urban ones, especially if stressors in a specific city do not match patterns described in figure 3*a*. Parsimony also suggests that *FKBP5* expression should track HPA flexibility consistently for each species, with higher *FKBP5* expression related in the same manner to EF across species (figure 3*b*). This proposition warrants investigation, though, as the relationship between HPA flexibility and *FKBP5* has as yet been studied in very few species. Further, the predictions in figure 3 are not intended to capture possible allelic variants of or epigenetic effects on *FKBP5*, partly because we presently know nothing about them in wildlife.

Despite the above open issues, there are many insightful opportunities implicit in figure 3. For instance, one could assess relationships between HPA flexibility and fitness over time in urban populations to resolve how populations adapt or at least cope endocrinologically with urban conditions. One might also measure *FKBP5* (and/or HPA flexibility) in several cities or parts of large cities to implicate the specific aspects of urbanization most consequential to colonization and/or persistence. Finally, one could survey HPA flexibility or *FKBP5* broadly across taxa, seeking to identify organisms most likely to act as exploiters. Extensive efforts and abundant funds have been devoted to identifying pest biomarkers; perhaps organisms with low *FKBP5* are the ones resource managers most need to find and control.

Before closing, we must briefly mention that urbanization is not the only dimension of HIREC for which HPA flexibility warrants study [127]. Climate-driven and human-facilitated range expansions, too, should be affected by HPA flexibility and *FKBP5*. Just as with urbanization, GC regulation is justifiably expected to be involved in range expansions [128], and some data support such relationships. House sparrows at the vanguard of range expansions across Kenya [129,130] and Senegal [131,132], for instance, regulated GCs quite differently from birds from the core of populations. A similar pattern was revealed in a southward-expanding tree swallow population relative to resident populations [133]. In cane toads (*Rhinella marina*) [134–136] and Egyptian mongooses (*Herpestes ichneumon*) [137], GCs varied with range expansion but in a manner different from that in the above passerines. Broadly, across more than 100 bird and reptile species, variation in GC concentrations was unrelated to where samples were collected in a species' range [97]. Another comparative study on *Peromyscus* mice likewise found no intelligible patterns when comparing GC concentrations between a few broadly and narrowly distributed species [138].

Whereas the role of GCs in range expansions and geographic distributions will probably be nuanced, future studies focused specifically on HPA flexibility might be quite insightful. Colonizers or individuals enduring

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suboptimal abiotic or biotic conditions at range margins might be more active, bolder and/or more exploratory (and therefore potentially more likely to disperse), traits that all are related to GC regulation [139]. Just how GCs cause this behavioural variation (i.e. how GCs encode information) might differ among species [108], and this possibility should be investigated. Still, we expect that HPA flexibility will be quite high and *FKBP5* expression will be low at expanding range edges or indeed in any environments where stressors are novel and numerous.

## 5. Looking forward

Right now, because HIREC is such a problem for our health and wildlife welfare, we need new measurable targets, and these two factors, HPA flexibility and *FKBP5*, could be as valuable to conservation as they have been to medicine. Experts have long agreed that investigations of how wildlife populations respond physiologically to HIREC are important to management [140,141]. Likewise, scientists have long understood that organisms experiencing HIREC might provide valuable basic perspective into evolutionary change [142–144] and ecological impact (e.g. zoonosis spillover, extirpation of native populations by pests, etc.) [124,145–148]. We agree in both senses, but we also argue strongly that we must reduce our reliance on simplistic approaches (i.e. using one or a few measures of GCs, especially in inert tissues or faeces), and direct attention instead to traits like HPA flexibility and *FKBP5* [149]. These traits capture better how hormones encode information and hence enable the phenotype to be adjusted to the environment. Whether HIREC takes the form of urbanization, climate change, or range shifts, the organisms most adept at enduring these challenges will tend to be the flexible ones [150]. Sometimes, flexibility will be mediated by *FKBP5*, but often other molecular capacitators of adaptive variation will be important, too [151,152]. Regardless of the specific mechanisms, as Callaghan *et al*. wrote [120, p. 411]: 'a species' adaptive capacity, caused by individual, population or species-level attributes, may be important for conservation since it is one component that can make a species vulnerable to environmental change.' We think that HPA flexibility and *FKBP5* are such attributes, and not only will they be important for conservation purposes, but also they will help us comprehend better how endocrine systems function and evolve.

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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All authors gave final approval for publication and agreed to be held accountable for the work performed herein.

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